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Lung cancer volume doubling time by computed tomography: A systematic review and meta-analysis

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ABSTRACT

Aim: Lung cancer growth rate influences screening strategies and treatment decisions. This review aims to provide an overview of primary lung cancer growth rate, quantified by volume doubling time (VDT) through computed tomography (CT) measurement.

Methods: Using PRISMA-DTA guideline, PubMed, EMBASE, and Web of Science were searched until March 2024 for studies reporting CT-measured VDT of pathologically confirmed primary lung cancer before intervention. Summary data were extracted from published reports by two independent researchers. Primary outcomes were pooled mean VDT of lung cancer by nodule type and histology, distribution of indolent lung cancer (defined as VDT>400 days or negative), and correlated factors.

Results: Thirty-three studies were eligible, comprising 3959 patients with primary lung cancer (mean age range:57.6–77.0 years; 60.0 % men). The pooled mean VDT for solid, part-solid, and nonsolid lung cancer were 207, 536, and 669 days, respectively ($p < 0.001$). When stratified by histology within solid lung cancer, the pooled mean VDT of adenocarcinoma, squamous cell carcinoma, small cell lung cancer, and others were 223, 140, 73, and 178 days, respectively ($p < 0.001$). Indolent lung cancer was observed in 34.9 % of lung cancer, predominantly in adenocarcinoma (68.9 %). Adenocarcinoma was associated with slower growth, whereas factors such as tumor size, solidity, TNM staging, and smoking history were positively associated with growth rates.

Conclusions: Pooled mean VDT of solid lung cancer was approximately 207 days, demonstrating significant variability in histology yet remaining under the 400-day referral threshold. Key predictors of growth rate include histology, size, solidity, and smoking history, essential for tailoring early intervention strategies.

Trial registration number: CRD42023408069

1. Introduction

Lung cancer represents a major global health concern, contributing to 11.6 % of all cancer diagnoses and 18.4 % of cancer-related mortality in both men and women worldwide. [1] Large-scale lung cancer screening trials, such as the National Lung Screening Trial (NLST) and

Abbreviations: VDT, volume doubling time; CT, computed tomography; NLST, National Lung Screening Trial; NELSON, the Dutch-Belgian Randomized Lung Cancer Screening Trial; SD, standard deviation; IQR, interquartile range; 95 % CI, 95 % confidence interval.

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the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), have underscored the value of early detection in significantly reducing lung cancer mortality. [2–4].

Understanding the growth rates of lung cancer is paramount, especially when considering implications for screening and clinical interventions. Despite the prevailing view of lung cancer as uniformly aggressive, recent evidence reveals indolent lung cancers do exist and are more prevalent than previously believed, accounting for 3 % to 45 % of cases. [5] Furthermore, lung cancer growth rates show considerable variability, potentially influenced by a range of factors, including patient factors (eg. gender, age, and smoking history) and tumor-specific factors (eg. tumor size, nodule type, clinical stage, histology subtypes, and genetic mutation). [6–8].

Volume doubling time (VDT), defined as time taken for a tumor to double in volume, is a pivotal imaging metric for assessing lung cancer growth. [9] While individual studies have reported VDT across various contexts— ranging from screening programs to clinical evaluations across different histologies and nodule types— the lack of a comprehensive synthesis limits the application of these insights.

Addressing this gap, our systematic review and meta-analysis seek to provide a comprehensive overview of primary lung cancer growth rates, assessed through CT-measured VDT. Our study synthesizes VDT data across nodule types and histologies, examines the distribution of growth rates, and investigates the factors influencing these growth rates.

2. Methods

2.1. Data sources and searches

PubMed, Embase, and Wed of Science databases were searched for articles published until March 2024. The search strategy used various keyword combinations related to volume doubling time, lung cancer, and computed tomography. The search was restricted to human studies and articles published in English. The study was conducted in accordance with Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. [10] Additional details regarding the search strategy can be found in Supplementary Table 1.

2.2. Study selection

Two reviewers (B.J. and D.H.) independently reviewed all titles and abstracts, and subsequently full-text articles according to prespecified eligibility criteria, with disagreements resolved through deliberations to reach a consensus. Studies from both screening and clinical settings were included when they: 1) reported CT-measured VDT; 2) included pathologically confirmed primary lung cancer; 3) had no intervening invasive diagnostic procedures or treatments before VDT calculation. Articles were excluded when they: 1) were reviews, abstracts, case reports, or letters; 2) lacked detailed information on histological subtypes necessary to confirm primary lung cancer; 3) reported VDT data exclusively for specific subgroups (e.g., COPD vs. non-COPD or detailed histological subtypes of adenocarcinoma) without an overall VDT estimate for the entire cohort; 4) had a sample size < 20. If publications used overlapping cohorts of patients, we used data from the study that provided the most detailed information on lung cancer growth rates.

