



Slow-growing lung cancer as an emerging entity: from screening to clinical management

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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 recognised in routine practice, slow-growing lung cancers do exist and are more common than previously thought.

Here, 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 evaluated 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.



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The increasingly common incidence of slow-growing lung cancer and its influence on clinical decision-making is discussed <http://ow.ly/oZ6c2>

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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 their lives are considered to be at immediate risk unless effective treatment is instituted without delay. Yet in 1984, a longitudinal study on 20 000 atomic bomb survivors who received biannual screening chest radiographs over 20 years already suggested that some patients could harbour slow-growing pulmonary tumours [4].

Later, indirect evidence derived from early randomised controlled trials of lung cancer screening with chest radiography 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 nonscreened 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 (VDT) of 36 days would require only 180 days (*i.e.* five doublings) to reach 3 cm in size, 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 summarised in [table 1](#).

Lung cancers detected by standard chest radiographs had short VDTs (*i.e.* shorter than the chosen cut-off) in >90% of the cases, but small lung cancers detected using computerised tomography (CT) had long VDTs in 23–51% of assessed cases, with the exception of the International Early Lung Cancer Action Program (I-ELCAP) series, where the figure was only 3% [16].

The cut-off for slow-growing lung cancer varied, but most authors utilised the 400-day limit proposed by YANKELEVITZ *et al.* [9]. Therefore, we eventually estimated the percentage of cases in each study that had a VDT of ≥ 400 days by taking into account the number of lung cancer cases with such a long VDT in each study. When a different cut-off was used, the data were extrapolated if possible. If not, the number of patients whose cancer did not grow at all was conservatively utilised 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 YANKELEVITZ *et al.* [9] for the Mayo Lung Project and Memorial Sloan-Kettering populations, and by HENSCHKE *et al.* [16] for the I-ELCAP patients. In contrast, some Japanese clinical studies reported 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 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 (22%) out of 516 cases 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 recognised 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 this 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 probably 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.

TABLE 1 Tumour volume doubling times in lung cancer series											
First author [ref.]	HAYABUCHI [4]	YANKELEVITZ [9]	HASEGAWA [10]	JENNINGS [11]	LINDELL [12]	HONDA [13]	MIKITA [14]	SONE [15]	HENSCHKE [16]	WILSON [17]	VERONESI [18]
Year	1983	2003	2000	2006	2007	2009	2012	2012	2012	2012	2012
Origin of patients	Screening	Screening [#]	Screening	Mixed ^{#,¶}	Screening	Clinical	Clinical ⁺	Mixed [¶]	Screening	Screening	Screening
Imaging test	CR	CR	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT	LDCT
Age years mean (range)	65	NR	65 (33–89)	72 (43–87) [§]	65 (53–79)	66 (39–83)	67 (46–86)	(33–80)	NR	NR	58 ± 5.6
Cancers n	107	114	82	393	68	51	34	87	111 ^f	148	175
VDT measured	37 (35)	87 (76)	61 (74)	149 (38)	48 (71)	51 (100)	34 (100)	45 (52)	111 ^f (100)	63 (43)	120 ^f (69)
VDT days											
Mean ± SD			452 ± 381	207	518 ± 1094	258	324		136	357	240
Median (range)		144–101		(26–∞) ^{##}		(69–∞) ^{##,¶¶} , 121				(NR– 4263)	(18–2555)
Cut-off days	>150	>400	>342 ^{§§}	>207 ^{f¶}	>400	[39–221] ⁺⁺	>700		>400	>365	>400
Slow-growing (measured/ overall)	29 (78/27)	4 (5/3)	31 (51/38)	74 (50/19)	13 (27/19)		8 (23/23)		3 (3/3)	30 (48/20)	31 (26/18)
VDT >400 days n (% overall)	11 (10)	4 (3)	14 ^{##} (17)	21 ^{##} (5)	13 (19)	16 (31)	13 (38)	39 (45)	3 (3)		31 (18)

