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Quantification of growth patterns of screen-detected lung cancers: The NELSON study

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A R T I C L E   I N F O

A B S T R A C T

Objectives: Although exponential growth is assumed for lung cancer, this has never been quantified in vivo. Aim of this study was to evaluate and quantify growth patterns of lung cancers detected in the Dutch-Belgian low-dose computed tomography (CT) lung cancer screening trial (NELSON), in order to elucidate the development and progression of early lung cancer.
Materials and methods: Solid lung nodules found at ≥ 3 CT examinations before lung cancer diagnosis were included. Lung cancer volume (V) growth curves were fitted with a single exponential, expressed as $V = V_1 \exp(t/\tau)$, with t time from baseline (days), V_1 estimated baseline volume (mm^3), and τ estimated time constant. The R^2 coefficient of determination was used to evaluate goodness of fit. Overall volume-doubling time for the individual lung cancer is given by $\tau * \log(2)$.
Results: Forty-seven lung cancers in 46 participants were included. Forty participants were male (87.0%); mean age was 61.7 years (standard deviation, 6.2 years). Median nodule size at baseline was 99.5 mm^3 (IQR: 46.8–261.8 mm^3). Nodules were followed for a median of 770 days (inter-quartile range: 383–1102 days) before lung cancer diagnosis. One cancer (2.1%) was diagnosed after six CT examinations, six cancers (12.8%) were diagnosed after five CTs, 14 (29.8%) after four CTs, and 26 cancers (55.3%) after three CTs. Lung cancer growth could be described by an exponential function with excellent goodness of fit (R^2 0.98). Median overall volume-doubling time was 348 days (inter-quartile range: 222–492 days).
Conclusion: This study based on CT lung cancer screening provides in vivo evidence that growth of cancerous small-to-intermediate sized lung nodules detected at low-dose CT lung cancer screening can be described by an exponential function such as volume-doubling time.

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1. Introduction

A tumor starts from a single cell that approximately doubles in volume with each cell division. Based on this principle, a theoretical exponential model for tumor growth was already introduced in 1956 [1]. It is assumed that this model also fits lung cancer growth, however this has not been proven in clinical practice. A wait-and-see principle is not commonly used when lung cancer is suspected, because of the aggressiveness of the disease. In vivo information on lung cancer growth patterns, from small nodules barely detectable by imaging techniques ($\sim$15 mm^3) to histologically proven lung cancers, is therefore scarce. With the introduction of low-dose computed tomography (LDCT) lung cancer screening, small-to-intermediate sized nodules, usually benign, are found in the majority of screenees [2–4]. Follow-up CTs are performed to determine nodule growth, in order to differentiate between benign and malignant nodules. Screening provides a unique opportunity to analyze lung cancer growth patterns in more detail. So far, there is one study in which growth dynamics of untreated, subclinical screen-detected lung cancers on CT examinations were evaluated [5]. They concluded that most of the eighteen lung cancers studied did not show exponential growth [5].

Currently, lung cancer screening by LDCT is already being implemented in daily practice in the United States. In Europe, decisions regarding the introduction of lung cancer screening will depend on the final results of ongoing trials [6]. A challenge in CT lung cancer screening is the high rate of false-positive screen results. At first detection, nodule management is based on nodule size. In the follow-up of both screen-detected nodules and nodules incidentally detected in routine clinical care, accurate detection of nodule growth is essential to reduce false-negative and false-positive screen results. One way to determine nodule growth is by calculating the volume-doubling time (VDT). However, this biomarker is based on the assumption that lung cancer grows exponentially.

In the study by Lindell et al., mentioned above, growth curves were based on diameter-based estimated volumes [5]. Furthermore, lung cancer growth patterns were only visually evaluated and not quantified. In the Dutch-Belgian randomized lung cancer screening trial (Dutch acronym: NELSON), nodule volumes were generated semi-automatically by software; a far more accurate way to determine nodule size [7,8]. In addition, for subsequent screening rounds VDTs were determined based on nodule volume [7,8]. This allows detailed evaluation of lung cancer growth, including quantification of growth curves. The purpose of this study was to evaluate and quantify growth patterns of lung cancers detected in LDCT lung cancer screening, in order to elucidate the development and progression of early lung cancer.

