Review Article

Slow-growing lung cancer: an emerging entity

From screening to clinical management

Maurizio Infante, MD [1], Thierry Berghmans, MD, PhD [2], Marjolein A. Heuvelmans, MD [3], Gunnar Hillerdal, MD [4], Matthijs Oudkerk, MD, PhD [3]

1. Department of Thoracic Surgery, IRCCS Istituto Clinico Humanitas, Milan, Italy
2. Oncology Thoracic Unit and Department of Intensive Care Institut Jules Bordet, Brussels Belgium
3. Center for Medical Imaging - North East Netherlands, Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
4. Department of Lung Medicine and Allergy, Karolinska Hospital, Stockholm, Sweden

Corresponding Author:
Maurizio Infante, MD
Department of Thoracic Surgery, IRCCS Istituto Clinico Humanitas
Via Manzoni 56, 20089 Rozzano Milan, Italy
Phone + 39 0282244668, Fax +39 0282244694
email: maurizio.infante@cancercenter.humanitas.it

Running title: Slow-growing lung cancer

Abstract

The current paradigm is that untreated lung cancer is invariably and rapidly fatal, therefore the medical community normally dismisses the idea that a patient could live with such a disease for years without any therapy.

Yet, evidence from lung cancer screening research and from recent clinical series suggests that, although rarely recognized in routine practice, slow-growing lung cancers do exist and are more common than previously thought.

Current evidence is reviewed and clinical cases are illustrated to show that slow-growing lung cancer is a real clinical entity, and the reasons why management protocols developed in the screening setting may also be useful in clinical practice are discussed. Features suggesting that a lung cancer may be slow-growing are described and appraised, areas of uncertainty are examined, modern management options for early-stage disease are appraised, and the influence that all this knowledge might have on our clinical decision-making is weighed. Further research directed at developing appropriate guidelines for these peculiar but increasingly common patients is warranted.

INTRODUCTION

The prognosis for patients with untreated lung cancer has always been grim, with a median survival time of only 10-14 months even for early-stage disease [1-3], and all of them are considered at immediate risk of their lives unless effective treatment is instituted without delay.

Yet in 1984, a longitudinal study on 20000 atomic bomb survivors who received biannual screening chest radiographs over 20 years' time already suggested that some patients could harbour slow-growing pulmonary tumours [4].

Later on, indirect evidence derived from early randomized controlled trials of lung cancer screening with chest X-rays also hinted that slow lung cancers, so slow that they would not cause harm or symptoms within the patient's lifetime even if left untreated (thereby termed indolent) might indeed exist, and even be fairly common. In these studies, significantly more lung cancers were actually detected with screening and treated at an early stage, but with a similar number of lung cancer deaths compared with the non-screened group, which suggested overdiagnosis of indolent disease [5-7].

According to the exponential cancer growth model [8], a 1-cm tumour with a volume doubling time of 36 days would require only 180 days (i.e. 5 doublings) to reach the size of 3 cm, and only 360 days (10 doublings) to become a 10-cm mass, at which time considerable symptoms and death are expected to occur. With a VDT of 365 days, the theoretical survival time from detection of a 1-cm tumour to death would be 3650 days - 10 years - even without therapy.

However, these are most often regarded as mere theoretical assumptions. In fact, the medical community normally dismisses the idea that some patients with lung cancer might live with their disease for years without treatment. But does slow-growing lung cancer really exist? And if so, how frequent is it?

Evidence supporting the existence of slow-growing lung cancer

In several early detection studies and in recent clinical series, patients with undetermined lung nodules that were eventually diagnosed as lung cancers have been intentionally followed for a number of reasons, and growing nodules have been retrospectively identified in prior scans, thus allowing calculation of their volume doubling times. These studies have been summarized in Table 1.

Table 1 – Tumour volume doubling times in lung cancer series

Author	Hayabuchi	Yankelevitz	Hasegawa	Jennings	Lindell	Honda	Mikita	Sone	Henschke	Wilson	Veronesi
[Reference]	[4]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]
Year	1984	2003	2000	2006	2007	2009	2011	2012	2012	2012	2012
Origin of patients	Screening	Screening[1]	Screening	Mixed[1]	Screening	Clinical	Clinical[2]	Mixed	Screening	Screening	Screening
Imaging Test	CXR	CXR	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT
Mean Age (range)	65	n.r.	65 (33-89)	72 [43-87] [a]	65 (53-79)	66 (39-83)	67 (46-86)	(33-80)	n.r.	n.r.	58 ± 5.6
N° cancers	107	114	82	393	68	51	34	87	111[#]	148	175
VDT Measured (%)	37 (35)	87 (76)	61 (74)	149 (38)	48 (71)	51 (100)	34 (100)	45 (52)	111[#] (100)	63 (43)	120[#] (69)
Mean VDT (days)	-	-	452 ± 381	-	518 ± 1094	-	324	-	136	-	
Median [range]	-	144-101	-	207 [26-∞]	-	258 [69-∞] [b] 121 [39-221] [c]	-	-	-	357 [n.r.-4263]	240 [18-2555]
Cut-off (Days)	>150	>400	>342†	>207§	>400	-	>700	-	>400	>365	>400
Slow-Growing (% measured)	29 (78)	4 (5)	31 (51)	74 (50)	13 (27)	-	8 (23)	-	3 (3)	30 (48)	31 (26)
(% Overall)	(27)	(3)	(38)	(19)	(19)	-	(23)		(3)	(20)	(18)
VDT> 400 days	11	4	14‡	21‡	13	16	13	39	3	-	31
(% Overall)	(10)	(3)	(17)	(5)	(19)	(31)	(38)	(45)	(3)	-	(18)

Legends
CXR=Chest X-rays, LDCT= Low-dose Computerized Tomography, Mixed: Including screening and clinically detected patients, n.r.: not reported,
[1] Stage I only, [2] Small solid nodules only, [a] Median [range], [b] Adenocarcinoma only, [c] Squamous carcinoma only,
Non-prevalent cases only, † Geometric Mean of VDTs, § Median VDT
∞ VDTs of regressing tumors would have negative value, but they are herewith expressed as an infinite value for clarity,
‡ Only tumours showing no growth included in computation

Lung cancers detected by standard chest radiographs had short VDTs (i.e. shorter than the chosen cut-off) in over 90% of the cases, but CT-detected small lung cancers had long VDTs in 23-51% of assessed cases, with the exception of the I-ELCAP series, where such figure was 3% only [16].

The cut-off for slow-growing lung cancer varied, but most Authors utilized the 400-days limit proposed by Yankelewitz and coll. [9]. Therefore, we eventually estimated the percentage of cases in each study that had a VDT of at least 400 days or longer by taking into account the number of lung cancer cases with such a long VDT in each study. When a different cut-off was utilized, the data was extrapolated if possible. If not, the number of patients whose cancer did not grow at all was conservatively utilized for two studies [10, 11], or omitted. We then divided that number by the overall number of patients included in each study, assuming that all cases that did not have a VDT assessment would be fast-growing.

The lowest percentages were reported by Yankelewitz et al. for the Mayo Lung Project and Memorial Sloan Kettering populations [9], and by Henschke et al. for the I-ELCAP patients [16]. Some Japanese clinical studies reported instead very high rates of slow-growing lung cancer [13-15].

The results of these studies should be interpreted with caution, as the percentage of cancers that did not have a VDT assessment in these patient populations is often not reported in retrospective studies, and varies widely even in prospective trials. For example VDT data is not reported for 405

baseline cancers in the I-ELCAP study [19]. Taking these into account, only 111 of 516 cases (22%) had a VDT assessment in that population. It is therefore difficult to estimate the real magnitude of this phenomenon.

Nevertheless, it is apparent that although still rarely recognized in clinical practice, slow-growing lung cancer is a real clinical entity and more common than previously thought.

Therefore, in theory our management strategies for lung cancer patients in the current era might be modulated to some extent according to such new evidence.

As usual, the first steps should be to ascertain whether the true nature of the nodule or lesion we are dealing with is benign or cancerous, and if cancer is confirmed, to assess the patient's underlying condition thoroughly.

Ideally we might also try to estimate whether it is more likely a fast, aggressive lung cancer or a slow-growing tumour; and eventually discuss the risks and benefits of all possible management strategies in the light of all the above elements.

1. Differentiating small lung cancers from benign lesions

In some screening programs, the prevalence of subjects with undetermined nodules may exceed 50%, and the formidable number of undetermined nodules detected by CT, only few of which are true early tumours, represents a major challenge.

Specific protocols had to be devised in order to avoid unnecessary patient anxiety, costs and morbidity related to the assessment of so many potentially dangerous but ultimately harmless nodules detected by CT, while preserving a high sensitivity for early lung cancer.

The probability of malignancy in an undetermined pulmonary nodule depends on its size, on its CT-features and on individual risk factors [20]; it is lowest for subcentimeter solid nodules (<1 to 7%) and highest for focal ground-glass lesions (59-73%) [21, 22] .

Though often suggestive, morphology alone is frequently misleading while both size and nodule growth rate are strong predictors for malignancy [12, 23-25]; therefore modern diagnostic work-up protocols for screening-detected pulmonary lesions are mainly based on size at detection and on follow-up CT scans at set intervals, with bi-dimensional (2D) or three-dimensional (3D) growth assessments.