Data are presented as n, mean ± SD or n (%), unless otherwise stated. VDT: volume doubling time; CR: chest radiography, LDCT: low-dose computed tomography; NR: not reported.
#: stage I only; ¶: including screening and clinically detected patients; +: small solid nodules only; §: data presented as median (range); ^f: nonprevalent cases only; ##: VDTs of regressing
tumours would have negative value, but they are herewith expressed as an infinite value for clarity; ¶¶: adenocarcinoma only; ++: squamous carcinoma only; §§: geometric mean of VDTs;
^{f¶}: median VDT; ##: only tumours showing no growth included in computation.

Differentiating small lung cancers from benign lesions

In some screening programmes, the prevalence of subjects with undetermined nodules may exceed 50% and the formidable number of undetermined nodules detected by CT, 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, its features on CT, and individual risk factors [20]; it is lowest for sub-centimetre solid nodules (<1–7%) and highest for focal ground-glass lesions (59–73%) [21, 22].

Although 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 two-dimensional (2D) or three-dimensional (3D) growth assessments.

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

Nodules with a volume <50 mm³ (5 mm in diameter) were ignored. Noncalcified nodules with a volume >500 mm³ (>9.8 mm) were considered positive and those in between (50–500 mm³) considered 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 rescheduled for a follow-up CT 1 year later (fig. 1). Sensitivity of the test after the first round was 94.6% and the negative predictive value