2. Materials and methods

2.1. Participants

The Dutch Ministry of Health approved the NELSON trial (ISRCTN63545820). Participants provided written informed consent. Recruitment and selection criteria have been published [9]. Participants (heavy (ex-)smokers, aged 50–75 years) were randomized to no screening (n = 7907) or screening (n = 7915) by chest LDCT at baseline (1st round), after 1 year (2nd round), 3 years (3rd round) and 5.5 years (4th round) [10].

For this sub-study, solid lung nodules diagnosed as lung cancer after three or more subsequent LDCT scans with successful semi-automated volume measurements were selected. Two lung cancers were excluded because of lack of a third volume measurement due to failing volume measurements with a volume too large for semi-automated measurements at the final CT. Furthermore, subsolid

lung cancers were excluded, since the Syngo LungCARE© software package was not able to calculate the volume of sub-solid nodules (1.9% of all non-calcified nodules). Growth curves of nineteen subsolid NELSON lung cancers have been published elsewhere [33].

2.2. Equipment and image reading

Sixteen-multi-detector (MD)CT scanners or, in later rounds, 64-MDCT scanners were used (Sensation-16 or Sensation-64, Siemens Medical Solutions, Forchheim, Germany, or Mx8000 IDT or Brilliance 16P or Brilliance 64, Philips Healthcare, Best, The Netherlands). Scanning parameters have been published, and were equal for all screenings [11,12].

Lung nodule evaluation was performed with software for semi-automated volume measurements (LungCARE© [Somaris/5 VA70C-W, Siemens Medical Solutions]) [11]. In the first two screening rounds, CT images were read twice [11,12]; if measured volume differed between the independent readers, second reader's measurements were used. In the next screening rounds, one radiologist with at least 6 years experience read the examinations.

Nodule margin was classified as smooth, lobulated, spiculated or irregular, based on the three-dimensional nodule segmentation [13–15].

2.3. Nodule management protocol

The nodule management protocol was previously described [11]. Screenings could lead to three outcomes: negative result (volume <50 mm^3; implication: next screening round), indeterminate result (volume 50–500 mm^3; short-term follow-up CT after 6–12 weeks) or positive result (volume >500 mm^3; referral to pulmonologist). For previously detected nodules, at least 25% volume increase led to VDT assessment. Nodules with VDT <400 days resulted in a positive result [11]. Positive screenees were referred to a pulmonologist for diagnostic workup. They received usual care according to (inter)-national guidelines [16–18]. NELSON's chief pathologist reassessed histological specimens of positive screenees.

2.4. Growth curves and statistical analyses

Lung cancer volume (V) growth curves were fitted as function of time t, assuming an exponential growth pattern, using

$$V = V_1 \cdot \exp\left(\frac{t}{\tau}\right) \tag{1}$$

with t time from baseline, V_1 the volume at baseline in mm^3 and τ the time constant (days). Curves were fitted using a least square estimation procedure, returning estimates for V_1 and τ. As measure for the goodness of fit, R^2 coefficient determination was used, where a perfect fit results in R^2 = 1. Normalized growth curves, including all lung cancers, were created by plotting normalized volume (V/V_1) on a logarithmic y-axis as function of normalized time, using

$$t* = \frac{t}{\tau}. \tag{2}$$

Overall VDT per lung cancer case was calculated from the estimated time constant τ using