The NELSON group was the first and only one that consistently used 3D assessments and VDT measurements alone for solid nodule evaluation (figure 1) in their early detection study [26].

Nodules with a volume less than 50 mm3 (5 mm in diameter) were ignored. Non-calcified nodules with a volume>500mm3 (>9.8 mm) were considered positive and those in between (50-500 mm3) tested indeterminate. Participants with an indeterminate nodule had follow-up low-dose CT 6 weeks to 4 months later and at that time the VDT was calculated. Pre-existing nodules

with a VDT<400 days tested positive, and nodules with a VDT of 400-600 days were indeterminate and were re-scheduled for a follow-up CT one year later (figure 1). Sensitivity of the test after the first round was 94.6%, and the negative predictive value was 99.9%, while 2.6% screened patients underwent higher-level investigation in the baseline round and 1.8% in the second round. At the second round, the positive predictive value for malignancy in solid nodules with a volume of 50-500 mm3 and VDT<400 days was 63% [27, 28]. Since even benign lesions may demonstrate growth [18], several workup protocols also include PET-scan and CT-guided percutaneous core biopsy as downstream tests to increase specificity [29-33].

The utility of PET-scan in the differential diagnosis between benign and malignant lung nodules has been repeatedly confirmed and recently endorsed by the American College of Chest Physicians [21, 22, 34]. Despite some variability related to the chosen cut-off for the Standardized Uptake Value (SUV) and to technical details, the reported sensitivity of PET imaging for lung cancer presenting as a solitary pulmonary nodule (SPN) is consistently high (80 to 100%), while specificity is more variable (40 to 100%). In a prospective study of 532 participants with newly detected SPNs a sensitivity and specificity of 0.92 and 0.82 were reported for PET-scan versus 0.96 and 0.41 for CT, and the Areas Under the Curve (AUC) were 0.93 for PET-scan and 0.82 for CT (p < 0.0001). The negative predictive value of PET-scan for lung cancer was 0.89, while the positive predictive value was 0.86 [35].

Because the limit of detection with old-generation PET scanners is approximately 10 mm (5-7 mm with newer PET-CT equipment), sensitivity is low for small tumours, which may especially be missed when located in lower lung portions, where respiratory movements could prevent an adequate image acquisition [36, 37]. In addition, neuroendocrine tumours and those with predominant lepidic growth pattern on pathological examination, formerly known as bronchioloalveolar carcinomas [38] have low FDG uptake, possibly due the reduced number of cellular receptors involved in FDG internalisation, making PET-scan inadequate for carcinoid tumour and ground glass lesions, unless the lesion has a sizable solid component [39-43].

Rather than in the early detection of lung cancer, the added value of PET-scan is thus mainly in reducing the rate of unnecessary invasive intervention for suspicious lesions after an adequate radiological work-up [44].

It should also be remembered that some infectious or inflammatory lesions may show a significant FDG uptake, in the range of that observed in malignancy [45], and that in some cases an antibiotic trial may be worthwhile prior to proceeding to percutaneous or surgical biopsy (figure 2).

Transbronchial or CT-guided percutaneous lung biopsy, VATS or thoracotomy with nodule removal and frozen sections are eventually considered if the lesion is still deemed suspicious based on all previous testing.

In most CT-screening programs, surgical biopsies carried out to confirm malignancy result in a benign nodule diagnosis in 15-25% of the cases, but the

benign rate can be even higher [28, 30-33, 46, 47].

Not surprisingly, this same occurrence is relatively frequent also in routine clinical practice due to the frequent discovery of incidental nodules in the CT era. For example, in a recent report 15% of lung resections in an academic hospital were carried out for clinically detected, harmless lesions [48]; a low threshold for lung biopsy in fact leads to high rates of "futile" invasive procedures in any setting.

Surgical biopsy in doubtful cases is prompted by fear that unrecognized lung cancer may progress beyond curability while being followed; however, the risk is low if the tumour characteristics favour slow growth, and the time frame for a thorough evaluation is reasonable. Only 6% of CT-detected lung cancers would progress beyond stage I within one year according to recent reports [32, 49]; in addition, delaying treatment for up to 90 days does not seem to reduce survival chances in stage I-II lung cancer patients [50].

Multistep nodule management protocols developed in the screening setting have been successful in reducing unnecessary invasive procedures while retaining a high sensitivity for early lung cancer, and may be useful in the clinical setting as well.

Ideally, the diagnostic work-up of incidental and screening-detected undetermined pulmonary nodules might be the same.

2- Discriminating between slow-growing and aggressive lung cancer

There are no validated biological indicators yet that could allow us to predict the clinical course of an individual lung cancer patient without therapy, unless the latter is intentionally left untreated for a sufficiently long period of time. Nonetheless, a number of features suggest that we could be dealing with a slow-growing tumour.

Growth rate

Tumour growth rate is intuitively the most important factor, but reproducibility of nodule volume measurements is of critical importance especially with small nodules.

Actually, 3D volume measurements are superior to 2D diameter measurements in terms of accuracy and reproducibility, because the whole nodule is analysed and not just its maximum diameter in an axial plane and because growth can be more easily assessed even if the nodule is non-spherical or if it grows asymmetrically [51-53]. Semi-automated or fully automated 3D volume evaluation is applicable with solid lesions [54] with a margin of error of 25-30% for repeat same–nodule assessments, which decreases with increasing nodule size. Although not negligible, this error margin is less than with 2D assessments.

For focal ground-glass lesions however, growth estimates are still largely based on 2D assessments because volume measurement variability with volumetric software is too high. Alternative methods based on changes in mass measurement (nodule volume x density) or CT attenuation values have been

proposed [55-57].

Morphological features

CT-detected pulmonary nodules are nowadays classified as solid and sub-solid, the latter also commonly termed ground-glass lesions or opacities (GGOs) [58].

The definition is based on whether the lesion completely obscures the underlying lung parenchyma (solid nodule), or instead normal parenchymal structures can still be seen through a hazy area of increased lung attenuation (sub-solid nodule). This area may be inhomogeneous, i.e. present an inner solid component and a hazy ground-glass area around it, in which case it would also be called a part-solid nodule or mixed GGO; or it may be completely hazy, in which case the lesion would also be called non-solid, or a pure GGO (figure 3).

Solid lesions tend to progress faster than part-solid lesions, and part-solid lesions tend to grow faster than non-solid ones [10, 55], so actually slow-growing lung cancers more commonly appear as focal ground-glass lesions in CT-scans.

Histologically, ground-glass lesions correspond to the spectrum of tumours with lepidic predominant growth which includes their putative precursor atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant, invasive adenocarcinoma (LPA) [38].

Current evidence suggests that the presence and size of any solid component in a ground-glass lesion are prognostically more relevant than whole tumour area, because they correlate better with local invasion at pathological examination, nodal metastasis, progression, and post-resection survival [15, 43, 59-61]. Progression of ground-glass lesions may become manifest as an increase in size or density of the whole tumour area, of its solid component, or as a combination of these.

In fact, the likelihood of local progression is low over several years' time, especially with pure ground-glass lesions. In three recent reports, progression of pure GGOs occurred in only 12-24% of the patients after 40-59 months, while 46-55% of mixed GGOs progressed over the same period [62-64].

In one such series [64] progression of pure GGOs was noted in 12 of 89 patients over a median follow-up period of 59 months (range 25–140). Eight of eleven lesions that were eventually resected in these twelve patients were either AIS (2) or MIA (6). Stage IA invasive adenocarcinoma was found in two patients; only one had progressed beyond stage I.

Thus, follow-up CT examinations at 6-month intervals are reasonably safe for GGOs, especially if the solid component is absent or minimal and the diameter is less than 30 mm [65], but since progression may become evident after years (figure 4), no time limit can be recommended for discontinuing surveillance [66].

Variability is under any circumstances high, and solid nodules too may grow

very slowly (figure 4), but more careful monitoring is warranted in such cases. If follow-up is chosen, a 3-month interval before the first follow-up CT is reasonable [28], and subsequent management should be based on serial VDT determinations.

FDG-uptake

The prognostic role of PET-scan in non-small cell lung cancer (NSCLC) has been assessed in a recent meta-analysis [67], which showed that the SUV of the primary tumour correlates with prognosis. Although these findings need further confirmation, they suggest that PET may be more useful than conventional imaging for prognostic purposes in locally advanced disease.

A correlation between preoperative FDG uptake, pathological stage, probability of nodal metastasis and outcomes has also been reported for the spectrum of adenocarcinoma associated with focal GGOs and for stage I NSCLC in general [43, 61, 68-71].

Tann et al. reported on a significant relationship between tumour growth rate as measured by serial CT scans and tumour metabolic activity as measured by FDG-uptake for stage I lung cancer [72]. In this series, only 3 of 51 cancers (6%) were classified as broncho-alveolar carcinoma.

Veronesi et al. [18] also recently reported that 44 % of PET-negative tumours had a VDT> 400 days in their series, and a very favourable outcome was observed for tumours with a VDT > 200 days and a negative PET-scan. The proportion of predominant lepidic tumours was not reported in this study.