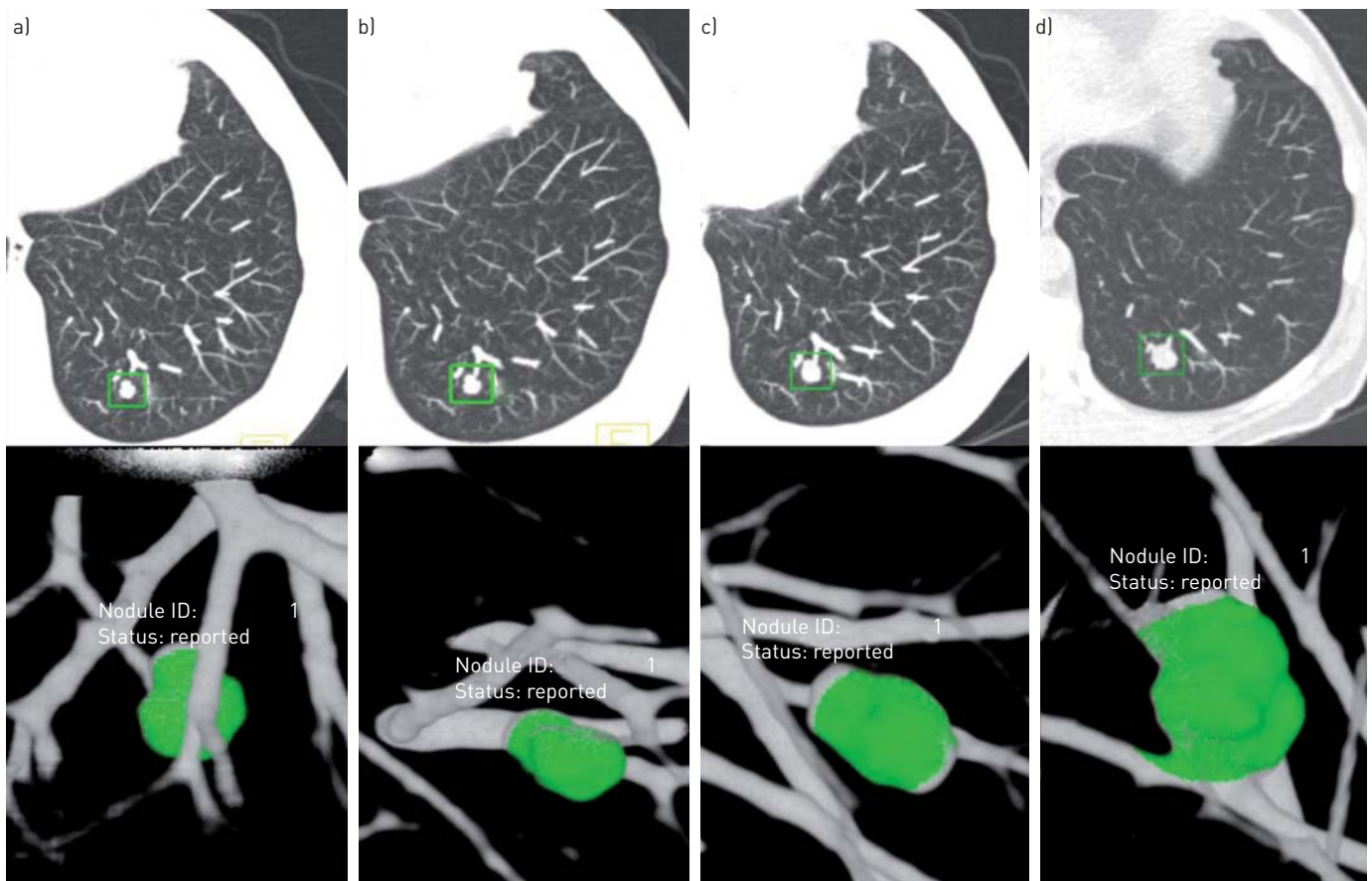


FIGURE 1 Three-dimensional assessment of computed tomography screening-detected lung cancer. a) An indeterminate nodule measuring 258 mm³ was detected at baseline in a 65-year-old current smoker in the NELSON trial [26]; b) at the 3-month follow-up examination, the nodule measured 270 mm³ (volume doubling time (VDT) 1465 days, negative screen result); c) 1 year after baseline, the volume was 424 mm³ (VDT 528 days); and d) 2 years later it measured 1139 mm³ (VDT 289 days, positive test). Subsequent work-up revealed stage IA adenocarcinoma.

was 99.9%, while 2.6% of 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 positron emission tomography (PET)-scan and CT-guided percutaneous core biopsy as downstream tests to increase specificity [29–33].

The utility of PET scans in the differential diagnosis of 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 standardised 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 (80–100%), while specificity is more variable (40–100%). 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, respectively, for CT, and the area under the curve was 0.93 for PET scan and 0.82 for CT ($p < 0.0001$). The negative predictive value of PET 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 ~10 mm (5–7 mm with newer PET–CT equipment), sensitivity is low for small tumours, which may particularly be missed when located in lower lung portions, where respiratory movements could prevent acquisition of an adequate image [36, 37]. In addition, neuroendocrine tumours and those with a predominant lepidic growth pattern on pathological examination, formerly known as bronchioloalveolar carcinomas [38], have low fluorodeoxyglucose (FDG) uptake, possibly due to the reduced number of cellular receptors involved in FDG internalisation, making PET scanning inadequate for carcinoid tumours and ground-glass lesions, unless the lesion has a sizeable solid component [39–43].

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

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

Transbronchial or CT-guided percutaneous lung biopsy, video-assisted thoracoscopy (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 programmes, surgical biopsies carried out to confirm malignancy result in a benign nodule diagnosis in 15–25% of cases, but the rate can be even higher [28, 30–33, 46, 47].

Not surprisingly, this occurrence is also relatively common 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