$$\text{VDT} = \tau \cdot \log(2) \tag{3}$$

Difference in overall VDT between nodules detected at different numbers of screening CT examinations before diagnosis of lung cancer was tested by the Kruskal–Wallis test. $P \leq 0.05$ was considered to indicate statistical significance. Analyses were performed
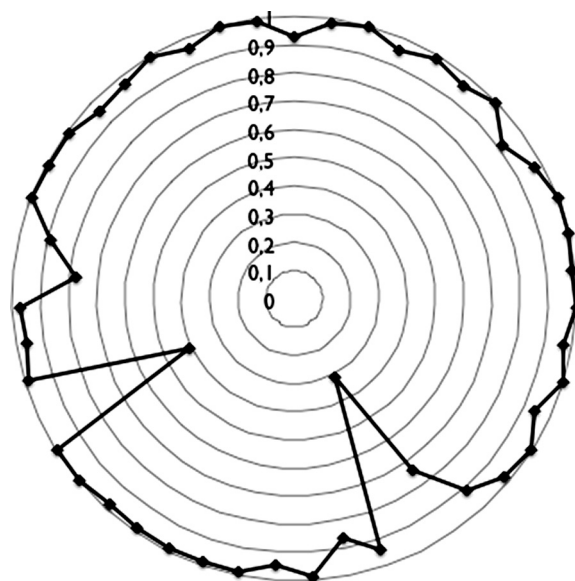
Fig. 1. Radar plot showing individual R^2-deviation for all 47 lung cancers.
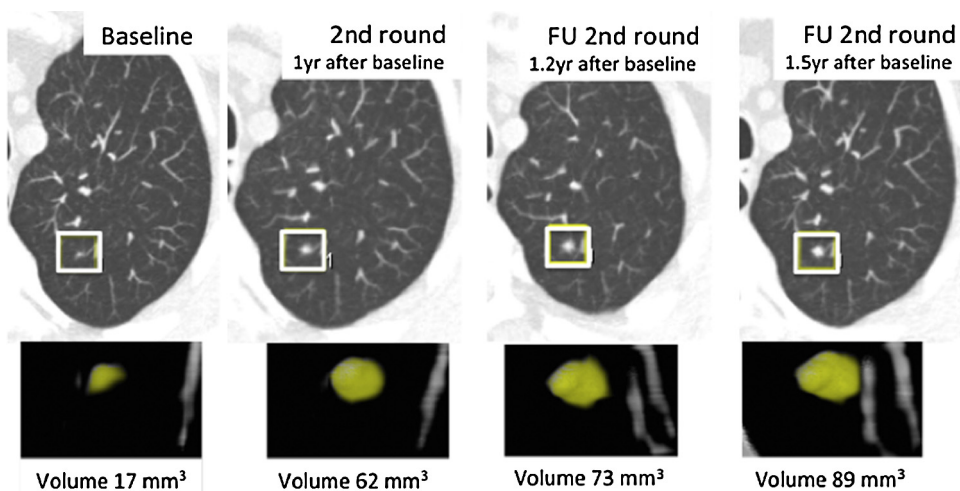

Fig. 2. CT examinations with semi-automated volume measurements of a lung nodule diagnosed as being malignant after four subsequent CT examinations. This nodule grew from 17.0 mm³ at baseline to 88.3 mm³ at time of referral after follow-up examination in the second screening round, 1.5-years after baseline. Growth curve of this nodule is shown in Fig. 3b.

using SPSS 20.0 (SPSS, Chicago, Ill, USA), and Octave (www.octave.org).

3. Results

3.1. Participants

In total, 46 participants with 47 screen-detected lung cancers based on a solid lung nodule found at ≥3 LDCTs before referral to a pulmonologist, were included. Mean age of these participants was 61.7 years (standard deviation, 6.2 years), 40 were male (87.0%). Twenty-seven participants (58.7%) were current smokers; mean smoked pack-years was 47.6 (21.1). Nodules were followed for a median of 770 days (IQR: 383–1102 days), before lung cancer was diagnosed. Median nodule size at baseline was 99.5 mm³ (IQR: 46.8–261.8 mm³). One cancer (2.1%) was referred for work-up and diagnosed after six CT examinations, six (12.8%) after five CTs, 14 (29.8%) after four CTs, and 26 cancers (55.3%) were diagnosed after three CT examinations.

3.2. Cancer characteristics

Lung cancer characteristics are presented in Table 1 . At time of diagnosis, the majority of lung cancers was stage I (35/47, 74.5%). Most cancers were adenocarcinoma (38/47, 80.9%). Furthermore, four squamous cell carcinomas (8.5%), one large cell carcinoma (2.1%), and one atypical carcinoid (2.1%) was found. Two cancers (4.2%) were diagnosed as non-small cell lung cancer not otherwise specified. One nodule (2.1%) was treated as a lung cancer by stereotactic radiotherapy, without final histological diagnosis.