Since carcinoid tumours and ground-glass lesions often do not uptake FDG significantly and both exhibit a particularly favourable clinical course, it is tempting to infer that FDG-PET may be used as an additional tool to decide on the aggressiveness of management, at least for early-stage disease.

Histology

Several Authors have reported on a significant correlation between histological type and tumour growth rate. For example, squamous cancer is generally faster than adenocarcinoma, but there is a significant overlap across all tumour types [4, 10, 11, 13, 14, 16, 17, 49, 73, 74]. In consequence, prediction of tumour behaviour cannot be reliably based on histological differentiation.

The only exception may be with tumours showing lepidic growth, but even in such cases stromal invasion may be impossible to estimate accurately on a small biopsy or on frozen sections [38]; thus, a sensible management plan should be devised on clinical grounds and based on typical imaging results.

The clinical context

Tumours that are detected due to symptoms or by a chest radiograph tend to be solid, greater that 1 cm or 500 mm3, and to have short VDTs [4, 9, 75].

A significant proportion of CT-screening detected tumours, prevalent cancers especially, have instead long VDTs. In the Pittsburgh study [17], 28 of 42 (67%) baseline-screen cancers had VDTs>365 days. Non-prevalent cases, i.e. those detected after a negative baseline screen tend to be faster (table 1).

Little is known to date about the growth rates of small lung cancers incidentally

detected by a CT-scan obtained for unrelated reasons, but since small, slow-growing tumours are more likely to be incidentally detected by CT, intuitively they might be assimilated to screening-detected prevalent cancers. Ground-glass lesions and small, slow-growing nodules that are often missed by chest X-ray examination are instead more easily detected by CT because of a longer "window of detection" - the time interval from when they become potentially detectable by the screening test to when symptoms appear, i.e. due to length-time bias [76]. The associations between detection by CT-scan, long VDTs and better outcomes are therefore due to selection.

Areas of uncertainty

The exponential model of tumour growth, which implies a constant cell replication rate throughout the life of the tumour, does not fully explain our clinical observations, and tumour growth rate, although important, may not be all we need to know.

A primary tumour with a long VDT should remain surgically curable for a longer period of time, provided that growth is constant, and that nodal spread or distant metastasis does not occur in the mean time.

Lung cancer growth may in fact be non-linear in some cases; and some tumours may actually show an accelerated growth phase after a period of constant slow increase in size, as demonstrated by Lindell and coll. [12]. Such phenomena have also been occasionally observed in the DANTE and in the NELSON trial.

It may be speculated that a slow growth rate is also associated with a lower rate of dissemination because the frequency of nodal metastasis is directly related to the size of the primary tumour, and current evidence suggests this is true for the spectrum of lepidic tumours; however, such relationship has not been investigated in depth for other histotypes.

Tumours with shorter VDTs have indeed higher 5-year recurrence rates after resection [11, 14, 73], but slow-growing lung cancers may merely recur later than fast-growing ones.

The information provided by PET in assessing tumour biology and aggressiveness, although promising, is to date still limited. Tumour growth rates have been correlated with FDG uptake in two studies only [18, 72] and correlations between FDG uptake and outcomes have only been explored after treatment. To our knowledge, no published study exists correlating FDG uptake with the natural history of untreated lung cancer.

3- Estimating risks and benefits

It is likely that we will end up treating most patients harbouring a (putative) slow-growing lung cancer, but because age and co-morbidities may outweigh cancer progression in such patients [77-79], individual risk factors, estimated treatment-related morbidity and mortality and expected long-term outcomes for each available therapeutic option should be even more carefully considered than usual (figures 3-5).

A thorough evaluation of the patient's underlying condition should be followed by pulmonary and cardiac function testing according to the guidelines published by the major international thoracic societies [80-82].

In general terms, five-year local recurrence rate is 13-30% and overall 5-year survival is roughly 50-70% after lobectomy for early-stage lung cancer [83-85]. Postoperative complications occur after lobectomy in 40-55% of the cases; the reported 30-day mortality is 1.3-4.2% and rises up to 5.4-7.8% after pneumonectomy [86-90]. Ninety-day mortality adds another 2-3% to the toll, mainly due to cardiovascular events occurring after discharge, but this data is seldom reported [89, 91]. Several risk models have been developed to stratify patients based on their surgical risk, however their performance is less than ideal [92-94].

Moreover, quality of life and functional well-being indicators may still show a detrimental impact of major lung resection up to 2 years postoperatively in a significant proportion of patients [95-99]. In one study, 24% of long-term cancer survivors still experienced a moderate, and 11% a severe limitation in their daily activities due to residual dyspnoea [100].

Both the risks of perioperative complications and of long-term disability increase several-fold in patients with advanced age, active smoking, poor lung function, prior myocardial infarction, extensive resection volume, previous lung resection and a high co-morbidity burden.

Co-morbidity is also an independent predictor of stage-specific lung cancer

survival. In a Danish cohort of 3152 patients [101], 5-year survival for pT1 disease was 69% if the Charlson Comorbidity Score (CCS) was 0, it was 54% if the CCS it was 1-2, and 38% if it was 3 or more. Similar figures were reported for N0, N1 and N2 disease. The Charlson score can be calculated manually or through a free on-line application [102].

4 - Tailored therapeutic approaches

Surgical options

Lobectomy is currently the standard of care because sublobar resections (wedge resection and segmentectomy) resulted in a significantly higher local recurrence rate compared with lobectomy in the only randomized trial conducted so far, in 1995 [103].

Easier patient acceptance of minimally invasive approaches led to the extension of the indications of VATS surgery to early-stage lung cancer resection with curative intent [104, 105].

Technically, VATS lobectomy is not a compromise procedure as the resection volume is no less than with open lobectomy, and lymphadenectomy should ideally be the same, but surgical trauma and postoperative pain are definitely reduced, and complication rates indeed lower in most recent reports that compare the two techniques. Mortality rates around 1% are regularly reported, with few exceptions. The benefits of VATS are more evident in patients with advanced age, poor lung function and higher co-morbidity burden [105-112].

In addition, lung cancer recurrence rates with VATS do not seem to be increased, and may even be decreased compared with lobectomy via the standard thoracotomy approach [112-114].

Recent reports suggest that local control and 5-year survival with sublobar resections, that limit the loss of functional lung tissue, may be equivalent to those obtained with lobectomy in selected cases, especially in elderly patients or in those with a compromised respiratory function [115-119].

Wedge resection is a simple procedure in which a portion of lung parenchyma encompassing the nodule is excised, normally with the aid of surgical staplers. For pure GGOs, 100% 5-year recurrence free survival has been reported [120, 121], although late recurrences may be observed [122]. Wedge resection may also be equivalent to lobectomy for patients with subcentimeter solid nodules [123, 124].

Segmentectomy is the removal of a complete pulmonary segment and requires individual division of segmental vessels and bronchi at their origin. It allows resection of more centrally located nodules with wider safety margins and the dissection of hilar lymphatics.

Advanced age, a nodule measuring less than 2 cm, a mixed ground-glass lesion with less than 75% solid component and a tumour-free margin of at least 2 cm are favourable indications for segmentectomy. Postoperative mortality for segmentectomy is 0-1%, with few exceptions [118, 125-129].

Limited resections have recently been endorsed for tumours with lepidic

growth, based on the new IASLC/ATS/ERS classification of adenocarcinoma [130]. Either alone or in combination with lobectomy, they may also be appropriate for patients with multifocal slow-growing tumours, based on the assumption that they represent independent foci of lung cancer rather than metastasis [131].

However, evidence in favour of limited resections is still inconclusive. Two large multi-institutional randomized trials are currently comparing limited resections versus lobectomy for early-stage lung cancer in the USA and in Japan [132, 133].

Non-surgical options

Conventional radiotherapy had limited efficacy on local control and survival of lung cancer patients and was traditionally reserved for medically inoperable patients.

However, modern stereotactic radiotherapy techniques allow for a much more precise administration of high radiation doses to the tumour, while substantially limiting exposure of adjacent tissues. Reported 3-year local control rates for small peripheral lesions are in the range of 80-90% [134, 135].

Advantages of stereotactic radiotherapy include short duration of treatment, minimal patient discomfort, limited pulmonary toxicity, low morbidity in the short term, and low impact on quality of life.

Potential disadvantages are the limited availability of long-term follow-up data

[136], lack of information about micrometastatic disease in lymphatics, and an increased risk (approximately 10%) of severe and fatal adverse events when centrally located lesions are treated [137, 138]. Local control and complication rates are dose-dependent.

Two randomized trials are currently exploring whether stereotactic radiotherapy may be equivalent to sublobar resection [139] or lobectomy [140] in patients who can tolerate surgery.

Radiofrequency ablation (RFA), microwave ablation and cryotherapy are means of thermal tissue destruction. RFA has been employed for over 10 years [141] and is the best studied of all such treatments. High intralesional temperatures (90° Celsius for 16-27 min) are obtained by means of a needle electrode implanted percutaneously into the tumour under CT guidance, under general anaesthesia or conscious sedation.