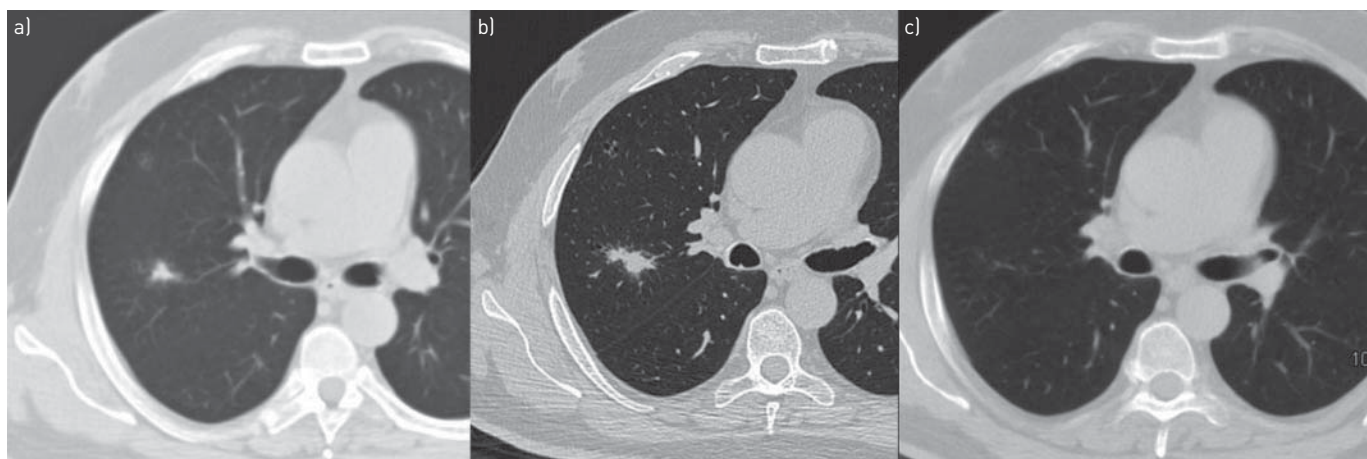


FIGURE 2 Role of positron emission tomography (PET) scanning in reducing unnecessary invasive procedures. a) Indeterminate lung nodule, measuring 13 × 9 mm, detected in a 70-year-old former smoker in the DANTE trial. Antibiotics were given and b) the computed tomography (CT) scan was repeated 45 days later, at which time the lesion measured 25 × 12 mm, had an irregular shape and spiculated margins. However, a PET scan showed no fluorodeoxyglucose uptake. 2 months later the lesion was fading and c) 10 months later it was no longer visible.

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 unrecognised 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 1 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 workup of incidental and screening-detected undetermined pulmonary nodules might be the same.

Discriminating between slow-growing and aggressive lung cancer

As yet, there are no validated biological indicators 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.

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 assessed more easily even if the nodule is nonspherical or if it grows asymmetrically [51–53]. Semiautomated 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 that in 2D assessments.

However, for focal ground-glass lesions, 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 \times density) or CT attenuation values have been proposed [55–57].

Morphological features

CT-detected pulmonary nodules are nowadays classified as solid and subsolid, 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 normal parenchymal structures can still be seen through a hazy area of increased lung attenuation (subsolid 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 nonsolid, or a pure GGO (fig. 3).

Solid lesions tend to progress faster than part-solid lesions and part-solid lesions tend to grow faster than nonsolid ones [10, 55], so in fact 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, adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA) and lepidic-predominant, invasive adenocarcinoma [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, 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].

