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Published in:
Expert review of respiratory medicine

DOI:
[10.1080/17476348.2017.1276445](https://doi.org/10.1080/17476348.2017.1276445)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Heuvelmans, M. A., Groen, H., & Oudkerk, M. (2017). Early lung cancer detection by low-dose CT screening: Therapeutic implications. *Expert review of respiratory medicine*, 11(2), 89-100.
<https://doi.org/10.1080/17476348.2017.1276445>

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To cite this article: Marjolein A Heuvelmans, Harry J M Groen & Matthijs Oudkerk (2017) Early lung cancer detection by low-dose CT screening: therapeutic implications, Expert Review of Respiratory Medicine, 11:2, 89-100, DOI: [10.1080/17476348.2017.1276445](https://doi.org/10.1080/17476348.2017.1276445)

To link to this article: <http://dx.doi.org/10.1080/17476348.2017.1276445>



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Accepted author version posted online: 22 Dec 2016.
Published online: 30 Dec 2016.



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REVIEW

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Early lung cancer detection by low-dose CT screening: therapeutic implications

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ABSTRACT

Introduction: Lung cancer screening by low-dose chest computed tomography is currently implemented in the U.S. After implementation of screening, a stage shift may be observed from around 15% stage I non-small cell lung cancers (NSCLCs) in routine clinical practice to up to 70% in screening patients. This indicates a move in treatment options from advanced to early lung cancers, especially in those with small suspected intrapulmonary nodules.

Areas covered: We have reviewed the current status of lung cancer screening from the different randomized controlled lung cancer screening studies and the clinical evidence so far for both surgical and non-surgical treatment options for (screen-detected) stage I NSCLC. Furthermore, we provide a step-wise approach for the treatment of stage I NSCLC.

Expert Commentary: Recommended treatment for stage I NSCLC remains (VATS) lobectomy in case of a medically operable patient, VATS sublobar resection for subcentimeter nodules, and SBRT otherwise. Currently, there is too limited evidence for the value of ablative techniques in curative treatment of early stage NSCLC. Therefore, these therapies should only be used in expert centers for selected patients in clinical studies.

ARTICLE HISTORY

Received 11 October 2016
Accepted 21 December 2016

KEYWORDS

Computed tomography;
lung cancer; screening;
stage I; treatment

1. Introduction

Lung cancer is a major health problem with no improvement in survival over the last decades. Lung cancer is the leading cause of cancer-related deaths worldwide, with 1.6 million lung cancer deaths each year [1]. After the age of 45 years, the incidence of lung cancer greatly increases in both males and females. Despite improvements in surgical treatment, chemotherapy and radiotherapy, the long-term survival of lung cancer remains low [2].

The lack of improvement in long-term survival is mostly due to the fact that lung cancer is still generally diagnosed at a late stage: more than two-thirds of the patients present with regional or distance metastases [3]. However, more recently the introduction of personalized medicine with targeted therapy and immunotherapy with PD1 – PD-L1 inhibitors may improve outcome for advanced disease. Most patients with early-stage lung cancer are asymptomatic that leads to delays in diagnosis. Lung cancer survival is strongly related to stage at time of diagnosis, with 5 year survival decreasing from 85% for treated stage IA disease, to around 6% for stage IV disease [4]. However, in routine clinical care, only 15% of lung cancer cases are stage I at diagnosis, and curability of lung cancer diagnosed at later stages greatly decreases [5,6].

1.1. Low-dose CT lung cancer screening

Low-dose computed tomography (CT) imaging was first introduced in the 1990s [7]. Advances in multi-detector CT

scanners have made high-resolution imaging in a single breath hold possible with radiation exposure less than 20% of the exposure from diagnostic chest CT scanning [8]. Recently, the largest lung cancer screening trial worldwide, the National Lung Screening Trial (NLST) concluded that annual screening by low-dose CT reduces lung cancer specific mortality by 20%, compared to screening by chest X-ray. Other trials compared CT-screening with no screening [9–13]. Most of these trials are ongoing.

The promising results of the NLST have led to a positive recommendation on lung cancer screening by the United States Preventive Services Task Force at the end of 2013, and to the announcement of the US Centers for Medicare and Medicaid services on the immediate cover of lung cancer screening with low dose computed tomography (LDCT) once per year in a high risk population [14,15]. Currently, lung cancer screening in the United States is rapidly expanding. Although none of the European trials have shown benefit of lung cancer screening by LDCT yet, also in Europe implementation of lung cancer screening is being discussed [16]. However, before lung cancer screening might be implemented in routine clinical care in Europe, some concerns should be clarified. First, the results of the largest European randomized controlled lung cancer screening trial, the Dutch–Belgian lung cancer screening trial (Dutch acronym: NELSON), or if necessary, the results of pooling of European trials with comparable screen parameters and nodule management [17], should indicate whether the results of the NLST are reproducible in

another population. Second, the false-positive rate of up to one out of four screenees as shown by the NLST should be reduced. A screening and nodule management strategy should be balanced, in terms of a high sensitivity for lung cancer diagnosis and minimization of potential harms like unnecessary additional CT examination and invasive workup for benign nodules. Third, in the NSLT about 23% of patients were diagnosed as stage IIIB/IV in incidence rounds for whom screening is not valuable [18]. In the NELSON study, the rate of stage IIIB/IV cancers increased from 7% after an annual screen, to 17% after a 2.5 year screen interval [19]. It might be that not all screenees should undergo regular screen CTs with equal screen intervals, but that certain subgroups can be identified based on prescreen lung cancer probability derived from modeling [20,21], or based on previous screen results in which the screen interval can be longer than 1 year to thereby decrease radiation dose and costs [22,23]. Nevertheless, a screen interval of 2.5 years seems to be too long [19].