Advantages of RFA include limited trauma, no radiation exposure, the possibility of re-treating recurrences and minimal impact on respiratory function, although reports are sometimes contradictory in this respect [142-144]. Complications such as pneumothorax and pleural effusion are frequent (around 30%), but mostly mild. However, severe complications may occur in 5-9% of the patients. Mortality after RFA is 0.5-2.6%, mainly due to acute respiratory failure or massive haemorrhage [144-146].

Local recurrences occur within three years in 30-50% of the cases, but results are better with nodules measuring less than 3 cm [144]. Local control rates

with RFA seem to be lower than with stereotactic radiotherapy [147].

Psychological profiles

Age, personality traits, social well-being, parenthood and risk perception have been linked to the acceptance of treatment by patients [148, 149]. Some patients with slow-growing lung cancer will accept or even solicit an aggressive approach, while others will be comfortable with being followed until the situation evolves.

As always, patients should be encouraged to express their expectations and fears and be educated regarding their condition in order to share the decision. However, patient preferences for exhaustive information and for an active role in the decision-making process vary widely, and many patients in fact prefer delegating the responsibility for the final decision [150].

With all the necessary clinical experience at hand, and even when mathematical models are used to help estimating the risk-benefit ratios of available options [20], the cut-off value will vary according to personal beliefs and inclinations of patients and doctors (figure 5).

Conclusions

With all patients, the foundation of clinical decision-making rests on a careful balance of competitive risks related to the natural course of the disease, life expectancy, and impact of treatment.

The management of lung cancer patients has been traditionally modelled by the tenet that their condition is almost always rapidly lethal. Once the diagnosis is established (and occasionally, even before that) immediate action is needed, and treatment-related risks may be acceptable, even if high, in the face of almost certain death in the short term.

Until recently, slow-growing lung cancer has been rarely recognized in routine clinical practice for several possible reasons: a lesion that does not grow visibly for at least two years would likely be interpreted as non-malignant [22]; patients in a poor underlying condition may be left with an undiagnosed slow-growing cancer; thirdly, as soon as a biopsy shows malignant cells, all patients in a reasonable underlying condition will be referred for definitive treatment, and no conclusion can be reached about their natural course in the absence of therapy. Evidence on the natural history of untreated lung cancer may thus be biased by involuntary case selection [151].

It nowadays appears that the biological behaviour of lung cancer instead spans across a whole spectrum, from fast and highly lethal to slow-growing and indolent, and that the mode of detection determines which one we are more likely to be dealing with [75].

Current trends in health care suggest that patients possibly harbouring the latter will be more and more frequently encountered [152, 153].

Ideally, our approach should thus be adjusted according to a new estimate of the probability that the cancer under consideration will cause harm *within a*

given time frame (normally, within the patient's expected life span), together with an estimate of the projected results of each strategy and of its potential impact on the patient's life expectancy and well being (table 2).

Table 2 —
Element that favour observation, tailored options, or standard management for patients with putative slow-growing lung cancer

Observation	Tailored options	Standard management
Relatively old age*	Relatively old age*	Relatively young age*
High co-morbidity burden	High co-morbidity burden	Low co-morbidity burden
Screening or incidental CT finding	Screening or incidental CT finding	Clinically detected
Relatively small size	Relatively small size	Relatively large size
Non-solid lesion	Part-solid lesion	Solid lesion
No progression or long VDT*	No progression or long VDT*	Relatively short VDT*
PET–negative or low SUV*	PET–negative or low SUV*	PET-positive, high SUV*
Unsuitable for sublobar resection	Suitable for sublobar resection SBRT or RFA available	Suitable for VATS lobectomy
Comfortable with being followed	Anxious, prefers certainty	Anxious, prefers certainty

Legend
* no conventional limit, SBRT= stereotactic body radiation therapy, RFA= radiofrequency ablation

Because lung cancer can actually be rapidly fatal and because individual predictors of tumour progression are not yet available, most patients will still be treated according to standard guidelines. Further research and specific prospective studies are needed on the value of volume-based tumour growth assessment by CT and of PET-scan for the identification of patients with relatively unaggressive lung cancer, and tailored management strategies

(standard treatment, limited resection, conservative options, or observation) based on VDT and FDG uptake still have to be validated.

Yet, the elements discussed above may be taken into account to devise a personalized, reasonable management approach and the timing of intervention, if any, for these peculiar cases. Clinical experience, intuition and empathy, though immeasurable, will be always needed in order to make the best possible choice for the patient before us.

References

1. McGarry RC, Song G, des Rosiers P, Timmerman R. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. *Chest* 2002: 121(4): 1155-1158.

2. Motohiro A, Ueda H, Komatsu H, Yanai N, Mori T. Prognosis of non-surgically treated, clinical stage I lung cancer patients in Japan. *Lung cancer (Amsterdam, Netherlands)* 2002: 36(1): 65-69.

3. Raz DJ, Zell JA, Ou SH, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest* 2007: 132(1): 193-199.

4. Hayabuchi N, Russell WJ, Murakami J. Slow-growing lung cancer in a fixed population sample. Radiologic assessments. *Cancer* 1983: 52(6): 1098-1104.

5. Kubik AK, Parkin DM, Zatloukal P. Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. *Cancer* 2000: 89(11 Suppl): 2363-2368.

6. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR, Bernatz PE, Payne WS, Pairolero PC, Bergstralh EJ. Screening for lung cancer. A critique of the Mayo Lung Project. *Cancer* 1991: 67(4 Suppl): 1155-1164.

7. Welch HG, Black WC. Overdiagnosis in cancer. *Journal of the National Cancer Institute* 2010: 102(9): 605-613.

8. Geddes DM. The natural history of lung cancer: a review based on rates of tumour growth. *British journal of diseases of the chest* 1979: 73(1): 1-17.

9. Yankelevitz DF, Kostis WJ, Henschke CI, Heelan RT, Libby DM, Pasmantier MW, Smith JP. Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. *Cancer* 2003: 97(5): 1271-1275.

10. Hasegawa M, Sone S, Takashima S, Li F, Yang ZG, Maruyama Y, Watanabe T. Growth rate of small lung cancers detected on mass CT screening. *The British journal of radiology* 2000: 73(876): 1252-1259.

11. Jennings SG, Winer-Muram HT, Tann M, Ying J, Dowdeswell I. Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. *Radiology* 2006: 241(2): 554-563.

12. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, Mandrekar JN. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology* 2007: 242(2): 555-562.

13.   Honda O, Johkoh T, Sekiguchi J, Tomiyama N, Mihara N, Sumikawa H, Inoue A, Yanagawa M, Daimon T, Okumura M, Nakamura H. Doubling time of lung cancer determined using three-dimensional volumetric software: comparison of squamous cell carcinoma and adenocarcinoma. *Lung cancer (Amsterdam, Netherlands)* 2009: 66(2): 211-217.

14.   Mikita K, Saito H, Sakuma Y, Kondo T, Honda T, Murakami S, Oshita F, Ito H, Tsuboi M, Nakayama H, Yokose T, Kameda Y, Noda K, Yamada K. Growth rate of lung cancer recognized as small solid nodule on initial CT findings. *European Journal of Radiology* 2012: 81(4): e548-553.

15.   Sone S, Hanaoka T, Ogata H, Takayama F, Watanabe T, Haniuda M, Kaneko K, Kondo R, Yoshida K, Honda T. Small peripheral lung carcinomas with five-year post-surgical follow-up: assessment by semi-automated volumetric measurement of tumour size, CT value and growth rate on TSCT. *European radiology* 2012: 22(1): 104-119.

16.   Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, Smith JP, Libby DM, Pasmantier MW, Miettinen OS, Writing Committee for the IEI. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology* 2012: 263(2): 578-583.

17.   Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, Weissfeld J. Doubling times and CT screen-detected lung cancers in the Pittsburgh Lung Screening Study. *American journal of respiratory and critical care medicine* 2012: 185(1): 85-89.

18.   Veronesi G, Maisonneuve P, Bellomi M, Rampinelli C, Durli I, Bertolotti R, Spaggiari L. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Annals of internal medicine* 2012: 157(11): 776-784.

19.   Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006: 355(17): 1763-1771.

20.   Ost DE, Gould MK. Decision making in patients with pulmonary nodules. *American journal of respiratory and critical care medicine* 2012: 185(4): 363-372.

21.   Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC, American College of Chest P. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007: 132(3 Suppl): 94S-107S.

22.   Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, Ost DE, American College of Chest P. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007: 132(3 Suppl): 108S-130S.

23.   Wisnivesky JP, Yankelevitz D, Henschke CI. Stage of lung cancer in relation to its size: part 2. Evidence. *Chest* 2005: 127(4): 1136-1139.

24.   Yankelevitz DF, Reeves AP, Kostis WJ, Zhao B, Henschke CI. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology* 2000: 217(1): 251-256.

25.   Revel MP, Merlin A, Peyrard S, Triki R, Couchon S, Chatellier G, Frija G. Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. *AJRAmerican journal of roentgenology* 2006: 187(1): 135-142.

26.   Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, Weenink C, Lammers JW, Groen H, Oudkerk M, van Klaveren R. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung cancer (Amsterdam, Netherlands)* 2006: 54(2): 177-184.

27.   Xu DM, van der Zaag-Loonen HJ, Oudkerk M, Wang Y, Vliegenthart R, Scholten ET, Verschakelen J, Prokop M, de Koning HJ, van Klaveren RJ. Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. *Radiology* 2009: 250(1): 264-272.