Articles were subsequently included in the meta-analysis if they: 1) reported lung cancer VDT differentiated by nodule type (solid, part-solid, and nonsolid) or histological subtype (adenocarcinoma, squamous cell carcinoma, small cell lung cancer, and other lung cancer); 2) provide sufficient statistical VDT data, including mean with standard deviation (SD) or median with interquartile range (IQR). Articles were excluded from meta-analysis if the median/mean CT interval was < 90 days to ensure the reliability of the VDT estimations.

2.2.1. Data extraction and quality assessment

A standardized data extraction form was used to collect the following items: characteristics of the study (geographical region, study date, sample size, and study type), characteristics of the patient cohort (gender, age, and smoking status), and characteristics of lung cancer (histology, nodule type, tumor stage, and tumor size) and relevant data characterizing VDT (measurement method, scan interval, VDT estimates) or factors correlated with growth rates. Two reviewers (B.J. and D.H.) collected data independently. Disagreement in data collection was resolved by consensus. Most included studies reported summary measures for VDT (mean with SD, median with IQR, and range). Studies with original data on tumor volume at different time points and scan intervals, permitting calculation of VDT, were collected if available. Calculation of VDT in days, when needed, was performed using Schwarz's formula [11]: $VDT = [(T - T0)\ln 2]/[\ln(V/V0)]$, where V and V0 are tumor volumes at time point T and T0, respectively, and ln is natural logarithm. In cases where studies utilized both diameter and volumetric methods to assess growth rates, preference was given to data derived from volumetric measurements for analysis. For adenocarcinoma, we included only invasive adenocarcinoma, excluding pre-invasive and minimally invasive adenocarcinoma to ensure data consistency across studies. For subsolid lung cancer, VDT calculated based on whole volume was extracted across all studies. We also collected VDT distribution and reported factors correlated with growth rate.

The two reviewers assessed the risk of bias for each study using a modified Newcastle-Ottawa scale [12] (Supplemental Table 2), which assesses selection of the patient cohort and adequacy of assessing the outcome of interest. Specifically, quality assessment was based on sample size, potential selection bias, representativeness of patient cohort, imaging quality, bias in assessing outcome, and appropriateness of statistical analysis. Disagreement in quality assessment was resolved by consensus. For each study, a quality score was calculated by assigning one point for each "yes" item and zero points for each "no" item, resulting in a total possible score of 9. A score ≥ 7 points was considered indicative of high quality, a score between 4–6 points indicated moderate quality, and a score ≤ 3 indicated low quality.

2.2.2. Data synthesis and analysis

We aimed to characterize tumor growth rates by CT-measured VDT (defined in days) and categorized them into different growth rate categories. In alignment with the predominantly adopted VDT cut-off of 400 days proposed by Yankelevitz et al [13], we defined rapid growth as VDT $\leq$ 400 days [14], slow growth as VDT $>$ 400 days, and shrinkage as VDT< 0 days. [5] The latter two categories are collectively classified as indolent lung cancer, defined as VDT$>$ 400 or < 0 days, which also implicitly included lung cancers that remain stable, leading to an infinite or extremely long VDT. The pooled mean VDT was obtained by calculating the mean and SD, or by deriving the estimated mean and SD using the formula provided by Wan et al, which considers the sample size, median, and IQR. [15] The pooled estimate of VDT was then calculated by pooling study-specific estimates using a random-effects model. Heterogeneity was assessed graphically using forest plots and statistically using the inconsistency index (I^2 with an I^2 of >75 % indicating significant heterogeneity). We conducted pre-planned subgroup analyses by region (Asian vs non-Asian), study type (screening vs clinical), and measurement method (volumetric and diameter) to explore potential differences. In addition to between-study analyses, we also examined within-study factors correlated with tumor growth rate. For statistical analyses, a two-sided p-value < 0.05 was considered significant. All data analyses were conducted using Stata V.14.2 (StataCorp LP, College Station, Texas). This study is registered with PROSPERO, CRD42023408069.

3. Results

3.1. Study selection

The electronic search of three databases returned 1874 results and then narrowed to 108 studies after a review of study titles and abstracts. After a full-text review, a total of 33 studies were included in the analysis until March 2024 (Figure 1). Seventeen studies were included in the meta-analysis of pooled mean VDT of lung cancer grouped by nodule types and histology subgroups. Detailed characteristics, eligibility criteria, and interventions of the included lung cancer screening trials can be found in Supplemental Table 3.