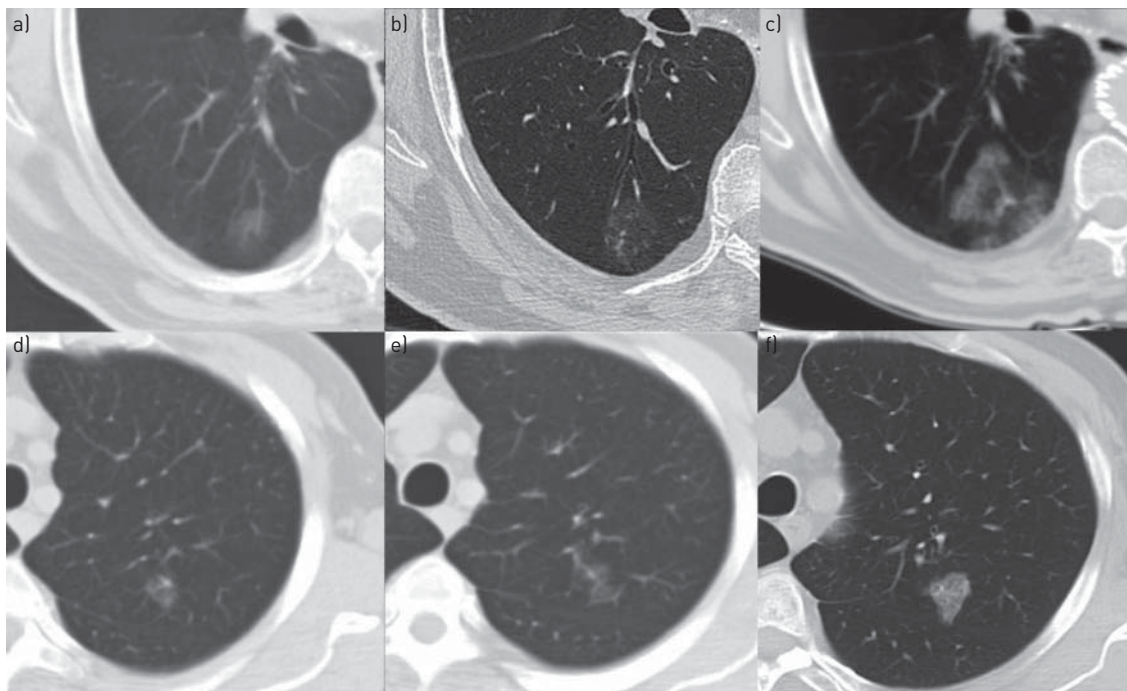


FIGURE 3 Slow evolution of nonsolid lung cancer (focal ground-glass lesions). a) Screening-detected pure ground-glass lesion in a 68-year-old former smoker. b) Follow-up was continued because of significant cardiovascular comorbidity until c) frank enlargement and increased density became evident, at age 77 years. Video-assisted thoracoscopic (VATS) wedge resection was carried out, and pathology revealed a 5.4-cm mucinous adenocarcinoma with lepidic and papillary aspects. The patient is currently disease-free 10 years after initial detection and 10 months after resection. d) Screening-detected focal ground-glass lesion in a 63-year-old former smoker, which e) did not change significantly over 3 years and was interpreted as focal fibrosis. f) 6 years after initial detection, the lesion had increased in size and density, and a positron emission tomography scan demonstrated fluorodeoxyglucose uptake. Percutaneous core biopsy was positive and VATS lobectomy was performed confirming stage IA adenocarcinoma with predominant lepidic features. The patient was disease-free 40 months after surgery.

In one such series [64], progression of pure GGOs was noted in 12 out of 89 patients over a median (range) follow-up period of 59 (25–140) months. Eight out of 11 lesions that were eventually resected in these 12 patients were either AIS (n=2) or MIA (n=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 <30 mm [65], but since progression may become evident after years (fig. 4), no time limit can be recommended for discontinuing surveillance [66].

Variability is high under any circumstances and solid nodules too may grow very slowly (fig. 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 scanning in nonsmall 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 pre-operative 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.* [72] 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. In this series, only three (6%) out of 51 cancers were classified as bronchoalveolar 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 lepidic-predominant tumours was not reported in this study.