28.   van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KA, van 't Westeinde S, van der Aalst C, Thunnissen E, Xu DM, Wang Y, Zhao Y, Gietema HA, de Hoop BJ, Groen HJ, de Bock GH, van Ooijen P, Weenink C, Verschakelen J, Lammers JW, Timens W, Willebrand D, Vink A, Mali W, de Koning HJ. Management of lung nodules detected by volume CT scanning. *The New England journal of medicine* 2009: 361(23): 2221-2229.

29.   International Early Lung Cancer Action P. Protocol Documents.

30.   Ashraf H, Dirksen A, Loft A, Bertelsen AK, Bach KS, Hansen H, Pedersen JH, Mortensen J. Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT scanning. *Thorax* 2011: 66(4): 315-319.

31.   Infante M, Chiesa G, Solomon D, Morenghi E, Passera E, Lutman FR, Bottoni E, Cariboni U, Errico V, Voulaz E, Ferraroli G, Testori A, Inzirillo F, Chiarenza M, Roncalli M, Cavuto S, Chiti A, Alloisio M, Ravasi G, Group DS. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2011: 6(2): 327-335.

32.   Veronesi G, Bellomi M, Veronesi U, Paganelli G, Maisonneuve P, Scanagatta P, Leo F, Pelosi G, Travaini L, Rampinelli C, Trifiro G, Sonzogni A, Spaggiari L. Role of positron emission tomography scanning in the management of lung nodules detected at baseline computed tomography screening. *The Annals of Thoracic Surgery* 2007: 84(3): 959-965; discussion 965-956.

33.   Menezes RJ, Roberts HC, Paul NS, McGregor M, Chung TB, Patsios D, Weisbrod G, Herman S, Pereira A, McGregor A, Dong Z, Sitartchouk I, Boerner S, Tsao MS, Keshavjee S, Shepherd FA. Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience. *Lung cancer (Amsterdam, Netherlands)* 2010: 67(2): 177-183.

34.   Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA : the journal of the American Medical Association* 2001: 285(7): 914-924.

35.   Fletcher JW, Kymes SM, Gould M, Alazraki N, Coleman RE, Lowe VJ, Marn C, Segall G, Thet LA, Lee K, Group VSCS. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2008: 49(2): 179-185.

36.   Kim SC, Machac J, Krynyckyi BR, Knesaurek K, Krellenstein D, Schultz B, Gribetz A, DePalo L, Teirstein A, Kim CK. Fluoro-deoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: assigning a probability of malignancy may be preferable to binary readings. *Annals of Nuclear Medicine* 2008: 22(3): 165-170.

37.   Herder GJ, Golding RP, Hoekstra OS, Comans EF, Teule GJ, Postmus PE, Smit EF. The performance of(18)F-fluorodeoxyglucose positron emission tomography in small solitary pulmonary nodules. *European journal of nuclear medicine and molecular imaging* 2004: 31(9): 1231-1236.

38.   Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, Garg K, Austin JH, Asamura H, Rusch VW, Hirsch FR, Scagliotti G, Mitsudomi T, Huber RM, Ishikawa Y, Jett J, Sanchez-Cespedes M, Sculier JP, Takahashi T, Tsuboi M, Vansteenkiste J, Wistuba I, Yang PC, Aberle D, Brambilla C, Flieder D, Franklin W, Gazdar A, Gould M, Hasleton P, Henderson D, Johnson B, Johnson D, Kerr K, Kuriyama K, Lee JS, Miller VA, Petersen I, Roggli V, Rosell R, Saijo N, Thunnissen E, Tsao M, Yankelewitz D. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2011: 6(2): 244-285.

39.   Khandani AH, Whitney KD, Keller SM, Isasi CR, Donald Blaufox M. Sensitivity of FDG PET, GLUT1 expression and proliferative index in bronchioloalveolar lung cancer. *Nuclear medicine communications* 2007: 28(3): 173-177.

40.   Song YS, Lee WW, Chung JH, Park SY, Kim YK, Kim SE. Correlation between FDG uptake and glucose transporter type 1 expression in neuroendocrine tumors of the lung. *Lung cancer (Amsterdam, Netherlands)* 2008: 61(1): 54-60.

41.   Chun EJ, Lee HJ, Kang WJ, Kim KG, Goo JM, Park CM, Lee CH. Differentiation between malignancy and inflammation in pulmonary ground-glass nodules: The feasibility of integrated (18)F-FDG PET/CT. *Lung cancer (Amsterdam, Netherlands)* 2009: 65(2): 180-186.

42.   Kim TJ, Park CM, Goo JM, Lee KW. Is there a role for FDG PET in the management of lung cancer manifesting predominantly as ground-glass opacity? *AJRAmerican journal of roentgenology* 2012: 198(1): 83-88.

43.   Okada M, Nakayama H, Okumura S, Daisaki H, Adachi S, Yoshimura M, Miyata Y. Multicenter analysis of high-resolution computed tomography and positron emission tomography/computed tomography findings to choose therapeutic strategies for clinical stage

IA lung adenocarcinoma. *The Journal of thoracic and cardiovascular surgery* 2011: 141(6): 1384-1391.

44.   Van't Westeinde SC, de Koning HJ, Thunnissen FB, Oudkerk M, Groen HJ, Lammers JW, Weenink C, Vernhout R, Nackaerts K, Mali W, van Klaveren RJ. The Role of the (18)F-Fluorodeoxyglucose-Positron Emission Tomography Scan in the Nederlands Leuvens Longkanker Screenings Onderzoek Lung Cancer Screening Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2011: 6(10): 1704-1712.

45.   Bryant AS, Cerfolio RJ. The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules. *The Annals of Thoracic Surgery* 2006: 82(3): 1016-1020.

46.   National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *The New England journal of medicine* 2011: 365(5): 395-409.

47.   Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, Luketich JD, Siegfried JM. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. *Am J Respir Crit Care Med* 2008: 178(9): 956-961.

48.   Kuo E, Bharat A, Bontumasi N, Sanchez C, Zoole JB, Patterson GA, Meyers BF. Impact of video-assisted thoracoscopic surgery on benign resections for solitary pulmonary nodules. *The Annals of Thoracic Surgery* 2012: 93(1): 266-272; discussion 272-263.

49.   Winer-Muram HT, Jennings SG, Tarver RD, Aisen AM, Tann M, Conces DJ, Meyer CA. Volumetric growth rate of stage I lung cancer prior to treatment: serial CT scanning. *Radiology* 2002: 223(3): 798-805.

50.   Quarterman RL, McMillan A, Ratcliffe MB, Block MI. Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. *The Journal of thoracic and cardiovascular surgery* 2003: 125(1): 108-113; discussion 113-104.

51.   Marten K, Engelke C. Computer-aided detection and automated CT volumetry of pulmonary nodules. *European radiology* 2007: 17(4): 888-901.

52.   Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? *Radiology* 2004: 231(2): 453-458.

53.   Reeves AP, Biancardi AM, Apanasovich TV, Meyer CR, MacMahon H, van Beek EJ, Kazerooni EA, Yankelevitz D, McNitt-Gray MF, McLennan G, Armato SG, 3rd, Henschke CI, Aberle DR, Croft BY, Clarke LP. The Lung Image Database Consortium (LIDC): a comparison of different size metrics for pulmonary nodule measurements. *Academic Radiology* 2007: 14(12): 1475-1485.

54.   Marchiano A, Calabro E, Civelli E, Di Tolla G, Frigerio LF, Morosi C, Tafaro F, Ferri E, Sverzellati N, Camerini T, Mariani L, Lo Vullo S, Pastorino U. Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening. *Radiology* 2009: 251(3): 919-925.

55.   Oda S, Awai K, Murao K, Ozawa A, Yanaga Y, Kawanaka K, Yamashita Y. Computer-aided volumetry of pulmonary nodules exhibiting ground-glass opacity at MDCT. *AJR American journal of roentgenology* 2010: 194(2): 398-406.

56.   de Hoop B, Gietema H, van de Vorst S, Murphy K, van Klaveren RJ, Prokop M. Pulmonary ground-glass nodules: increase in mass as an early indicator of growth. *Radiology* 2010: 255(1): 199-206.

57.   Zhang L, Yankelevitz DF, Carter D, Henschke CI, Yip R, Reeves AP. Internal growth of nonsolid lung nodules: radiologic-pathologic correlation. *Radiology* 2012: 263(1): 279-286.

58.   Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, Macchiarini P, Crapo JD, Herold CJ, Austin JH, Travis WD. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology* 2013: 266(1): 304-317.

59.   Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. *The Annals of Thoracic Surgery* 2006: 81(2): 413-419.

60.   Matsuguma H, Yokoi K, Anraku M, Kondo T, Kamiyama Y, Mori K, Tominaga K, Tsuura Y, Honjo S. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. *The Journal of thoracic and cardiovascular surgery* 2002: 124(2): 278-284.

61.   Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, Okada M. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *The Journal of thoracic and cardiovascular surgery* 2012: 143(3): 607-612.

62.   Silva M, Sverzellati N, Manna C, Negrini G, Marchiano A, Zompatori M, Rossi C, Pastorino U. Long-term surveillance of ground-glass nodules: evidence from the MILD trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012: 7(10): 1541-1546.