1.2. Lung cancer screening studies and outcome

A number of single-arm cohort studies have been performed, showing that lung cancer can be detected in an early stage by screening by low-dose chest CT [24–28]. The two largest low-dose CT randomized controlled lung cancer screening trials worldwide are the NLST and the NELSON trial. In the NLST, 53,454 current or former heavy smokers aged 55–74 years were randomized to receive three annual low-dose chest CT screenings or three annual screenings by chest X-ray. They found that over a 7 year period, fewer participants died from lung cancer in the CT screen group compared to the control group screened by chest X-ray (17.6 per 1000 versus 20.7 per 1000, respectively). In the CT-screen group, 649/26,722 (2.4%) of the participants was diagnosed with lung cancer, and the majority of lung cancers were detected in stage I (60.6%, Table 1).

The NELSON trial was launched in September 2003. Primary object of this ongoing trial is to investigate whether chest CT screening in year 1, 2, 4 and 6.5 will decrease lung cancer mortality by at least 25% in high-risk (ex-) smokers between 50 and 75 years of age compared to a control group receiving no screening. The NELSON trial is the first large lung cancer screening trial in which nodule management is based on semiautomatically determined nodule volume, instead of manually measured nodule diameter, resulting in a lower false-positive rate [9]. At incidence rounds, nodule growth of previously detected nodules, in terms of volume-doubling

time (VDT), is decisive for the screen result. The final results, expected in the upcoming years, will indicate whether a volumetry- and VDT based CT protocol is more efficient in terms of detection rate, morbidity, mortality, recall rate, and cost-effectiveness, compared to other approaches. Similar to the NLST, a high percentage of 69% stage I cancers was detected in the NELSON study (Table 1). Not only cancers from nodules already detected at baseline were proven to be stage I in the majority of cases, also more than two-third of malignant nodules newly detected after baseline, and therefore relatively fast-growing, were found to be stage I at time of diagnosis [34].

Additionally, a number of smaller randomized controlled low-dose CT lung cancer screening trials were performed in Europe [17]. Three of these studies already published their final results. None of these studies showed a significant lung cancer mortality benefit for the CT screen group [29,32,35], possibly due to the limited sample sizes and unfavorable randomization to the CT screen group [29]. The percentage stage I cancers of the smaller trials, 45% to 72%, was far higher than the percentage stage I cancers detected outside a screening program (Table 1).

Non-small cell lung cancer (NSCLC) accounts for over 85% of lung cancer cases. Due to different screening approaches, in terms of screen interval, number of screening rounds and follow-up after screening, the exact lung cancer detection rate and percentage of lung cancer stage per screenings study should be compared with caution. However, Table 1 shows that the percentage of lung cancers (NSCLC and SCLC) detected in early stage (stage I or stage II, according to the seventh TNM classification [36]) is much higher in lung cancer screening patients, compared to routine clinical care. Results of the different randomized controlled lung cancer screening trials showing only a limited number of stage II cancers detected in screening (4–19%, mean 7.6%, Table 1 and Figure 1) suggest that stage II represents a relatively short period in the development in lung cancer. In other words, a lung cancer develops fast from a stage I cancer with relatively good 5 years survival results when treated, into a stage III cancer with far more limited survival.

1.3. Shift in treatment options for early stage lung cancers

Up to 70% of screen-detected NSCLCs published by the different lung cancer screening trials were detected in stage IA

Table 1. Lung cancer stages and histology of different randomized-controlled lung cancer screening studies.

	NLST [8]	NELSON [19]	DLCS [29]	MILD [30]	LUSI [31]	ITALUNG [12]	DANTE [32]	UKLS [33]
Number of rounds	3	4	5	5 or 10	5	4	5	1
Screen interval (years)	1	1, 2, and 2.5	1	1 or 2 (randomized)	1	1	1	NA
Lung cancer detection rate (%)	649/26,722 (2.4)	255/7915 (3.2)	100/2052 (4.9)	50/2303 (2.5)	58/2028 (2.9)	35/1613 (2.2)	104/1264 (8.2)	42/1991 (2.1)*
Stage I cancers (%)	400/649 (60.6)	176/255 (69.0)	50/100 (50.0)	28/50 (56.0)	42/58 (72.4)	23/35 (65.7)	47/104 (45.2)	28/42 (66.7)
Stage II cancers (%)	46/649 (7.1)	21/255 (8.2)	4/100 (4.0)	4/50 (8.0)	6/58 (10.3)	*	7/104 (6.7)	8/42 (19.0)
Stage III cancers (%)	108/649 (16.6)	42/255 (16.5)	23/100 (23.0)	6/50 (12.0)	7/58 (12.1)	*	17/104 (16.3)	3/42 (7.1)
Stage IV cancers (%)	81/649 (12.5)	16/255 (6.3)	23/100 (23.0)	9/50 (18.0)	3/58 (5.2)	*	26/104 (25.0)	3/42 (7.1)

*Not published separately; number of cancers stage II–IV: 12/35 (34.3%).

DLST: Danish Lung Cancer Screening Trial; ITALUNG: Italian Lung Study; LUSI: German Lung Cancer Screening Intervention Trial; MILD: Multicentric Italian Lung Detection; NELSON: Nederlands Leuvens Longkanker Screenings Onderzoek (Dutch–Belgian Lung Cancer Screening Trial); NSLT: National Lung Screening Trial.

Table 2. Stepwise approach for the treatment of (screen-detected) stage I NSCLC.

1	Define nodule consistency. Pure ground glass nodule: consider watchful waiting; (Partial)-solid: proceed to step 2.
2	Test if patient is eligible for, and willing to undergo surgery: Yes: proceed to step 3; No: proceed to step 4.
3	Define nodule size ≤1 cm: Consider VATS sublobar resection >1 cm: recommended treatment: (VATS) lobectomy. Alternative for selected patients*: VATS sublobar resection, preferably segmentectomy.
4	Specify stage and location: Stage IA (≤3 cm), peripheral: proceed to step 5; Stage IA (≤3 cm), central: proceed to step 6; Stage IB (>3–5 cm) peripheral: proceed to step 7; Stage IB (>3–5 cm) central: proceed to step 7.
5	Recommended treatment: SBRT. Investigational alternatives that might be considered in a clinical study: RFA, MWA, PCT
6	Recommended treatment: SBRT. Investigational alternatives that might be considered in a clinical study: (NSCLC <1 cm): PCT, PDT
7	Recommended treatment: SBRT.