3.2. Study characteristics

Thirty-three studies included a total of 3959 participants diagnosed with primary lung cancer (Table 1). Mean or median patient age ranged from 57.6 to 77.0 years, with 60.0 % being male. Median sample size was 51 (IQR:24–112) cases. Geographically, 20 studies (60.6 %) were conducted in Asia, seven (21.2 %) in USA and six (18.2 %) in Europe. 25

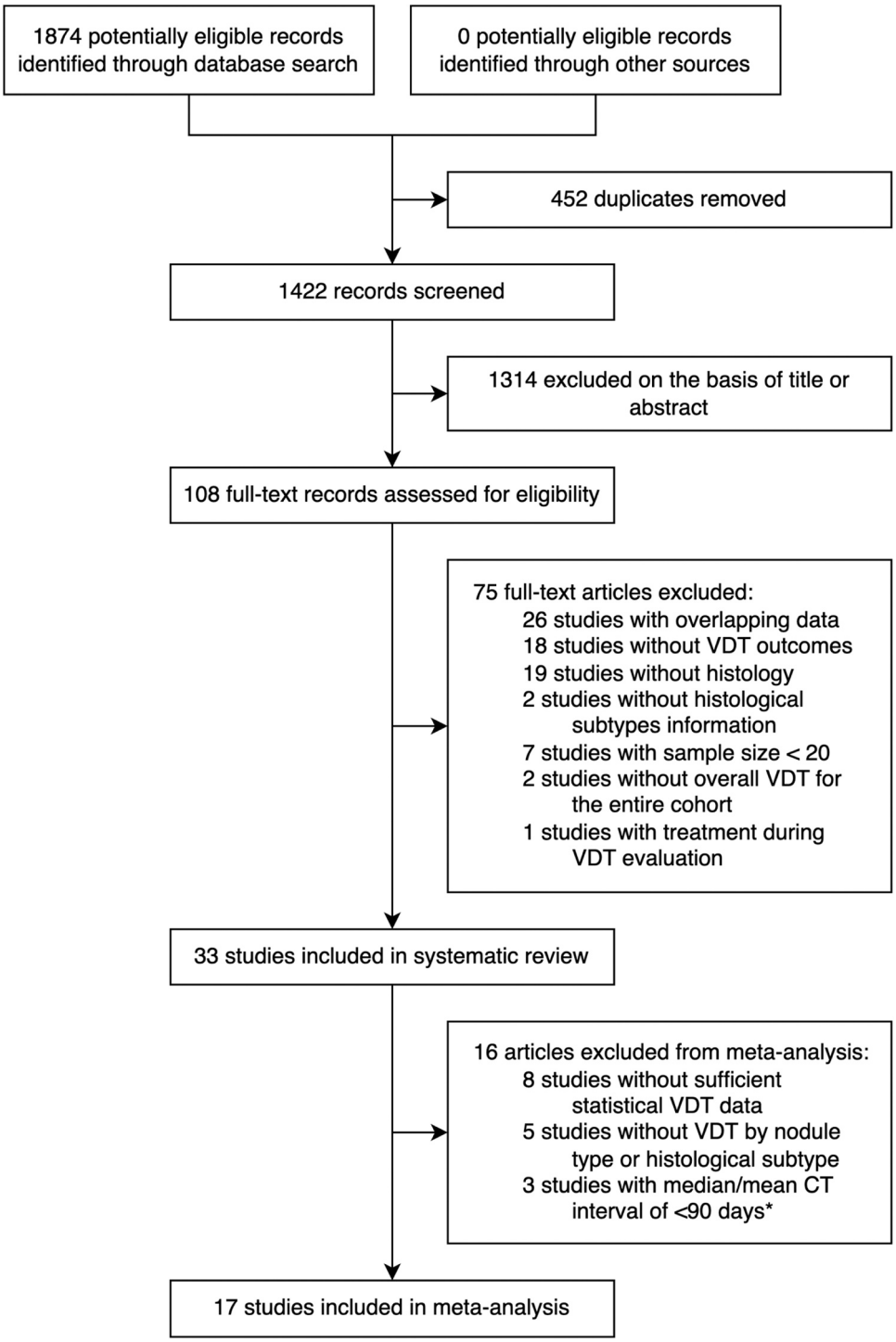

Fig. 1. Study selection. *An exception was made for Jiang (2023), where 27 small cell lung cancer cases with a 58-day follow-up were included in the meta-analysis, as its rapid growth allows for significant changes in shorter intervals. VDT, volume doubling time.