63.   Matsuguma H, Mori K, Nakahara R, Suzuki H, Kasai H, Kamiyama Y, Igarashi S, Kodama T, Yokoi K. Characteristics of subsolid pulmonary nodules which show growth during follow-up with computed tomography. *Chest* 2012.

64.   Chang B, Hwang JH, Choi YH, Chung MP, Kim H, Kwon OJ, Lee HY, Lee KS, Shim YM, Han J, Um SW. Natural History of Pure Ground-Glass Opacity Lung Nodules Detected by Low-Dose Computed Tomography. *Chest* 2012.

65.   Sawada S, Komori E, Nogami N, Segawa Y, Shinkai T, Yamashita M. Evaluation of lesions corresponding to ground-glass opacities that were resected after computed tomography follow-up examination. *Lung cancer (Amsterdam, Netherlands)* 2009: 65(2): 176-179.

66.   Min JH, Lee HY, Lee KS, Han J, Park K, Ahn MJ, Lee SJ. Stepwise evolution from a focal pure pulmonary ground-glass opacity nodule into an invasive lung adenocarcinoma: an observation for more than 10 years. *Lung cancer (Amsterdam, Netherlands)* 2010: 69(1): 123-126.

67.   Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, Mascaux C, Meert AP, Roelandts M, Scherpereel A, Terrones Munoz V, Sculier JP, European Lung Cancer Working Party aobotILCSP. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2010: 5(5): 612-619.

68.   Okereke IC, Gangadharan SP, Kent MS, Nicotera SP, Shen C, DeCamp MM. Standard uptake value predicts survival in non-small cell lung cancer. *The Annals of Thoracic Surgery* 2009: 88(3): 911-915; discussion 915-916.

69.   Dooms C, van Baardwijk A, Verbeken E, van Suylen RJ, Stroobants S, De Ruysscher D, Vansteenkiste J. Association between 18F-fluoro-2-deoxy-D-glucose uptake values and tumor vitality: prognostic value of positron emission tomography in early-stage non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2009: 4(7): 822-828.

70.   Kadota K, Colovos C, Suzuki K, Rizk NP, Dunphy MP, Zabor EC, Sima CS, Yoshizawa A, Travis WD, Rusch VW, Adusumilli PS. FDG-PET SUVmax combined with IASLC/ATS/ERS histologic classification improves the prognostic stratification of patients with stage I lung adenocarcinoma. *Annals of surgical oncology* 2012: 19(11): 3598-3605.

71.   Nair VS, Barnett PG, Ananth L, Gould MK, Veterans Affairs Solitary Nodule Accuracy Project Cooperative Studies G. PET scan 18F-fluorodeoxyglucose uptake and prognosis in patients with resected clinical stage IA non-small cell lung cancer. *Chest* 2010: 137(5): 1150-1156.

72.   Tann M, Sandrasegaran K, Winer-Muram HT, Jennings SG, Welling ME, Fletcher JW. Can FDG-PET be used to predict growth of stage I lung cancer? *Clinical radiology* 2008: 63(8): 856-863.

73.   Arai T, Kuroishi T, Saito Y, Kurita Y, Naruke T, Kaneko M. Tumor doubling time and prognosis in lung cancer patients: evaluation from chest films and clinical follow-up study. Japanese Lung Cancer Screening Research Group. *Japanese journal of clinical oncology* 1994: 24(4): 199-204.

74.   Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, Hasegawa M, Kawakami S, Kubo K, Haniuda M, Yamanda T. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. *British journal of cancer* 2001: 84(1): 25-32.

75.   Detterbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2008: 3(7): 781-792.

76.   Patz EF, Jr., Goodman PC, Bepler G. Screening for lung cancer. *N Engl J Med* 2000: 343(22): 1627-1633.

77.   Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ (Clinical research ed)* 2004: 328(7455): 1519.

78.   Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proceedings of the American Thoracic Society* 2005: 2(1): 8-11.

79.   Streppel MT, Boshuizen HC, Ocke MC, Kok FJ, Kromhout D. Mortality and life expectancy in relation to long-term cigarette, cigar and pipe smoking: the Zutphen Study. *Tobacco control* 2007: 16(2): 107-113.

80.   Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, Licker M, Ferguson MK, Faivre-Finn C, Huber RM, Clini EM, Win T, De Ruysscher D, Goldman L, European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical t. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2009: 34(1): 17-41.

81.   Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, Kerr K, Macfie A, McGuigan J, Padley S, Popat S, Screaton N, Snee M, Waller D, Warburton C, Win T, British Thoracic S, Society for Cardiothoracic Surgery in Great Britain and I. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010: 65 Suppl 3: iii1-27.

82.   Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT, American College of Chest P. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007: 132(3 Suppl): 161S-177S.

83.   Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, Boyd JA. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. *Cancer* 2009: 115(22): 5218-5227.

84.   Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009: 136(1): 260-271.

85.   Pepek JM, Chino JP, Marks LB, D'Amico TA, Yoo DS, Onaitis MW, Ready NE, Hubbs JL, Boyd J, Kelsey CR. How well does the new lung cancer staging system predict for local/regional recurrence after surgery?: A comparison of the TNM 6 and 7 systems. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2011: 6(4): 757-761.

86.   Strand TE, Rostad H, Damhuis RA, Norstein J. Risk factors for 30-day mortality after resection of lung cancer and prediction of their magnitude. *Thorax* 2007: 62(11): 991-997.

87.   Kozower BD, Sheng S, O'Brien SM, Liptay MJ, Lau CL, Jones DR, Shahian DM, Wright CD. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. *The Annals of Thoracic Surgery* 2010: 90(3): 875-881; discussion 881-873.

88.   Seely AJ, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, Gilbert S, Maziak DE, Shamji FM, Sundaresan RS. Systematic classification of morbidity and mortality after thoracic surgery. *The Annals of Thoracic Surgery* 2010: 90(3): 936-942; discussion 942.

89.   Rueth NM, Parsons HM, Habermann EB, Groth SS, Virnig BA, Tuttle TM, Andrade RS, Maddaus MA, D'Cunha J. Surgical treatment of lung cancer: predicting postoperative morbidity in the elderly population. *The Journal of thoracic and cardiovascular surgery* 2012: 143(6): 1314-1323.

90.   Rivera C, Falcoz PE, Bernard A, Thomas PA, Dahan M. Surgical management and outcomes of elderly patients with early stage non-small cell lung cancer: a nested case-control study. *Chest* 2011: 140(4): 874-880.

91.   Bryant AS, Rudemiller K, Cerfolio RJ. The 30- versus 90-day operative mortality after pulmonary resection. *The Annals of Thoracic Surgery* 2010: 89(6): 1717-1722; discussion 1722-1713.

92.   Bernard A, Rivera C, Pages PB, Falcoz PE, Vicaut E, Dahan M. Risk model of in-hospital mortality after pulmonary resection for cancer: a national database of the French Society of Thoracic and Cardiovascular Surgery (Epithor). *The Journal of thoracic and cardiovascular surgery* 2011: 141(2): 449-458.

93.   Ferguson MK, Durkin AE. A comparison of three scoring systems for predicting complications after major lung resection. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2003: 23(1): 35-42.

94.   Bradley A, Marshall A, Abdelaziz M, Hussain K, Agostini P, Bishay E, Kalkat M, Steyn R, Rajesh P, Dunn J, Naidu B. Thoracoscore fails to predict complications following elective lung resection. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2012: 40(6): 1496-1501.

95.   Moller A, Sartipy U. Predictors of postoperative quality of life after surgery for lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012: 7(2): 406-411.

96.   Ilonen IK, Rasanen JV, Knuuttila A, Sihvo EI, Sintonen H, Sovijarvi AR, Salo JA. Quality of life following lobectomy or bilobectomy for non-small cell lung cancer, a two-year prospective follow-up study. *Lung cancer (Amsterdam, Netherlands)* 2010: 70(3): 347-351.

97.   Schulte T, Schniewind B, Dohrmann P, Kuchler T, Kurdow R. The extent of lung parenchyma resection significantly impacts long-term quality of life in patients with non-small cell lung cancer. *Chest* 2009: 135(2): 322-329.

98.   Schulte T, Schniewind B, Walter J, Dohrmann P, Kuchler T, Kurdow R. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2010: 68(1): 115-120.

99.   Ferguson MK, Parma CM, Celauro AD, Vigneswaran WT. Quality of life and mood in older patients after major lung resection. *The Annals of Thoracic Surgery* 2009: 87(4): 1007-1012; discussion 1012-1003.

100. Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, Grannis F. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest* 2004: 125(2): 439-445.

101. Luchtenborg M, Jakobsen E, Krasnik M, Linklater KM, Mellemgaard A, Moller H. The effect of comorbidity on stage-specific survival in resected non-small cell lung cancer patients. *European journal of cancer (Oxford, England : 1990)* 2012: 48(18): 3386-3395.

102. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. *BMC cancer* 2004: 4: 94.

103. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *The Annals of Thoracic Surgery* 1995: 60(3): 615-622; discussion 622-613.