VATS: video-assisted thoracoscopy; SBRT: stereotactic body radiation therapy; RFA: radiofrequency ablation; MWA: microwave ablation; PCT: percutaneous cryoablation; PDT, photodynamic therapy.

* Might be considered for elderly patients with peripheral stage I (adenocarcinoma) ≤2 cm in size

(up to 3 cm diameter) or IB (>3–5 cm diameter; Table 1, Figure 1), compared to up to 15% stage I NSCLCs in routine clinical care [5,6]. The percentage screen-detected stage I cancers may be lower as a result of a different screen protocol, nodule management protocol, or selection of screen participants. The higher rate of early stage cancers indicates that, after implementation of lung cancer screening in routine clinical care, a shift in lung cancer treatment options will take place, from mainly management for advanced stage to treatment options with curative intent for early stage cancers. Currently, anatomic surgical resection with systematic lymph node evaluation is recommended as standard treatment for operable patients with early stage NSCLC according to the National Comprehensive Cancer Network (NCCN) guidelines [34]. For medically inoperable patients stereotactic body

radiation therapy (SBRT) is currently the recommended treatment. Interest in alternative investigative nonsurgical treatment options such as radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous cryotherapy (PCT) photodynamic therapy (PDT) and heavy particle irradiation is increasing, although these techniques are still experimental and are used in the setting of clinical studies. Up to now, no randomized trials were finished comparing the different treatment options. This article will review the pros and cons and clinical evidence so far for both surgical and nonsurgical treatment options for clinical stage I NSCLC.

1.4. Should all patients with screen-detected stage I cancers be treated?

If patients with stage I NSCLC are left untreated, median survival is less than a year [37–39]. However, it is very important to differentiate stage I NSCLC presenting as solid or partial-solid nodules from those presenting as pure ground glass opacity [40]. The latter group, mostly representing adenocarcinoma *in situ* or minimally invasive adenocarcinoma, distinguish themselves from other stage I NSCLCs in terms of their nonaggressive behavior. In a sub analysis on nonsolid nodules detected in two studies on lung cancer screening, it was shown that despite the relatively high risk of malignancy in these nodules, progression to cancer stage beyond stage I was extremely rare [41,42]. Yankelevitz et al. reported a lung cancer survival rate for patients with a malignant nonsolid nodule of 100% after a median follow-up period of 78 months since diagnosis, regardless the size of the nonsolid nodule [41]. Thus immediate resection of pure ground glass nodules mostly should be discouraged, and close follow-up of nonsolid nodules (SSNs) by annual LDCT usually is sufficient, to reduce overdiagnosis and overtreatment of lung cancer screening participants.

1.5. Importance of histopathological diagnosis

In a substantial part of patients undergoing minimal invasive treatment methods like SBRT for a suspicious solitary pulmonary nodule, no definitive tissue diagnosis will be obtained.

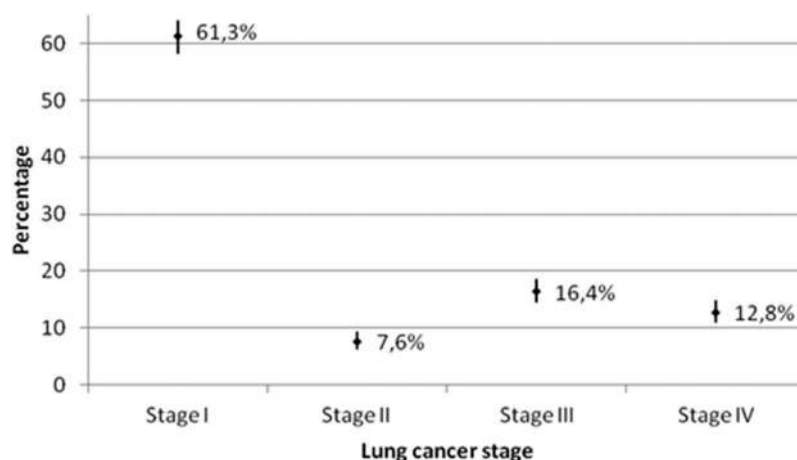


Figure 1. Total overview cancer stage distribution of the randomized-controlled low-dose CT lung cancer screening trials, shown as percentage (dots) with standard deviation (vertical bars). A total of 1,258 lung cancers in 46,075 screen participants were described by the different studies. ITALUNG data were excluded because of missing stage distribution for cancers beyond stage I.

Recently, models for estimation of lung cancer probability were established, indicating that patients with positron emission tomography (PET)-positive new or growing solitary pulmonary nodules with a >85% pretest probability of malignancy are eligible for treatment with SBRT [43]. No difference in overall survival or local control in patients with or without pathologically proven lung cancer was found in a population with a low incidence of benign PET-positive lung nodules [44].

The smaller the nodule, the less likely that histopathological diagnosis can be obtained. In such cases nodule growth will determine the probability of malignancy, as the majority of very small lung cancers (<8 mm) will be FDG negative [45,46]. These patients will be treated as if having stage I NSCLC. Some centers will prefer a wait-and-see policy, some use transthoracic needle biopsy before treatment to obtain tissue for confirmation of malignancy, and some start with a video assisted thoracoscopic wedge resection. Therefore, different algorithms have been advocated to estimate the risk for malignancy.