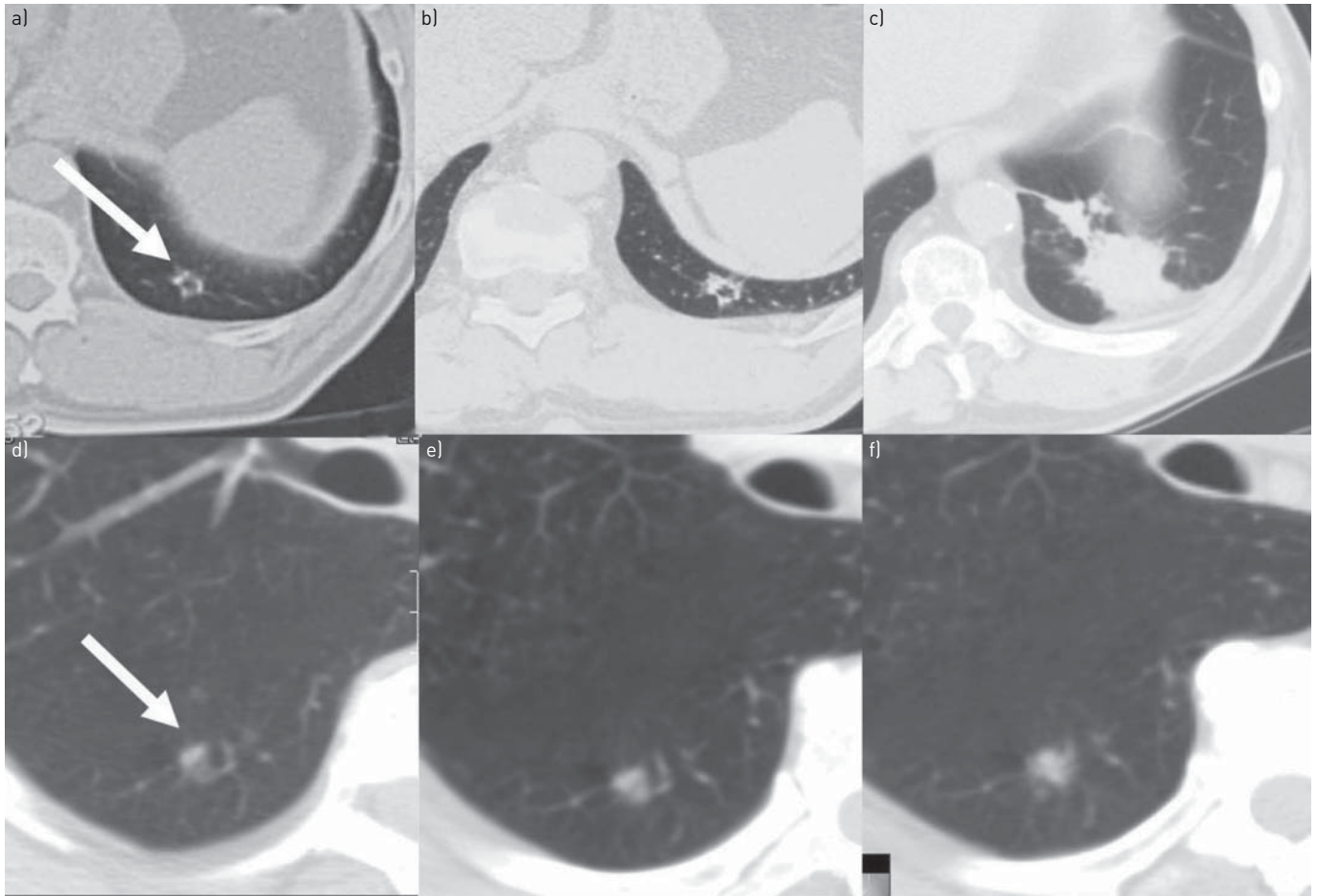


FIGURE 4 Slow evolution of small solid lung cancer. a–c) Screening-detected 1-cm excavated lesion (arrow) in a 71-year-old male smoker. b) 2 years after detection, modest increases in size and fluorodeoxyglucose uptake were demonstrated. Computed tomography (CT)-guided biopsy was recommended but the patient refused and discontinued follow-up. c) 6 years later a new CT scan was obtained, showing overt progression. Lobectomy was performed, and pathology showed stage III adenocarcinoma. The patient died with liver metastasis 1 year after surgery and 9 years after the initial detection of the tumour, at age 80 years. d) Sub-centimetre lesion in the right lower lobe (arrow) of a 64-year-old male patient in the DANTE trial who had undergone prior left lower lobectomy for stage IA adenocarcinoma at the age of 61 years. e) The lesion was retrospectively visible but smaller in a CT scan obtained at age 62 years. Follow-up was continued for several years because of the patient's own preferences. f) At age 67 years, the lesion had grown to 12 mm. Anatomic segmentectomy was performed and an additional 4-mm nodule in the upper lobe was excised. Pathology was multifocal stage IA adenocarcinoma with predominant lepidic features. The patient was alive and well 12 months after the second lung resection.