104. Hansen HJ, Petersen RH, Christensen M. Video-assisted thoracoscopic surgery (VATS) lobectomy using a standardized anterior approach. *Surgical endoscopy* 2011: 25(4): 1263-1269.

105. Flores RM, Park BJ, Dycoco J, Aronova A, Hirth Y, Rizk NP, Bains M, Downey RJ, Rusch VW. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. *The Journal of thoracic and cardiovascular surgery* 2009: 138(1): 11-18.

106. Handy JR, Jr., Asaph JW, Douville EC, Ott GY, Grunkemeier GL, Wu Y. Does video-assisted thoracoscopic lobectomy for lung cancer provide improved functional outcomes compared with open lobectomy? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2010: 37(2): 451-455.

107. Phillips JD, Merkow RP, Sherman KL, DeCamp MM, Bentrem DJ, Bilimoria KY. Factors affecting selection of operative approach and subsequent short-term outcomes after anatomic resection for lung cancer. *Journal of the American College of Surgeons* 2012: 215(2): 206-215.

108. Swanson SJ, Meyers BF, Gunnarsson CL, Moore M, Howington JA, Maddaus MA, McKenna RJ, Miller DL. Video-assisted thoracoscopic lobectomy is less costly and morbid than open lobectomy: a retrospective multiinstitutional database analysis. *The Annals of Thoracic Surgery* 2012: 93(4): 1027-1032.

109. Gopaldas RR, Bakaeen FG, Dao TK, Walsh GL, Swisher SG, Chu D. Video-assisted thoracoscopic versus open thoracotomy lobectomy in a cohort of 13,619 patients. *The Annals of Thoracic Surgery* 2010: 89(5): 1563-1570.

110. Ceppa DP, Kosinski AS, Berry MF, Tong BC, Harpole DH, Mitchell JD, D'Amico TA, Onaitis MW. Thoracoscopic lobectomy has increasing benefit in patients with poor pulmonary function: a Society of Thoracic Surgeons Database analysis. *Annals of Surgery* 2012: 256(3): 487-493.

111. Nakanishi R, Yamashita T, Oka S. Video-assisted thoracic surgery lobectomy for non-small cell lung cancer in patients with a Charlson comorbidity index score of two or more. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2010: 5(1): 56-61.

112. Rueth NM, Andrade RS. Is VATS lobectomy better: perioperatively, biologically and oncologically? *The Annals of Thoracic Surgery* 2010: 89(6): S2107-2111.

113. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009: 27(15): 2553-2562.

114. Flores RM, Ihekweazu UN, Rizk N, Dycoco J, Bains MS, Downey RJ, Adusumilli P, Finley DJ, Huang J, Rusch VW, Sarkaria I, Park B. Patterns of recurrence and incidence of second primary tumors after lobectomy by means of video-assisted thoracoscopic surgery (VATS) versus thoracotomy for lung cancer. *The Journal of thoracic and cardiovascular surgery* 2011: 141(1): 59-64.

115. Carr SR, Schuchert MJ, Pennathur A, Wilson DO, Siegfried JM, Luketich JD, Landreneau RJ. Impact of tumor size on outcomes after anatomic lung resection for stage 1A non-small cell lung cancer based on the current staging system. *The Journal of thoracic and cardiovascular surgery* 2012: 143(2): 390-397.

116. Kilic A, Schuchert MJ, Pettiford BL, Pennathur A, Landreneau JR, Landreneau JP, Luketich JD, Landreneau RJ. Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly. *The Annals of Thoracic Surgery* 2009: 87(6): 1662-1666; discussion 1667-1668.

117. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *The Journal of thoracic and cardiovascular surgery* 2006: 132(4): 769-775.

118. Schuchert MJ, Abbas G, Awais O, Pennathur A, Nason KS, Wilson DO, Siegfried JM, Luketich JD, Landreneau RJ. Anatomic segmentectomy for the solitary pulmonary nodule and

early-stage lung cancer. *The Annals of Thoracic Surgery* 2012: 93(6): 1780-1785; discussion 1786-1787.

119. Whitson BA, Groth SS, Andrade RS, Mitiek MO, Maddaus MA, D'Cunha J. Invasive adenocarcinoma with bronchoalveolar features: a population-based evaluation of the extent of resection in bronchoalveolar cell carcinoma. *The Journal of thoracic and cardiovascular surgery* 2012: 143(3): 591-600.e591.

120. Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. *The Annals of Thoracic Surgery* 2002: 73(4): 1071-1075.

121. Kim HK, Choi YS, Kim J, Shim YM, Lee KS, Kim K. Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2010: 5(2): 206-210.

122. Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K, Hishida T, Nishimura M, Nagai K. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012: 7(10): 1563-1566.

123. Schuchert MJ, Kilic A, Pennathur A, Nason KS, Wilson DO, Luketich JD, Landreneau RJ. Oncologic outcomes after surgical resection of subcentimeter non-small cell lung cancer. *The Annals of Thoracic Surgery* 2011: 91(6): 1681-1687; discussion 1687-1688.

124. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer<=1 cm in size: a review of SEER data. *Chest* 2011: 139(3): 491-496.

125. Whitson BA, Groth SS, Andrade RS, Maddaus MA, Habermann EB, D'Cunha J. Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis. *The Annals of Thoracic Surgery* 2011: 92(6): 1943-1950.

126. Billmeier SE, Ayanian JZ, Zaslavsky AM, Nerenz DR, Jaklitsch MT, Rogers SO. Predictors and outcomes of limited resection for early-stage non-small cell lung cancer. *Journal of the National Cancer Institute* 2011: 103(21): 1621-1629.

127. Nomori H, Mori T, Ikeda K, Yoshimoto K, Iyama K, Suzuki M. Segmentectomy for selected cT1N0M0 non-small cell lung cancer: a prospective study at a single institute. *The Journal of thoracic and cardiovascular surgery* 2012: 144(1): 87-93.

128. Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S. Prognostic predictors in non-small cell lung cancer patients undergoing intentional segmentectomy. *The Annals of Thoracic Surgery* 2012: 93(6): 1788-1794.

129. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE, 2nd, Landreneau RJ, Inculet RI, Jones DR, Meyers BF, Harpole DH, Putnam JB, Jr., Rusch VW, Group AZS. Morbidity and

mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *The Annals of Thoracic Surgery* 2006: 81(3): 1013-1019; discussion 1019-1020.

130. Van Schil PE, Asamura H, Rusch VW, Mitsudomi T, Tsuboi M, Brambilla E, Travis WD. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2012: 39(2): 478-486.

131. Kim HK, Choi YS, Kim K, Shim YM, Jeong SY, Lee KS, Kwon OJ, Kim J. Management of ground-glass opacity lesions detected in patients with otherwise operable non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2009: 4(10): 1242-1246.

132. Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, Nakamura S, Tada H, Tsuboi M. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). *Japanese journal of clinical oncology* 2010: 40(3): 271-274.

133. National Cancer I. Phase III Randomized Study of Lobectomy Versus Sublobar Resection in Patients With Small Peripheral Stage IA Non-Small Cell Lung Cancer. CALGB-140503.

134. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman B, Senan S. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2011: 101(2): 240-244.

135. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Karasawa K, Hayakawa K, Niibe Y, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Kozuka T, Arimoto T, Hara R, Itami J, Araki T. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *International journal of radiation oncology, biology, physics* 2011: 81(5): 1352-1358.

136. Matsuo Y, Shibuya K, Nagata Y, Norihisa Y, Narabayashi M, Sakanaka K, Ueki N, Mizowaki T, Hiraoka M. Preliminary report of late recurrences, at 5 years or more, after stereotactic body radiation therapy for non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012: 7(2): 453-456.

137. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. *The New England journal of medicine* 2012: 366(24): 2327-2329.

138. Rowe BP, Boffa DJ, Wilson LD, Kim AW, Detterbeck FC, Decker RH. Stereotactic body radiotherapy for central lung tumors. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012: 7(9): 1394-1399.

139. Mayo Clinic Clinical T. Stereotactic Body Radiotherapy (SBRT) Versus Sublobar Resection for High-Risk Patients With Early Stage Non-Small Lung Cancer (NSCLC).

140. Center MDAC. Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer (STARS).

141. Dupuy DE. Image-guided thermal ablation of lung malignancies. *Radiology* 2011: 260(3): 633-655.

142. Lanuti M, Sharma A, Willers H, Digumarthy SR, Mathisen DJ, Shepard JA. Radiofrequency ablation for stage I non-small cell lung cancer: management of locoregional recurrence. *The Annals of Thoracic Surgery* 2012: 93(3): 921-927; discussion 927-988.

143. Tada A, Hiraki T, Iguchi T, Gobara H, Mimura H, Toyooka S, Kiura K, Tsuda T, Mitsuhashi T, Kanazawa S. Influence of radiofrequency ablation of lung cancer on pulmonary function. *Cardiovascular and interventional radiology* 2012: 35(4): 860-867.

144. Ambrogi MC, Fanucchi O, Cioni R, Dini P, De Liperi A, Cappelli C, Davini F, Bartolozzi C, Mussi A. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2011: 6(12): 2044-2051.

145. Kashima M, Yamakado K, Takaki H, Kodama H, Yamada T, Uraki J, Nakatsuka A. Complications after 1000 lung radiofrequency ablation sessions in 420 patients: a single center's experiences. *AJRAmerican journal of roentgenology* 2011: 197(4): W576-580.