3.3. Growth patterns

Good fit to exponential growth was confirmed by the high R^2 coefficient of determination for the individual cancer growth curves (median 0.98; IQR: 0.94–0.99). An overview of the R^2 coefficient of determination for the individual lung cancers is shown in Fig. 1. R^2 of pulmonary nodules found at ≥4 CT examinations before lung cancer diagnosis did not differ significantly from R^2 of nod-
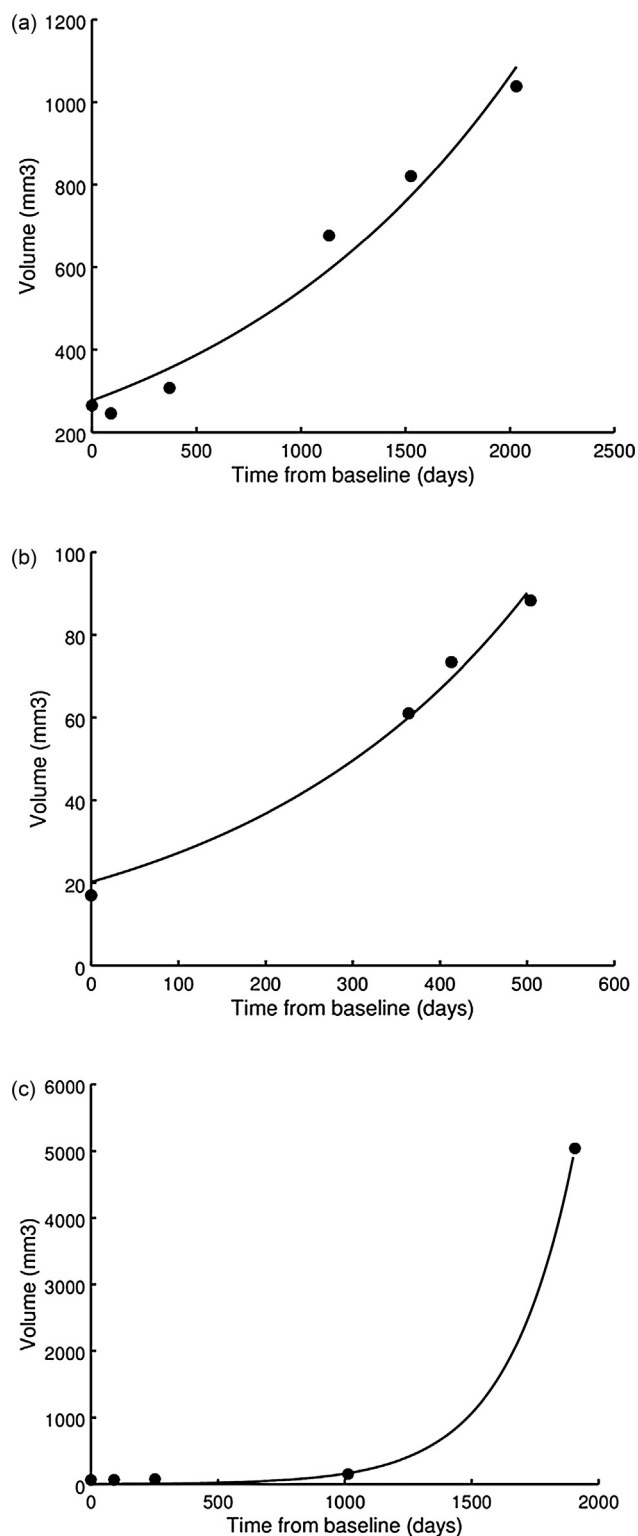
Fig. 3. Examples of lung cancer growth pattern. (a) Growth curve of a lung nodule that was detected on six subsequent CT examinations before lung cancer diagnosis was made. The nodule grew from 264.8 mm^3 at baseline to 1038.8 mm^3 at time of referral after the fourth screening round, 5.5-years after baseline. The exponential fit (using Eq. (1)), is nearly perfect ($R^2 = 0.97$), with estimated initial volume $V_1 = 276.5$ mm^3 and time constant $\tau = 1484$ days, resulting in an overall volume-doubling time (VDT) of 1027 days. (b) Growth curve of a lung nodule diagnosed as being malignant after four subsequent CT examinations. This nodule grew from 17.0 mm^3 at baseline to 88.3 mm^3 at time of referral after follow-up examination in the second screening round, 1.5-years after baseline. The fitted exponential (with

Table 1
Characteristics of solid lung cancers diagnosed after ≥3 CT examinations.