Since carcinoid tumours and ground-glass lesions often do not take up 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 a significant correlation between histological type and tumour growth rate. For example, squamous cancer is generally faster-growing than adenocarcinoma, but there is a significant overlap across all tumour types [4, 10, 11, 13, 14, 16, 17, 49, 73, 74]. Consequently, 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, >1 cm or >500 mm³, and to have short VDTs [4, 9, 75].

In contrast, a significant proportion of CT-screening detected tumours, prevalent cancers especially, have long VDTs. In the Pittsburgh Lung Screening Study [17], 28 (67%) out of 42 baseline-screen cancers had VDTs >365 days. Nonprevalent 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 detected incidentally 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 radiographic 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 do not occur in the meantime.

Lung cancer growth may in fact be nonlinear 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 *et al.* [12]. Such phenomena have also been occasionally observed in the DANTE and the NELSON trials.

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 that this is true for the spectrum of lepidic tumours; however, such a relationship has not been investigated in depth for other histotypes.

Tumours with shorter VDTs indeed have 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.

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 comorbidities 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 considered even more carefully than usual (figs 3–5).

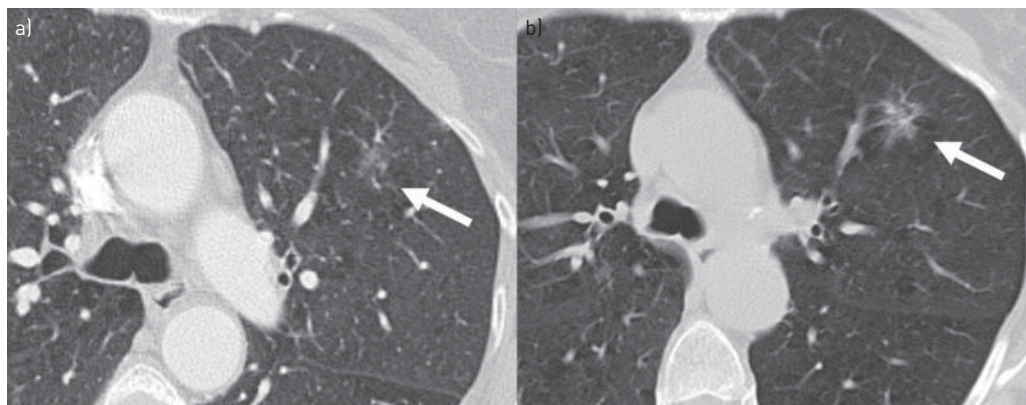


FIGURE 5 A typical controversial case. A 65-year-old female patient with moderately compromised lung function. In 2008, at the age of 61 years, limited resection of the right upper lobe was carried out for bronchioalveolar carcinoma with minimal invasive component. a) At that time a small infiltrate (arrow) was visible in the left upper lobe; b) 4 years later an increase in size and density is evident. The patient prefers to remain in follow-up; should we press her to obtain a tissue diagnosis and, if malignant (highly likely), treat her? If yes, how?

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, the 5-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]. Post-operative complications occur after lobectomy in 40–55% of the cases; the reported 30-day mortality is 1.3–4.2% and rises to 5.4–7.8% after pneumonectomy [86–90]. 90-day mortality adds another 2–3% to the toll, mainly due to cardiovascular events occurring after discharge, but these data are 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 wellbeing indicators may still show a detrimental impact of major lung resection up to 2 years post-operatively in a significant proportion of patients [95–99]. In one study, 24% and 11% of long-term cancer survivors still experienced moderate and severe limitations, respectively, in their daily activities due to residual dyspnoea [100].