Since a single positive lymph node will lead to an upstaging from stage I to at least stage II NSCLC, pretreatment mediastinal staging is important. Imaging tools such as a diagnostic CT and PET are valuable in the evaluation of mediastinal lymph nodes, however false-negative (5–15%) and false-positive (up to 53%) may not be neglected. Therefore, nowadays lymph node staging is supplemented with endobronchial ultrasound-guided (EBUS) or endoscopic ultrasound transbronchial needle aspiration (EUS). In patients treated with surgery, the American College of Chest Physicians (ACCP) and other societies recommend systematic mediastinal lymph node sampling at time of anatomic resection for accurate pathologic staging [47].

2. Surgical treatment options along the line of lobectomy, segmentectomy, wedge resections

Since the implementation of lobectomy, it has been the recommended first-line treatment for patients with early-stage NSCLC who are able to undergo surgery [48]. Nevertheless, it is important that lung cancer surgery is performed in a center with high procedure volume, to increase survival, in particular in the early postoperative period [49]. One great benefit of surgical techniques compared to nonsurgical techniques as discussed below, is the possibility to gather a definitive tissue diagnosis and the best local tumor control. Based on the lung cancer's histologic subtype and mediastinal lymph node staging, an accurate pathological staging can be performed. Furthermore, the histologic sample can be used to obtain information on lung cancer's DNA mutation status, which is especially valuable in case of progressive disease.

2.1. Prior to surgery: eligibility of the patient

According to the U.S. Preventive Services Task Force, persons eligible for lung cancer screening have smoked at least 30 pack-years. Since smoking is the most important risk factor not only for lung cancer, but also for severe comorbidities like chronic obstructive pulmonary disease (COPD). and coronary

heart disease, it is not surprising that up to 25% of patients with screen detected lung cancer are not eligible for surgery [50,51]. According to the ACCP step-by-step approach for the preoperative evaluation of lung cancer patients, patients who are candidates for surgical treatment should undergo both spirometry (forced expiratory volume in 1 second [FEV₁]) and measurement of diffusing capacity for CO (DLCO) [52]. In patients with FEV₁ or DLCO <60% of predicted, the postoperative predicted volume is estimated. In case of postoperative predictive volume between 30% and 60%, the participant is designated of being at increased operative risk. For those patients, it is necessary to evaluate patient's exercise capacity, for instance by ergometry (Vo₂ max estimation) or a 6 min walk test (cutoff point eligible for surgery of 400 m). In case of a calculated postoperative predictive FEV₁ or DLCO of <30%, this cardiopulmonary exercise test gives an indication of the risk on perioperative morbidity and mortality [52]. Treatment options for early stage NSCLC patients with comorbid conditions precluding surgical resection are discussed below.

2.2. Lobectomy, open thoracotomy versus minimally invasive techniques

Lobectomy via thoracotomy including mediastinal lymphadenectomy has been the standard-of-care for years. Five-year overall survival rates for patients with stage I NSCLC treated with lobectomy via open thoracotomy are in the range of 60% to 80% [53,54]. Another approach is video-assisted thoracoscopic surgery (VATS) which is a minimally invasive alternative to open thoracotomy. A randomized controlled trial comparing open thoracotomy and VATS for the treatment of stage I NSCLC in terms of survival has not been performed. However, in a large study using data of the National Cancer Data Base, retrospectively analyzing over 30,000 lobectomies performed for stage I lung cancer between 2010 and 2012, was found that about one-third of lobectomies were performed minimally invasive via VATS or robot-assisted [55]. After comparison with open lobectomy, they found that minimally invasive lobectomy was associated with shorter length of hospital stay, and was not associated with increased perioperative mortality or reduced short-term survival when compared with the open approach [55]. Another advantage of the VATS approach over open thoracoscopy is the fact that it can be performed in patients with worse preoperative pulmonary function tests [56]. Nodal upstaging beyond stage I was found to occur more commonly in open thoracoscopy compared with minimally invasive lobectomy (12.8% versus 10.3%), but this difference was no longer statistically significantly different for patients who were treated in an experienced clinic. This suggests that minimally invasive lobectomies should be performed only in high-volume centers with significant experience [57]. Comparable results have been described by other studies [58–61], indicating lobectomy via VATS as a more favorable approach in the treatment of stage I NSCLC compared to open thoracoscopy. Recently, a randomized controlled trial was published comparing postoperative pain and quality of life for patients with early lung cancer treated by VATS lobectomy or open lobectomy. VATS lobectomy was found to be associated with less postoperative pain and better

quality of life compared to lobectomy by anterolateral thoracotomy for the first year after surgery [62]. Therefore, the authors suggest that VATS should be the preferred surgical approach for lobectomy in stage I NSCLC. The major question is whether the hilar and mediastinal lymph nodes are adequately explored when a VATS is performed. As indicated this is mainly determined by experience of the surgeon.

More recently, robot-assisted thoracoscopic surgery has been used in the treatment of stage I NSCLC. Compared to open lobectomy, robot-assisted thoracoscopic surgery was associated with shorter in-hospital stay and lower morbidity and mortality, but significantly longer operating times [63,64]. Only few small retrospective studies have been performed comparing VATS and robot-assisted thoracoscopic surgery. These studies suggest comparable perioperative outcomes with fewer conversions for uncontrolled bleeding using the robot-assisted thoracoscopic approach [65]. However, there is a steep learning curve for robot-assisted thoracoscopic surgery, and long-term randomized studies evaluating robotic-assisted lobectomy and VATS lobectomy are still lacking [66].