Characteristics	Lung cancer nodule ($n = 47$)
Histological type (n (%))	
Adenocarcinoma	38 (80.9)
Squamous cell carcinoma	4 (8.5)
Large cell carcinoma	1 (2.1)
Carcinoid	1 (2.1)
NSCLC, not specified	2 (4.2)
No histology obtained	1 (2.1)
Cancer stage (n (%))	
IA	33 (70.2)
IB	2 (4.3)
IIA	3 (6.4)
IIB	1 (2.1)
IIIA	4 (8.5)
IIIB	1 (2.1)
IV	3 (6.4)
Follow-up time after baseline (days)	
Median (IQR)	770 (383–1102)
Margin (n (%))	
Smooth	5 (10.6)
Lobulated	29 (61.7)
Spiculated	7 (14.9)
Irregular	6 (12.8)

Note: Unless otherwise indicated, data are numbers of nodules, with percentages in parentheses. IQR, inter-quartile range.

ules found at three CT examinations (median 0.97 [IQR: 0.91–0.99] versus 0.99 [IQR: 0.96–1.00], respectively [$p = $ NS]).

In Figs. 2 and 3, examples of, respectively, CT images and growth patterns of lung cancers are shown. Not all cancers showed a growth pattern with fast growth immediately from first detection; five nodules showed an almost constant (small) volume for at least 500 days before growth expansion and diagnosis of lung cancer, see Fig. 3c. Still, growth patterns of these nodules could be described by the exponential function with an excellent fit (median 1.00 [IQR: 0.98–1.00]). After normalization of volume measurements and of time from baseline for the individual lung cancers, linear growth on a logarithmic scale was found, indicative of an exponential growth pattern (Fig. 4).

3.4. Overall volume-doubling times

Median overall VDT from baseline until last screen evaluation before cancer diagnosis was 348 days (IQR: 222–492); range 80–4271 days. When comparing overall VDT of nodules followed for a different number of CT examinations before lung cancer diagnosis, VDT turned out to be lower in participants who received less CTs (median 270 days [IQR: 182–357 days] in case of three CTs, median 368 days [IQR: 305–554 days] in case of four CTs, and median 960 days [IQR: 462–1039 days] in case of five or six CTs [$p < 0.01$]). An overview of the number of lung cancers per overall VDT is shown in Fig. 5.

3.5. Non-fitting growth curves

Although most lung cancers showed an excellent fit to an exponential curve, there were some exceptions. Two cases with $R^2 < 0.5$ were visually re-evaluated. In one cancer, semi-automated volume measurements were not accurate since this nodule was pleural attached. In this case, the software was not able to differentiate