Table 1
Characteristics of studies included in the systematic review.

Study	Study site	Period	Study type	Measurement	Patients	Male	Age*	Smoker	Histology	TNM stage	Nodule type	Size*	Volume doubling time (days)			
author year					*n*	*%*	*years*	*%*	*ad/sq/sc/o*	*I/II/III/IV*	*S/PS/NS*	*mm*	*mean±SD*	*median (IQR)*	*min*	*max*
All lung cancer																
Hasegawa 2000[6]	Japan	1996 –1998	Screening	Diameter	61	62.3	65.0	49.2	49/8/4/0	54/3/3/1	23/19/19	11.4[#]	452 ± 381		52	1733
Jennings 2006[29]	USA	1996 –2004	Clinical	Volumetric	149	99.3	72.0		70/48/0/31	149/0/0/0	149/0/0		161 ± 117	207	26	
Lindell 2007[52]	USA	1999 –2004	Screening	Diameter	48	37.5	65.0	100.0	31/8/3/6	34/6/5/0	25/15/8	16.4	518 ± 1094	166	10	5810
Quint 2008[53]	USA	2002 –2006	Clinical	Volumetric	33	48.1	65.3		15/11/4/3		33/0/0	11 –17[#]			23	2239
Honda 2009[16]	Japan	2001 –2006	Clinical	Volumetric	51	68.6	66.5		40/11/0/0	37/7/11/1	51/0/0	20 –22[#]	248 ± 188	200 (106 –336)	39	18678
Mikita 2012[26]	Japan	1996 –2009	Clinical	Diameter	34	61.8	67.4	73.5	20/7/1/5		34/0/0		325		47	2629
Murai 2012[54]	Japan	2004 –2010	Clinical	Diameter	201	68.7	77.0		135/66/0/0	201/0/0/0				131		
Veronesi 2012[17]	Italy	2004 –2005	Screening	Volumetric	120	70.0	57.7	100.0	89/13/9/9	80/14/17/8		11.4		240	18	2555
Wang 2012[55]	USA	2003 –2010	Clinical	Volumetric	34	67.6	68.0		6/12/0/16	5/5/22/2	34/0/0			139		
Wilson 2012[18]	USA	2002-	Screening	Volumetric	63	50.8	51 –82	100.0	46/8/0/9	(45)/(18)				357 (236 –630)		4263
Heuvelmans 2013 [14]	Netherlands	2004 –2007	Screening	Volumetric	27	85.2	63.8	100.0	15/6/1/5		27/0/0			198 (122 –264)		
Koike 2014[22]	Japan	2006 –2009	Clinical	Volumetric	71	70.6	65.0		64/7/0/0		33/23/14	19 –22			41	3829
Mackintosh 2014 [19]	Australia	2003 –2011	Clinical	Volumetric	46	54.3	69.0	82.6	36/6/0/4	31/6/9/0	46/0/0	20.5		191	54	2256
Nakamura 2014 [21]	Japan	2006 –2013	Clinical	Diameter	102	61.8	71.0	64.7	69/23/0/10	80/12/8/2		29.2	619 ± 1236	188	24	9686
Walter 2016[30]	Netherlands	2003 –2006	Screening	Volumetric	50	85.7	61.0	100.0	19/11/5/15	34/3/10/0	50/0/0			139 (104 –211)		
Ostrowski 2019[56]	Poland	2009 –2017	Screening	Volumetric	212	59.0	62 –67	100.0	128/53/17/14					112		1426
Setojima 2020[57]	Japan	2012 –2015	Clinical	Diameter	258	59.3	67.0	68.6	191/(67)	243/15/0/0	160/98/0		375 ± 745			6359
Zhang 2020[57]	China	2010 –2017	Clinical	Volumetric	219	35.6	59.0	21.5	208/7/0/4		72/70/77	18.5		526		
Yamamichi 2021 [58]	Japan	2007 –2020	Clinical	Volumetric	100	86.0	70.0		51/32/0/17	67/15/18/0	100/0/0			204 (103 –448)		
Adler 2022[28]	USA	2016 –2020	Clinical	Diameter	158	48.7	69.0	74.7	113/25/0/20	158/0/0/0	158/0/0	< 30		254 (138 –450)		
Nakahashi 2022 [20]	Japan	2006 –2020	Clinical	Diameter	284	66.5	70.0	69.7	200/65/0/19	237/29/18/0	284/0/0	18.0		347 (134 –777)	9	27210
Karita 2023[59]	Japan	2013 –2021	Clinical	Diameter	560	61.3	69.2		420/112/0/28	411/81/60/8		25.2				
Adenocarcinoma																
Sone 2012[60]	Japan	2001 –2005	Screening	Volumetric	32	31.3	62.0	25.0	32/0/0/0	66/2/4/0	6/35/27	9.6	662 ± 398	467 (356 –934)	138	1357
Borghesi 2016[61]	Italy	2004 –2014	Clinical	Volumetric	22	63.2	67.4	94.7	22/0/0/0		0/17/5	20.8		729 (461 –953)	259	2196
Li 2018[23]	China	2011 –2016	Clinical	Volumetric	114	54.5	61.2		114/0/0/0		40/45/29	15.8				