2.3. Sublobar resection versus lobectomy

Sublobar resection refers to either wedge-resection or segmentectomy. Sublobar resection may be considered for patients who cannot tolerate a lobectomy due to limited pulmonary function, advanced age, or other extensive comorbidity. Comparing segmentectomy with wedge-resection, Sienel et al. found a better cancer-related survival for patients who underwent a segmentectomy [[67]. However, another recent study suggests that for carefully staged cT1N0M0 NSCLC, segmentectomy and wedge-resection are associated with comparable outcome in terms of survival [68]. Only limited data comparing sublobar resection with (VATS) lobectomy is available. Dai et al. compared overall survival and lung cancer-specific survival among 15,760 patients with stage IA NSCLC after lobectomy, segmentectomy, or wedge resection [69]. They found that lobectomy showed better survival than sublobar resection. For NSCLC patients in whom lobectomy is unsuitable, they recommended segmentectomy for tumors >1 to 2 cm because of better survival compared to wedge resection, whereas for tumors ≤1 cm survival was similar after treatment with segmentectomy and wedge resection [69]. Tsutani et al. studied 610 patients with stage IA adenocarcinoma who underwent surgical resection by either lobectomy or segmentectomy, and looked into radiological characteristics predicting survival. In a subgroup of 239 patients with ground-glass-opacity-dominant (subsolid) primary tumors, no significant difference in 3 year recurrence-free survival was observed between patients who underwent lobectomy (96.4%), segmentectomy (96.1%), and wedge resection (98.7%) [70].

Using data of the National Cancer Data Base, it was found that patients with stage IA NSCLC treated with sublobar resection had significant worse overall survival compared with lobectomy [71]. Median OS for lobectomy, segmentectomy, and wedge resection were 100, 74, and 68 months, respectively ($p < .001$). This retrospective study showed that surgical margins were more often positive, fewer lymph nodes were

examined and significantly lower rates of nodal upstaging were found in patients treated with sublobar resections [71].

Two multicenter, prospective, randomized studies comparing lobectomy versus sublobar resection for small (≤ 2 cm) peripheral NSCLC are currently ongoing (Cancer and Leukemia Group B 140503; Japanese Clinical Oncology Group 0802/West Japan Oncology Group 4607L). Results of these trials will help to define the selection criteria for sublobar resection in the treatment of NSCLC patients. The first prospective, multicenter, randomized controlled trial comparing sublobar resection and lobectomy for elderly patients with clinical stage T1N0M0 NSCLC has recently been announced. Primary outcome of this trial is 3 years disease-free survival. In total 339 subjects will be enrolled, and participants will be followed-up every 6 months post-operation for 3 years [72]. Until now, sublobar resections may have equivalent outcomes to lobectomy in well-selected patients with small (up to 2 cm) NSCLC, and in whom an adequate resection margin can be achieved, for instance those with small peripherally located tumors with favorable histopathology, and with ground-glass opacity on imaging [73–75].

2.4. After surgery: adjuvant chemotherapy or postoperative radiotherapy

Adjuvant chemotherapy might be considered for patients with a stage IB NSCLC with diameter of more than 4 cm. For patients with resected stage IA tumors, adjuvant chemotherapy is not indicated. Postoperative radiotherapy is only indicated for patients with stage I NSCLC with positive surgical margins.

2.5. Summary surgical treatment options

In summary, lobectomy, preferably via VATS, including mediastinal lymph node dissection is the recommended treatment option for patients with stage I NSCLC with adequate lung function and no major comorbid conditions precluding surgery. Sublobar resection preferably segmentectomy via VATS can be performed in well-selected patients with small (<2 cm) peripheral ground-glass-opacity-dominant nodules or semisolid nodules, and in whom an adequate resection margin can be achieved.

3. Nonsurgical treatment options

About 25% of patients with screen detected lung cancer are not eligible for surgery due to comorbid conditions, often caused by smoking. A disadvantage of lobectomy for a small subcentimeter nodule is the relative large loss of normal lobar tissue. After a lobectomy loss in lung function is about 11%. If for such patients VATS with wedge or segmentectomy is not feasible, radiotherapy is an option.

SBRT has been shown to be an effective and safe alternative for treatment of early stage lung cancer in medically inoperable patients [76]. Furthermore, knowledge on other, investigational, minimal invasive techniques like radiofrequency ablation, microwave ablation, percutaneous cryotherapy and photodynamic

therapy is increasing [76]. In particular SBRT has been advocated to be equivalent to surgical resection in terms of local control and survival outcomes in some cases.

3.1. Stereotactic body radiation therapy

SBRT, also known as stereotactic ablative radiotherapy (SABR) uses precisely targeted radiation with very large doses per fraction by using multiple convergent beams. The aim of the technique is to destroy cancerous tissue, causing as little toxicity to adjacent normal tissue as reasonably possible. SBRT is considered the standard treatment for stage I NSCLC patients with comorbidities precluding surgical resection. Compared to lobectomy or sublobar resection, it has a lower complication rate with similar overall mortality [77]. Furthermore, in a randomized controlled trial, the global health related quality of life and indirect costs were found to be significantly favorable and cheaper in patients treated with SBRT compared to patients treated surgically [78].

A study on patients with severe COPD and early stage NSCLC showed that patient treated with SBRT had significant lower 30-days mortality compared to patients treated with lobectomy, with comparable survival rates at one and 3 years despite negative selection of SBRT patients in terms of comorbidities [79].

In a large retrospective study on SBRT in 676 patients with early-stage NSCLC a 5 year local control of 89.5% was found. After 5 years, any recurrence, most often isolated distant recurrences that will probably not be affected by the local treatment used, had occurred in 30% of patients. Median overall survival was 40.7 months [80]. Other prospective stage II studies on small, peripheral, biopsy-proven NSCLC showed comparable 5 year local control rates of around 90% [81].

For elderly patients until at least age 85 years with stage I NSCLC with multiple comorbid conditions precluding surgical resections, treatment with SBRT (median overall survival 29 months) is found to be associated with improved survival compared with observation alone (median survival 10 months; $p < .01$) [82]. In addition, another study analyzing results of 251 patients stratified by age showed that elderly patients (at least 75 years old) had similar rate of efficacy and risk of toxicity as younger patients after SBRT treatment [83]. In this particular group of elderly patients, a definitive treatment of NSCLC sometimes is abandoned, due to limited estimated survival time of the patient. However, results of Nanda et al. and Mancini et al. suggest that SBRT should always be considered for elderly patients with an early stage lung cancer [82,83].