$R^2 = 0.99$) returns $V_1 = 20.2$ mm^3 and $\tau = 334$ days with overall VDT = 232 days. (c) Example of a cancer showing a period of constant small volume before growth expansion. Shown is the growth curve of a lung nodule that was detected on five subsequent CT examinations before lung cancer diagnosis was made. The nodule grew from 65 mm^3 at baseline to 5042 mm^3 at time of referral after the fourth screening round, 5.5-years after baseline.
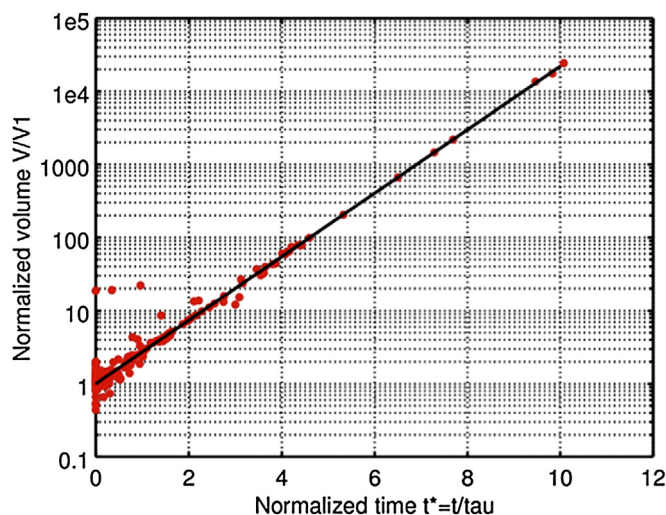
Fig. 4. Graph of normalized growth curves of the individual lung cancers. The y-axis represents normalized nodule volume (V/V_1) on a logarithmic scale. The x-axis represents normalized time $t^* = t/\tau$.
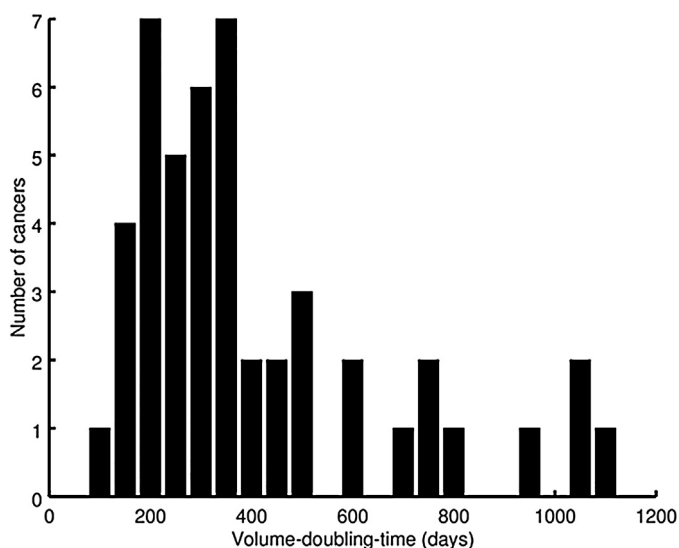

Fig. 5. Overall volume-doubling time (VDT) for 46 lung cancers. One case with outlier VDT of 4271 days was not depicted in this figure.

pleura from nodule and underestimated nodule volume, and the participant was referred based on visual nodule growth. The second case comprised a participant with a double tumor. The participant received a positive test result based on a larger, fast-growing nodule. At time of surgery, however, also a smaller nodule in another lobe was resected. This nodule turned out to be lung cancer as well.

4. Discussion

We show that growth of lung cancers, detected in a LDCT lung cancer screening trial, usually can be described by an exponential growth function. Information on growth patterns of lung cancer is of great importance, since after the introduction and continual improvement of CT, and the more recent introduction of lung cancer screening by LDCT, a large number of nodules with smaller dimensions is detected, most being benign [2–4]. For those small-to-intermediate sized pulmonary nodules, the definitive diagnosis still remains a dilemma for radiologists. As morphologic nodule evaluation alone is not sufficient [19], follow-up is necessary. For intermediate-sized nodules, the decision for (invasive) workup usually depends on growth rate. The malignant potential of these nodules is often suggested by rapid growth rate in terms of a short VDT [4,20]. The use of VDT, however, is based on the assumption of an exponential growth pattern of lung cancers.

This multi-center study is one of the first to actually quantify and confirm, not only by visual analysis, that growth in early lung cancers can be described by using an exponential function, and indicates that lung cancer growth can be monitored by the VDT as imaging biomarker. It provides unique insight in the natural behavior of lung cancer; a type of malignancy that, untreated, usually cannot be followed over a longer time period in clinical care.

The median overall VDT of lung cancers in this study was 348 days (IQR: 222–492 days), and comparable to VDTs reported in other lung cancer screening trials [21–23]. Since at least three monitoring points are necessary for growth pattern evaluation, lung cancers referred after the first short-term follow-up CT were not included in this analysis. The latter nodules usually show fast growth rates below 232 days [24].

It has been suggested that lung cancers grow according to a Gompartzian growth model, which means that growth rate slowly decreases to reach a certain plateau, after a period of exponential growth [25,26]. In the current study, in which the majority of lung cancers was early stage, we found that cancers showed exponential growth throughout the observational period. A decrease in growth rate was not observed possibly because tumors were too small to reach that point at diagnosis and participants were treated after lung cancer diagnosis was made.