(*continued on next page*)

Table 1 (*continued*)

Study	Study site	Period	Study type	Measurement	Patients	Male	Age*	Smoker	Histology	TNM stage	Nodule type	Size*	Volume doubling time (days)		
de Margerie-Mellon 2020 [25]	USA	2005 –2018	Clinical	Volumetric	20	30.4	70.0	78.3	20/0/0/0		0/24/50		678 (392 –916)		
Park 2020 [62]	Korea	2010 –2018	Clinical	Volumetric	268	53.4	64.0	41.8	269/0/0/0	212/22/34/0	100/120/48	21.1	529 (278 –872)	31	2911
Yoon 2020 [63]	Korea	2003 –2011	Clinical	Volumetric	52	50.0	60.1	34.6	52/0/0/0			22#	1159 ± 2015		
Qi 2021 [64]	China	2012 –2019	Clinical	Volumetric	47	34.5	57.6		95/0/0/0		0/22/25	15.0	1436 ± 1188		
Tan 2021 [24]	China	2012 –2018	Clinical	Volumetric	407	60.4	58.5	93.4	407/0/0/0	407/0/0/0	82/165/160	8.9			
He 2023 [65]	China	2007 –2021	Clinical	Volumetric	24	31.6	65.5	82.9	24/0/0/0		0/0/24	7.4#	969 ± 490		
Squamous cell lung cancer Sugawara 2023 [66]	Japan	2014 –2019	Clinical	Diameter	65	84.6	72.8	96.9	0/65/0/0	55/8/2/0	58/(7)		137 (75 –261)		
Small cell lung cancer Jiang 2023 [27]	China	2015 –2022	Clinical	Volumetric	27	92.6	64.8	77.8	0/0/27/0	14/6/7/0	27/0/0	17.9	71 (49 –103)		

The studies are grouped by the histology type investigated (all lung cancer types or specific histological subtypes). *Indicates that data is presented by mean or median (or range of mean/median). Histology is ordered by ad/sq/sc/o (adenocarcinoma/squamous cell carcinoma/small cell lung cancer/other lung cancer). Nodule types are ordered by S/PS/NS (solid/part-solid/nonsolid). Default sizes are based on preoperative CT scans; sizes marked with # indicate measurements from initial CT scans. Blank cells indicate that information was not provided in the studies. Adeno, adenocarcinoma; USA, United States of America. SD, standard deviation; IQR, interquartile range.

(75.8 %) were clinical studies and eight (24.2 %) were lung cancer screening studies. 23 studies (69.7 %) used volumetric measurement method and 10 (30.3 %) used diameter method. Regarding histology, 22 studies (66.7 %) investigated all lung cancer histology, while nine (27.3 %) focused only on adenocarcinoma, one (3.0 %) on squamous carcinoma, and one (3.0 %) on small cell lung cancer. For clinical studies, 21 studies obtained histology results from surgical resections, one via fine-needle aspiration biopsy, and three through pre-radiation therapy cohort. Screening studies utilized combined methods to obtain histology results.

3.3. Pooled mean volume doubling time

Our meta-analysis, integrating data from 17 studies and encompassing 1343 cases of primary lung cancer, reveals substantial heterogeneity in tumor growth rates, stratified by nodule type and histology. The pooled mean VDT of lung cancer across all nodule types was 440 days (95 %-CI:381–500). Solid lung cancer exhibited the shortest pooled mean VDT at 207 days (95 %-CI:166–247) with heterogeneity (I^2 =88.3 %, $p < 0.001$). In contrast, part-solid and nonsolid lung cancer had significantly longer VDTs of 536 days (95 %-CI:321–750) and 669 days (95 %-CI:480–950), respectively (Fig. 2a). In subgroup analyses for solid lung cancer, no significant difference was found by study type, region, and measurement method ($p > 0.05$) (Supplement Figure 1).