146. Simon CJ, Dupuy DE, DiPetrillo TA, Safran HP, Grieco CA, Ng T, Mayo-Smith WW. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology* 2007: 243(1): 268-275.

147. Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interactive cardiovascular and thoracic surgery* 2012: 15(2): 258-265.

148. Strohschein FJ, Bergman H, Carnevale FA, Loiselle CG. Patient decision making among older individuals with cancer. *Qualitative health research* 2011: 21(7): 900-926.

149. Yellen SB, Cella DF. Someone to live for: social well-being, parenthood status, and decision-making in oncology. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1995: 13(5): 1255-1264.

150. Elkin EB, Kim SH, Casper ES, Kissane DW, Schrag D. Desire for information and involvement in treatment decisions: elderly cancer patients' preferences and their physicians' perceptions. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007: 25(33): 5275-5280.

151. Hillerdal G. Indolent lung cancers--time for a paradigm shift: a review. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2008: 3(3): 208-211.

152. Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, Strauss GM, Swanson SJ, Travis WD, Sugarbaker DJ. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *The Journal of thoracic and cardiovascular surgery* 2012: 144(1): 33-38.

153. Nicholas J. Harmonizing lung cancer screening guidelines. *Journal of the National Cancer Institute* 2012: 104(20): 1531-1532.
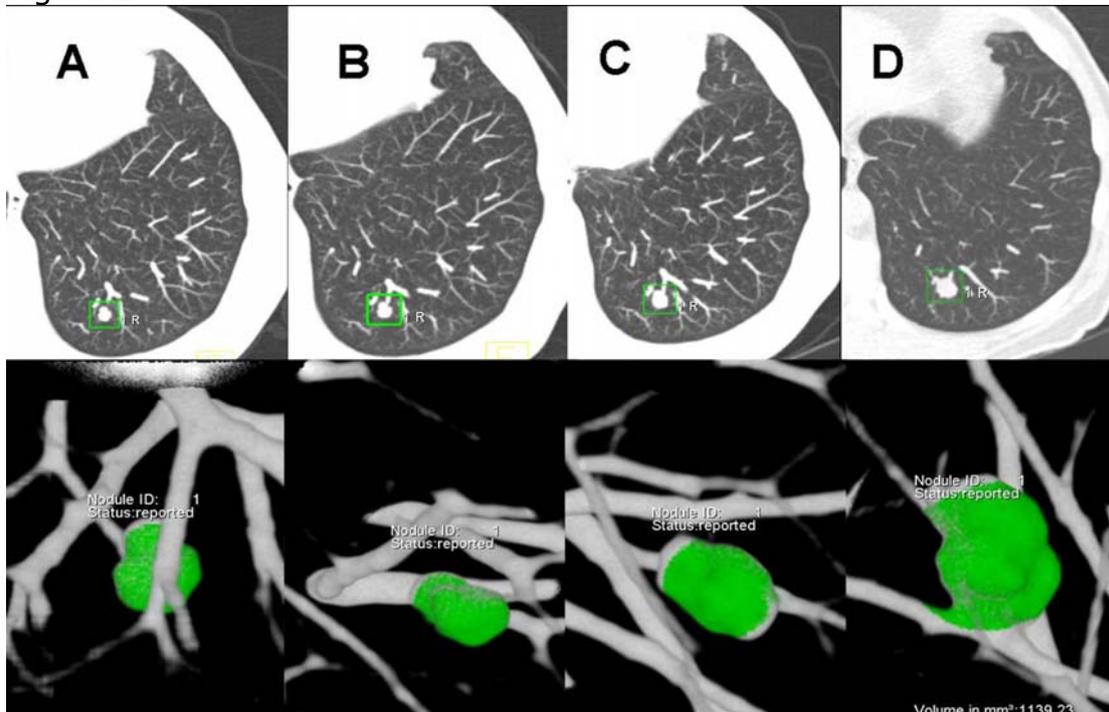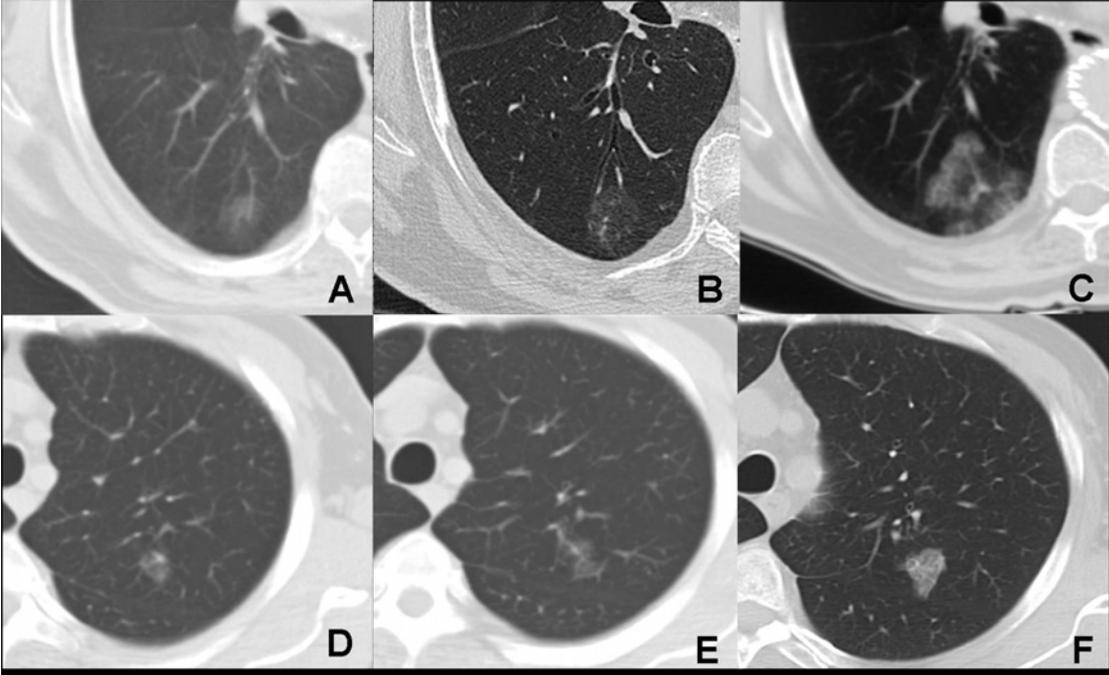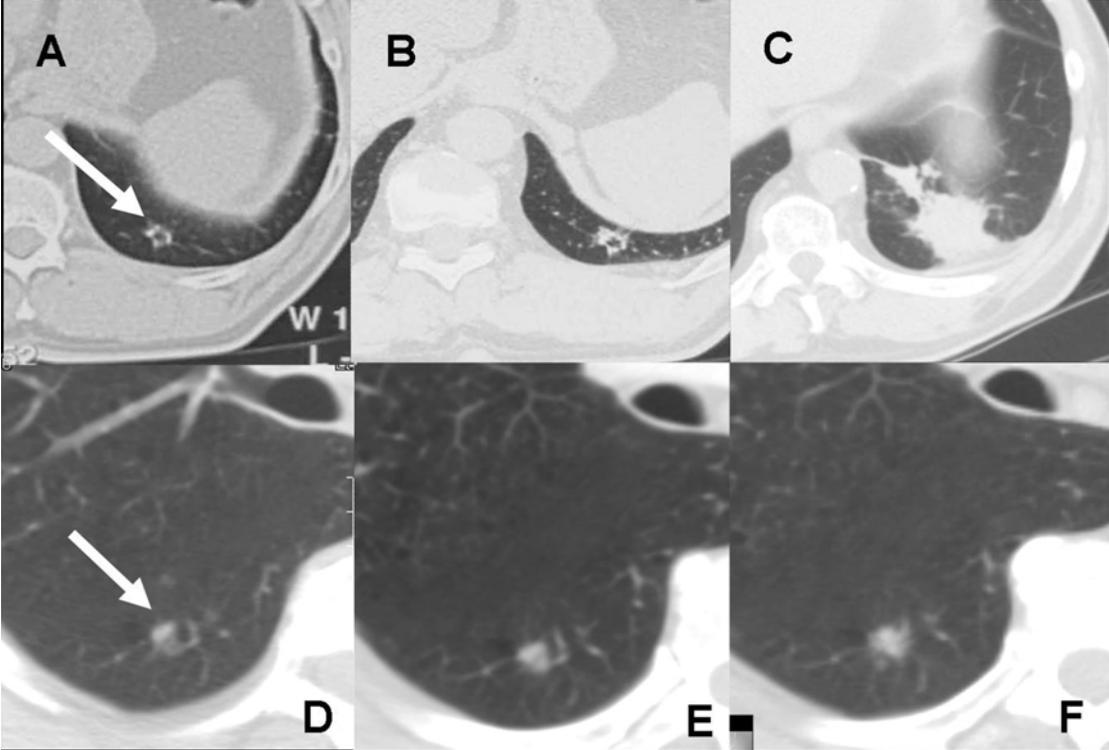
Figure 1

Figure 2

Figure 3

Figure 4

Figure 5