The risks both of perioperative complications and 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 comorbidity burden.

Comorbidity 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 was 0; 54% if the score was 1–2; and 38% if it was ≥ 3 . Similar figures were reported for N0, N1 and N2 disease. The Charlson score can be calculated manually or through a free online application [102].

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 randomised 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 post-operative pain are definitely reduced, and complication rates are indeed lower in most recent reports that compare the two techniques. Mortality rates of $\sim 1\%$ are regularly reported, with few exceptions. The benefits of VATS are more evident in patients with advanced age, poor lung function and a higher comorbidity 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, which 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 subcentimetre 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 < 2 cm, a mixed ground-glass lesion with $< 75\%$ solid component and a tumour-free margin of ≥ 2 cm are favourable indications for segmentectomy. Post-operative 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 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society 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 randomised trials are currently comparing limited resections *versus* lobectomy for early-stage lung cancer in the USA and in Japan [132, 133].

Nonsurgical 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 the 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 (~10%) of severe and fatal adverse events when centrally located lesions are treated [137, 138]. Local control and complication rates are dose-dependent.

Two randomised 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 >10 years [141] and is the best studied of all such treatments. High intralesional temperatures (90°C 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 retreating 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 (~30%), but mostly mild. However, severe complications may occur in 5–9% of patients. Mortality after RFA is 0.5–2.6%, mainly due to acute respiratory failure or massive haemorrhage [144–146].

Local recurrences occur within 3 years in 30–50% of cases, but results are better with nodules measuring <3 cm [144]. Local control rates with RFA seem to be lower than with stereotactic radiotherapy [147].

Psychological profiles

Age, personality traits, social wellbeing, 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 estimate the risk–benefit ratios of available options [20], the cut-off value will vary according to personal beliefs and inclinations of patients and doctors (fig. 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 recognised in routine clinical practice for several possible reasons: a lesion that does not grow visibly for ≥ 2 years would probably be interpreted as nonmalignant [22]; patients in a poor underlying condition may be left with an undiagnosed slow-growing cancer; and 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].

TABLE 2 Elements that favour observation, tailored options or standard management for patients with putative slow-growing lung cancer

	Observation	Tailored options	Standard management
Age	Relatively old [#]	Relatively old [#]	Relatively young [#]
Comorbidity burden	High	High	Low
Detection	Screening or incidental CT finding	Screening or incidental CT finding	Clinically detected
Size	Relatively small	Relatively small	Relatively large
Morphology	Nonsolid	Part-solid	Solid
VDT	No progression or long VDT [#]	No progression or long VDT [#]	Relatively short VDT [#]
PET/SUV	PET-negative or low SUV [#]	PET-negative or low SUV [#]	PET-positive, high SUV [#]
Surgical options	Unsuitable for sublobar resection	Suitable for sublobar resection	Suitable for VATS lobectomy
Nonsurgical options		SBRT or RFA available	
Psychological profile	Comfortable with being followed	Anxious, prefers certainty	Anxious, prefers certainty

VDT: volume doubling time; PET: positron emission tomography; SUV: standardised uptake value; CT: computed tomography; SBRT: stereotactic body radiation therapy; RFA: radiofrequency ablation; VATS: video-assisted thoracoscopy. [#]: no conventional limit.

It appears that the biological behaviour of lung cancer instead spans across a spectrum, from fast and highly lethal to slow-growing and indolent, and that the mode of detection determines which we are more likely to be dealing with [75]. Current trends in health care suggest that patients possibly harbouring the latter will be increasingly 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 lifespan), together with an estimate of the projected results of each strategy and of its potential impact on the patient's life expectancy and wellbeing (table 2).

Because lung cancer can 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 scanning 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 personalised, 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.

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