When delving into histological subtypes within solid lung cancers (Fig. 2b), small cell lung cancer presented the most rapid growth with a pooled mean VDT of 73 days (95 %-CI:60–87), followed by squamous cell carcinoma and other lung cancer of 140 days (95 %-CI:126–155) and 178 days (95 %-CI:138–218), respectively. Solid adenocarcinoma showed the slowest VDT of 223 days (95 % CI: 187–259) with heterogeneity (I^2 =75.4 %, $p < 0.001$). For part-solid and nonsolid adenocarcinoma, VDTs were substantially prolonged, observed at 536 days and 863 days, respectively. Overall, adenocarcinomas across all nodule types showed a mean VDT of 539 days (95 % CI: 494–583) (Fig. 2c). Regional subgroup analyses for solid adenocarcinoma indicated significant differences ($p < 0.001$), with a shorter VDT in non-Asia of 207 days compared to 262 days in Asia, whilst no significant difference was observed by study type and measurement method ($p > 0.05$) (Supplement Figure 2).

3.4. Distribution of lung cancer growth rates

From 1761 patients with primary lung cancer across twelve studies provided VDT distribution by cut-off of 400 days, 34.9 % (347/993) of lung cancer across all histology were classified as indolent lung cancer (VDT>400 or <0 days) (Table 2a). Adenocarcinoma had the highest proportion at 68.9 % (593/861), whereas squamous cell carcinoma, small cell lung cancer, and other lung cancers were less likely to be indolent, at 3.0 % (1/33), 0.0 % (0/30), and 21.1 % (4/19), respectively (Table 2b).

3.5. Factors correlated with growth rate within studies

Table 3 summarises factors investigated for their correlation with growth rate in lung cancer across individual studies. Histology was identified as the most significant factor associated with growth rate, with adenocarcinoma consistently linked to slow growth. [6,16–20] Three studies found TNM stage was positively associated with rapid growth. [17,20,21] Increased solidity was found to be associated with rapid growth. [6,22–24] Additionally, four studies reported a positive link between initial size and rapid growth in all lung cancer [20,21] and adenocarcinoma. [24,25].

Patient demographics, including sex, [6,18–20,24–27] age, [17,18,20,21,24,26,27] and smoking pack-years, [17–19,25] generally showed no significant association with growth rate. Four studies found that smokers tend to have more rapid growth of lung cancer than