3.1.1. Surgical resection versus SBRT in patients eligible for surgery

After these positive results of the mostly smaller studies, showing comparable survival after treatment with SBRT and surgery, there has been increased interest in using SBRT as the primary treatment for patients who are healthy enough for surgery but prefer a less invasive treatment. Retrospective comparisons of patients treated with SBRT or lobectomy showed less favorable outcome for patients treated with

SBRT [84,85]. However, results of these comparisons were possibly affected by patient selection bias, since patients treated with SBRT are more likely to be older and have more comorbidities, making them less eligible for surgery. Rosen et al. retrospectively compared survival data of patients with stage I NSCLC that were healthy enough for surgery but preferred SBRT over lobectomy [39]. In total, 13,652 patients underwent lobectomy and 1781 patients medically fit for operation underwent SBRT due to personal preferences. Patients treated with SBRT were generally older and were less likely to have adenocarcinoma. The first 7.5 months after treatment, there were no differences in survival for the two treatment options, but after 7.5 months survival lobectomy was associated with a significantly better outcome than stereotactic body radiotherapy [39].

Up to now, no large randomized controlled trials comparing surgical resection with SBRT for early-stage NSCLC has been finished due to poor accrual. Recently, pooled results of two early-closed randomized controlled trials comparing SBRT and lobectomy, the ROSEL and the STARS trial were published. From the pooled results, including 58 patients randomized to SBRT (31 patients) or surgery (27 patients), it was concluded that SBRT could be a reasonable therapeutic option for operable stage I lung cancer with better overall survival (3 year overall survival of 95% for SBRT versus 79% for lobectomy [76]. However, these results should be interpreted carefully because of the limited sample size and short follow-up: the possible 'head-start effect' for SBRT, where perioperative mortality may obscure a later mortality benefit of surgery [76]. Several retrospective studies have been performed comparing SBRT and surgical resection. Direct comparison of the two treatment methods is challenged by the fact that most patients treated with SBRT were older and had more comorbidities. Therefore, larger randomized controlled trials are awaited to confirm the findings of Chang et al.

3.2. Lung ablation

In case patients with early-stage NSCLC, not eligible for both SBRT and surgical resection, are able to undergo percutaneous CT-guided needle biopsy, they might be candidates for image-guided tumor ablation techniques like RFA, MWA or PCT. These techniques are relatively new in the area of lung cancer treatment, and were initially introduced for the percutaneous treatment of hepatic malignancies. The goals of tumor ablation are (1) ablation of the entire tumor and a margin of normal parenchyma surrounding it, (2) to quickly create this large ablation area, and (3) to avoid injury to critical structures [86]. Up to now, there are no randomized controlled trials comparing the different ablation techniques with each other, with SBRT, or with surgical resection. Pending such studies, ablative therapies for the treatment of NSCLC should only be used for patients within clinical studies in expert centers.

3.2.1. Radiofrequency ablation

Among image-guided ablation as a treatment for stage I NSCLC, RFA is the most common used technique, and the major advantage of RFA over other ablation techniques is experience. During RFA, an alternative current is generated

by a radiofrequency generator, moving from an active electrode inserted within the tumor, usually performed under CT guidance, to dispersive electrodes placed on the patient. A high-frequency electrical current is generated, causing heating and coagulation of tumor tissue.

Important contraindications for treatment with RFA are tumors surrounded by larger vessels and airways and centrally located tumors. Due to the so-called heat-sink effect, the phenomenon by which medium to large-sized blood vessels and airways dissipate the thermal and electrical energy away from adjacent tissue and target lesions [86], tumors near these structures may show less response than expected. Furthermore, RFA is discouraged for central nodules and nodules located in the lung apex or within 1 cm of major vessels, bronchus, nerves, and esophagus, because of the risk of thermal injuries. A relative contraindication for RFA is tumor size; local control is reduced in tumors with diameter >3 cm [87]. Complications of RFA frequently occur, with a rate of major complications of around 10% of lung ablations. The most common complications include pneumothorax, postprocedural pain, hemoptysis, bronchopleural fistula, and rib fractures.

Most studies analyzing the efficacy of RFA in the treatment of stage I NSCLC were performed retrospectively. These studies concluded that RFA is a safe, feasible, and effective procedure in medically inoperable clinical stage I NSCLC patients. In a review of 14 studies regarding RFA for stage I NSCLC, 1-, 2-, 3-, and 5 year overall survival rates were 78–100%, 53–86%, 36–88%, and 25–61%, respectively [88]. The median survival time ranged from 29 to 67 months. Recently, two prospective multicenter studies published their results. Dupuy et al. studied RFA in 51 eligible patients. They found overall 1 and 2 year survival rates of 86.3% and 69.8%, respectively. For tumor size <2 cm, overall 2 year survival rate increased to 83% [89]. Gobara et al. enrolled 33 patients from eight institutions, however only seven patients had stage I NSCLC [90]. For these seven patients, 1- and 2-year overall survival rates comparable to Dupuy et al. were found (83% and 63%, respectively).

3.2.2. Microwave ablation

MWA is perceived as a potentially superior treatment option to RFA, due to enhanced tumor coagulation of tumor cells as a result of improved energy deposition in the lung leading to higher temperatures within the tumor in a shorter time period and a larger ablation area. MWA uses electromagnetic waves in the microwave energy spectrum that produce tissue-heating effects. By inducing kinetic energy within water molecules surrounding the probe, these molecules start rotating rapidly, and they transfer some of their kinetic energy to surrounding tissue leading to tissue heating [86]. It is a novel technique in the treatment of early stage lung cancer, with complications comparable with RFA although MWA is associated with less procedural pain. Compared with RFA, the heat-sink effect is found to be smaller in MWA. However, in lesions close to large vessels, treatment response can be less than expected.