Lindell et al. [5] were the first to plot growth curves of 18 lung cancers diagnosed after at least four serial CT examinations. It was concluded that lung cancer growth was not limited to an exponential pattern, and thus questioned the application of VDT as part of nodule management algorithms in LDCT lung cancer screening. That study, however, had some limitations. First, the majority of studied lung cancers ($n = 11$; 61%) was sub-solid. Volume for all nodules was calculated based on nodule diameter ($V = 1/6 * \pi * [ab^2]$, with a the longest and b the perpendicular diameter). Especially in sub-solid nodules, but also in solid nodules, diameter measurements are less accurate than volume measurements [7,8]. Furthermore, the study used relatively thick slice-thickness (3.75–5 mm) and large reconstruction intervals (5 mm) that may have contributed to even more imprecise diameter measurements, especially for sub-centimeter nodules. In the NELSON study, slice thickness of 1.0 mm with reconstruction interval of 0.7 mm was used to provide isometric voxels for accurate semi-automated volume measurements. These semi-automated measurements were found to be highly reproducible for the large majority of solid nodules, also in phantom studies [27–29], with high reader agreement and volume differences >15% between two readers in only 4% of solid nodules [27–29]. Besides, in Lindell's study lung cancer growth curves were plotted and visually evaluated, but growth patterns were not quantified. They only included lung cancers diagnosed after ≥4 CT examinations, since they stated that four was the minimal number of monitoring points required for generating growth curves [5]. We have included cancers diagnosed after three CTs as well. We found that the exponential fit in terms of the R^2 coefficient of determination of lung cancers diagnosed after ≥4 CTs was comparable to lung cancers diagnosed after three CTs.

A second study evaluated growth curves of thirteen primary lung cancers with at least three serial CT examinations [30]. Nodule volumes were derived semi-automatically. Analysis of lung cancer growth curves was limited, and restricted to a plot of the growth curves on a log scale, only analyzed visually. Growth rates appeared approximately constant on the log scale, consistent with exponential growth.

In our study, five of 47 lung cancers showed an almost constant (small) volume for at least 500 days before growth expansion and diagnosis of lung cancer. It is known that the carcinogenic process leading to lung cancer evolves slowly depending on the accumulation rate of DNA aberrations in the ancestor cells, for over 20 years [31]. In a screening setting, incidental detection of a slower growing cancer is more likely than it is in general practice. Another cause for the period of constant volume may be a proliferation rate in balance with the apoptotic rate.

In lung cancer screening programs and in clinical practice, nodule management is not only based on nodule size at first detection, but also on change in size in case of a prevalence nodule. In most diameter-based nodule management protocols, including the recently published Lung-RADS guideline [32], nodule growth is defined as a fixed increase in diameter, regardless of the time interval between two subsequent screenings. Our study suggests that this linear method cannot accurately represent the rate of nodule growth. A linear method might lead to false-negative classification of small, fast-growing cancers at short-term follow-up.

The major limitation of this study is the fact that only growth patterns of relatively slow-growing lung cancers (about one-fifth of total screen-detected cancers) could be evaluated, since more aggressive lung cancers did not have follow-up of at least three CT examinations but were earlier referred to a pulmonologist, which may limit the generalizability of our results. Compared to the overall group of screen-detected cancers in the first to third NELSON round, this study comprised more adenocarcinomas (80.9% versus 51.2%), known as a relatively slower growing type of lung cancer, whereas no small cell lung cancers (4.8% of total cancers), usually fast-growing and advanced staged, were followed by at least three CTs. Notwithstanding, the percentage stage I cancers in this study (74.5%) was comparable to the percentage stage I cancers in the overall group of cancers in the first to third screening round (70.9%).

4.1. Conclusion

This study based on CT lung cancer screening provides in vivo evidence that growth of cancerous small-to-intermediate sized lung nodules detected at LDCT lung cancer screening can be described by an exponential function such as volume-doubling time.

Conflicts of interest

Acknowledgements

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