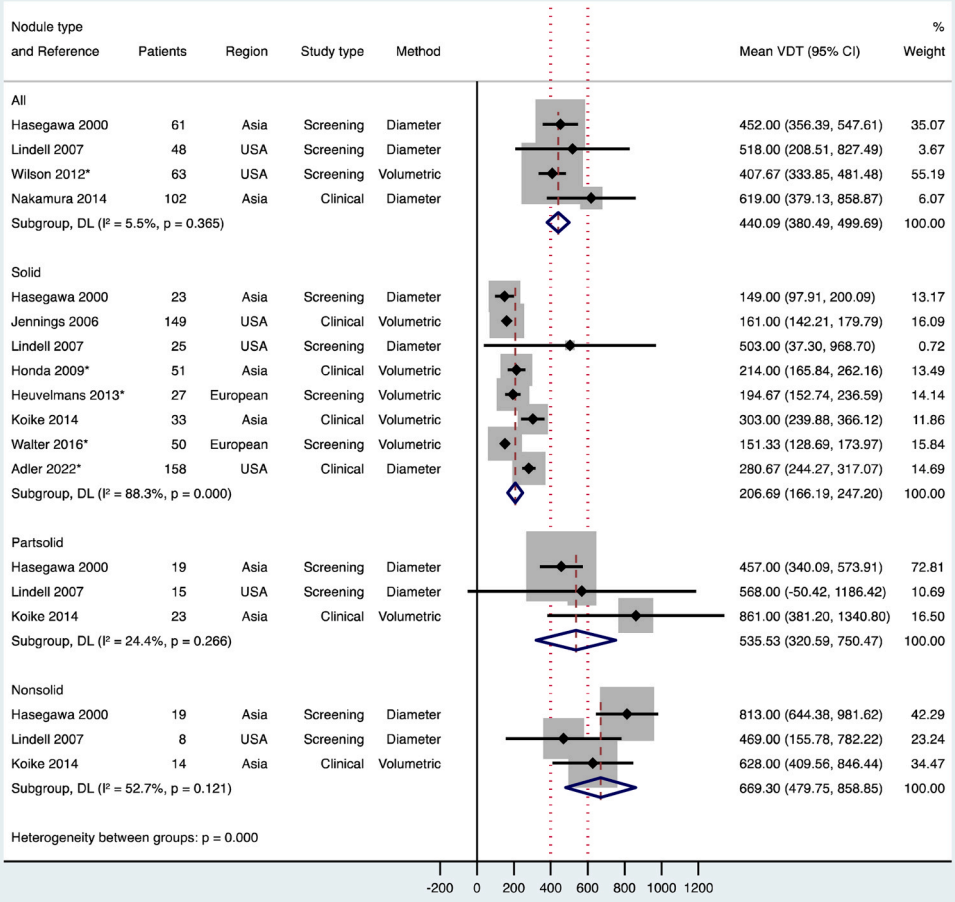

Fig. 2. (a) Forest plot, pooled mean volume doubling time for lung cancer by nodule types. *Indicates mean VDT (95 % CI) of the study was estimated from median and interquartile range. Red dashed lines represent reference VDTs of 400 and 600 days. VDT, volume doubling time; 95 % CI, 95 % confidence interval. Fig. 2**b** Forest plot, pooled mean volume doubling time for solid lung cancer by histology.*Indicates mean VDT (95 % CI) of the study was estimated from median and interquartile range. Red dashed lines represent reference VDTs of 100, 200, 300, and 400 days. VDT, volume doubling time; 95 % CI, 95 % confidence interval. Fig. 2**c** Forest plot, pooled mean volume doubling time for adenocarcinoma by nodule types. *Indicates mean VDT (95 % CI) of the study was estimated from median and interquartile range. Red dashed lines represent reference VDTs of 400 and 600 days. VDT, volume doubling time; 95 % CI, 95 % confidence interval.

non-smokers across all histology [6,19,21,26], however, this trend does not reach statistical significance within specific histological subtypes such as adenocarcinoma [24,25] and small cell lung cancer [27].

3.6. Study quality

Quality assessment results are presented in Supplemental Table 3. Among the 33 included studies, 18 (54.5 %) were rated as high quality, 13 (39.4 %) as moderate quality, and only two (6.1 %) as low quality which were excluded from the meta-analysis. Several factors influenced the quality of the studies. Firstly, eight (24.2 %) studies employed specific inclusion criteria, such as focusing exclusively on stage I lung cancer [20,24,28,29] and new nodules, [30] which limited the scope and generalisability of the findings. Secondly, ten (30.3 %) studies had small sample sizes of less than 50 patients, which could diminish the statistical power and hence the conclusiveness of those studies. Finally, ten (30.3 %) studies used non-volumetric method to assess VDT, which may compromise measurement precision and affect the validity of the VDT estimations presented.

4. Discussion

Our systematic review analyzed data from 33 studies encompassing 3959 patients to provide a nuanced understanding of lung cancer growth rate via CT-measured volume doubling time (VDT). We observed significant variations in VDTs across different lung cancer types, with solid, part-solid, and nonsolid lung cancer demonstrating pooled mean VDT of 207, 536, and 669 days, respectively ($p < 0.001$). For histological subtypes, pooled mean VDT of adenocarcinoma, squamous cell carcinoma, small cell lung cancer, and others were 223, 140, 73, and 178 days, respectively ($p < 0.001$). Indolent lung cancer, characterized by a VDT of > 400 or < 0 days, was observed in 34.9 % of all lung cancer cases, most prominently in adenocarcinoma at 68.9 %. Factors associated with rapid growth included non-adenocarcinoma histology, larger tumor size, higher solidity, higher TNM staging, and smoking history, while patient demographics like sex, age, and smoking pack years lacked a significant correlation with growth rates.

Our meta-analysis provides critical insights for refining current screening protocols. Our research validates the ≤ 400 days VDT as a robust threshold for clinical referrals, with solid lung cancer consistently below this cut-off (Figure 3). In Table 4, we demonstrate varied growth