Up to now, only few clinical studies on MWA, most of them including both primary NSCLC and pulmonary metastases, have been published. In a study by Wolf et al. of 50 patients with 82 pulmonary masses (primary or pulmonary metastasis,

exact numbers not provided) treated with MW ablation, cancer-specific was 83%, 73%, and 61% at 1, 2, and 3 years post-ablation, respectively [91]. After a mean follow-up of 10 months, 26% of patients had residual disease at the ablation site, and 67% had local control at 1 year. Belfiore et al. studied 69 unresectable lesions (44 NSCLC, 25 pulmonary metastases) in 56 patients, and found comparable survival rates [92]. One-year, 2 year and 3 year cancer-specific survival was 69%, 54%, and 49%, respectively. The estimate mean survival time was 27.8 months. None of the patients developed local recurrence during the study (mean follow-up time not described). A study retrospectively analyzing 47 patients with stage I medically inoperable NSCLC who were treated with MWA found a median cancer-specific survival of 47.4 months [93]. Tumors ≤3.5 cm were associated with better survival compared with lesions >3.5 cm. Pneumothorax was by far the most common complication in the different studies, with incidence of up to 64% [93], however chest tube insertion was only necessitated in the minority of these cases and 30-days mortality was very low.

3.2.3. Percutaneous cryoablation therapy

In contrary to the two heat-based ablation techniques, PCT uses cold to destroy tissue. When a pressurized gas, usually argon, reaches the end of the probe, located in the tumor under CT-guidance, the gas expands and reaches ultralow temperatures of as cold as −140 °C. An ice-ball is formed in the tissue surrounding the probe, and cryogenic destruction occurs directly as a result of protein denaturation and cell rupture from ice crystals and osmotic shifts between intracellular and extracellular water, and indirectly as result of hypoxic tissue injury due to vasoconstriction, freezing of blood in small vessels or occluded blood vessels [86,94]. PCT is performed using an ablation scheme consisting of both freeze periods and thaw periods, to reduce the chance of air leaks and bleeding. One or more probes can be placed in a tumor depending on its size, but lesions <3 cm are preferred.

The advantages of PCT over RFA include larger tumor ablation volumes and less procedural pain due to the analgesic effect of freezing [94]. Since PCT is able to preserve collagenous tissue and cellular architecture, in contrary to RFA, this ablation technique is safer for patients with extensive emphysema and for lesions near vascular structures or bronchi. Furthermore, a highly visible ablation zone is created, which allows for easy follow-up during the procedure. Drawbacks of PCT compared to MWA and RFA include the relatively long procedural time and the increased chance of bleeding along the needle tract requiring intervention like tract coagulation with fibrin glue.

Three studies focused on PCT for stage I NSCLC. Zemlyak et al. studied 27 patients [95]. After a mean follow-up of 33 months, they found a local control rate of 89%. 3 year overall survival was 77%. Yamauchi et al. studied 22 patients with 34 tumors who underwent 25 sessions of PCT for clinical stage I NSCLC [96]. Median follow-up period was 23 months. Local tumor progression after cryoablation was observed in one squamous cell carcinoma (3%) of 1.6 cm in size. 3 year overall survival was 88%. The third study retrospectively

evaluated the 5 year survival in 45 patients with 47 primary stage I NSCLC after PCT. 5 year overall survival was 68%. There were no deaths associated with the cryoablation, however a pneumothorax was seen in over 50% of cases and bleeding occurred in two-fifth of cases, although most of which minor [97].

3.2.4. Summary lung ablation

In summary, knowledge on ablative therapies in the treatment of medically inoperable patients with stage IA NSCLC is increasing. Most of the studies have been performed on larger tumors. Ablation by cryo, microwave or radiofrequency procedures may be reconsidered for small growing nodules with novel positioning technologies.

A retrospective study compared the outcome of patients with stage I NSCLC treated with either sublobar resection (N = 25) or RFA (N = 12) or cryoablation (N = 27) in 64 patients [95]. They found a comparable 3 year cancer-specific survival for the three treatment options (90.6%, 87.5%, and 90.2%, respectively). However, larger randomized-controlled trials with longer follow-up comparing the different ablative treatment options and comparing ablative therapies with SBRT and lobectomy in the treatment of medically inoperable patients with stage IA NSCLC need to be performed to confirm the first results and to make recommendations for therapy. In these comparison studies, patients of all treatment arms should undergo comparable pre-treatment evaluation of the presence of mediastinal or distance metastases. Pending such studies, ablative therapies for the treatment of NSCLC should only be used in the scope of clinical studies in expert centers.

3.3. Other treatment options

Other novel investigative techniques for the treatment of stage I NSCLC include heavy particle irradiation and photodynamic therapy.

3.3.1. Heavy particle irradiation

In patients with stage I NSCLC, both proton beam and carbon ion therapy have been used on an experimental basis. Through the characteristic Bragg peak where protons and carbon ions give the majority of their energy on the depth where the radiation penetrates maximal in the tumor, the dose to surrounding normal tissue is significantly reduced. Preliminary results of a number of small studies investigating proton beam and carbon ion therapy for stage I NSCLC suggest that these approaches may yield results similar to conventionally fractionated RT. Furthermore, a number of larger clinical trials are underway [98]. For now, until more evidence has been collected, heavy particle irradiation should not be used in the treatment for stage I NSCLC outside the scope of clinical trials.

3.3.2. Photodynamic therapy

Over the last several years, PDT has been used more frequently in the treatment of thoracic malignancies. PDT uses a photosensitizer combined with light to produce singlet oxygen ($^1\text{O}_2$) that leads to damage of cancer cells through apoptotic, necrotic, or autophagic tumor cell death. Simone et al.

reviewed available literature on the use of PDT for the treatment of stage I NSCLC. They concluded from the different studies with small sample sizes that PDT is most effective for tumors with lengths ≤ 1 cm that have no extra cartilaginous invasion and no radiologic findings on high-resolution CT imaging, and that treatment by PDT might be an alternative for surgery in medically inoperable tumors with a central stage I NSCLC of < 1 cm diameter [99]. More evidence on the effectiveness of PCT for treatment of stage I NSCLC in larger clinical studies should be collected to investigate the possible role of this technique in the treatment of such cancers.

4. Summary

In conclusion, implementation of lung cancer screening, currently already in the United States and perhaps in the upcoming years also in other parts of the world, will have major therapeutic implications. Among screening participants, a stage shift will occur from up to 15% stage I non-small cell lung cancers (NSCLCs) in routine clinical practice to up to 70% in lung cancer screening patients. This indicates that, after implementation of lung cancer screening in routine clinical care, a shift in lung cancer treatment options for advanced stage to treatment options with curative intent for early stage cancers may occur. Some of the pure ground-glass, nonaggressive, lung cancers will not require immediate treatment, but close follow-up by CT-scans instead. For (partial) solid stage I NSCLCs in medically operable patients, (VATS) lobectomy remains the standard of care, with sublobar resection as an alternative treatment option in specific patient populations such as subcentimeter solid nodules. For medically inoperable patients, or in patients not willing to undergo surgery, SBRT is the treatment of choice. In case of a patient with a stage IA cancer presenting in a specialized clinic, more investigational options like ablation may be considered only in scope of a clinical study. More (prospective) studies on more investigative noninvasive treatment options like radiofrequency ablation, microwave ablation, percutaneous cryotherapy and photodynamic therapy, and randomized controlled trials comparing the different treatment options, in particular surgery and SBRT, are awaited.

5. Expert commentary

Lung cancer screening by low-dose chest CT for high-risk patients is already being implemented in routine clinical care in the United States. From the different screening trials we have learned that the large majority of screen-detected NSCLCs is diagnosed in stage I (Table 1). For Europe, lung cancer screening programs are not recommended yet, and the final result of the largest European trial, the NELSON trial, probably will be decisive in that discussion. Nevertheless, the promising results of the NLST may not be neglected. Furthermore, results of the different screening trials showing only a limited number of stage II cancers detected in screening (4% to 19%), suggest that stage II represents a relatively short period in the development in lung cancer. In other words, a lung cancer develops fast from a stage I cancer with relatively good 5 years survival when treated, into a stage

III cancer with far more limited survival, indicating the value of screening programs.

Recommended treatment for stage I NSCLC remains (VATS) lobectomy in case of a medically operable patient, VATS sublobar resection for subcentimeter nodules, and SBRT otherwise. Although novel techniques seem promising, there is too limited evidence for the value of radiofrequency ablation, microwave ablation, cryoablation, and photodynamic therapy in curative treatment of early stage NSCLC. Therefore, these therapies should only be used in expert centers for selected patients in clinical studies (see Table 2).

6. Five-year view

With implementation of lung cancer screening, and further optimization of imaging techniques, more and more small pulmonary nodules inside and outside of lung cancer screening programs will be detected. Patients with screen-detected lung cancer are much more likely to present with stage I lung cancer than are patients with lung cancer diagnosed after medical symptoms. Thus, it might be expected that discussion on the different treatment options for early-stage lung cancer will increase. The selection criteria for different surgical approaches will be evaluated in clinical trials and sublobar resections in selected medically operable patients will become implemented. However, in particular for lung cancer screening patients with a stage I pure ground-glass lung cancer, watchful waiting should be considered because of the nonaggressive behavior of these specific cancers. For medically inoperable patients, SBRT is the standard of care. Although experience on ablation techniques like RFA, MWA and PCT for treatment of early stage lung cancers is increasing, prospective, preferably randomized controlled trials in small tumors, should be performed to gain more insight in the value of these techniques compared to the current standard care. In these studies, patients of all treatment arms should undergo comparable pretreatment evaluation of the presence of mediastinal or distance metastases to ensure stage I disease. These patients should be eligible for all treatment arms to avoid selection bias. It might be expected that in the upcoming years newer techniques such as heavy particle irradiation and PDT will be further elaborated in clinical studies.

Key issues

- In routine clinical practice, only about 15% of lung cancers are still stage I at time of diagnosis.
 - In high-risk patients screened by low-dose chest CT, up to 70% is diagnosed with stage I lung cancer.
 - Implementation of lung cancer screening will lead to a shift in treatment options for lung cancer in advanced stage to treatment options in early staged cancers.
 - Current guidelines recommend lobectomy as a first choice for operable patients with early stage lung cancers.
 - Sublobar resection refers to wedge resection or segmentectomy. Since local recurrence rate is higher in patients undergoing wedge resection, segmentectomy is recommended as an alternative for lobectomy in selected patients
- unable to undergo lobectomy, for instance elderly patients with peripheral stage I adenocarcinoma presenting as a ground-glass-opacity-dominant nodule ≤ 2 cm in size.
 - VATS sublobar resection is preferred for subcentimeter nodules.
 - For medically inoperable patients with stage I NSCLC, stereotactic body radiation therapy is the recommended first choice treatment.
 - Randomized controlled trials comparing stereotactic body radiation therapy and lobectomy for operable patients have been closed early due to poor accrual. Results of a pooled analysis suggested that SBRT could be a reasonable therapeutic option for operable stage I lung cancer with better overall survival. However, more evidence from randomized controlled is necessitated.
 - Currently, there is only limited evidence for the value of radiofrequency ablation, microwave ablation, cryoablation, and photodynamic therapy in curative treatment of early stage NSCLC. Therefore, these therapies should only be used in expert centers for selected patients within clinical studies.

Funding

This article was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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