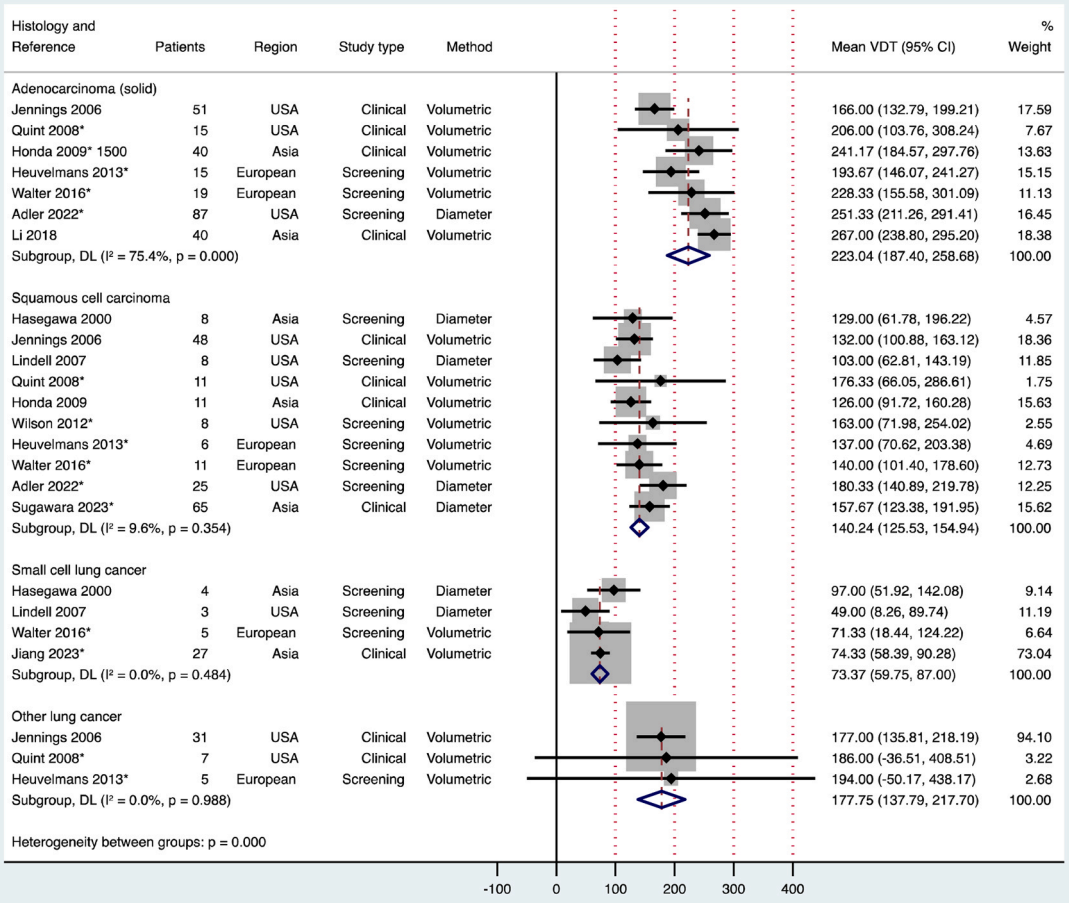

Fig. 2. (*continued*).

trajectories based on pooled mean VDT for different lung cancer types, illustrating the need for tailored follow-up strategies. Annual screening is sufficient for most solid lung cancers, however, the aggressive growth of small cell lung cancer, with a VDT of 73 days and a 31-fold annual volume increase, necessitates more frequent follow-ups to ensure timely detection. This aligns with Fleischner Society's guidelines and NELSON+ protocols, the latter recommend three-month follow-ups for indeterminate nodules ranging 100–300mm^3 . [9,31] Conversely, the longer VDT for part-solid (536 days) and nonsolid (669 days) lung cancers suggests adopting more lenient VDT cut-offs—600 days for part-solid nodules and 800 days for nonsolid nodules. These adjusted VDT cut-offs could serve as a guideline for close follow-up (eg. 1 year) rather than immediate intervention, to monitor the subsolid nodules until significant growth or an accelerated growth rate in the solid component is detected, ensuring interventions are reserved for clinically justified cases to prevent overdiagnosis and overtreatment of indolent lung cancers. Our findings also support the feasibility of biennial screenings for subsolid nodules, which could reduce the burden on patients and healthcare systems without compromising early cancer detection. Furthermore, in line with Fleischner Society recommendations, we advocate extending follow-up periods for subsolid nodules to up to at least five years to confirm stability and effectively rule out cancer [31–34].

Additionally, our findings highlight the potential of using pooled mean VDT as a pre-biopsy predictor of histological subtype. For example, faster-growing nodules with shorter VDTs may indicate more aggressive cancer types, such as small cell lung cancer (mean VDT ~70 days) or squamous cell carcinoma (mean VDT ~140 days), while slower-growing nodules could suggest adenocarcinoma (mean VDT ~220 days). This predictive capability aids clinicians in making more informed decisions regarding patient management and treatment options.

This review is the first to aggregate data on CT-measured VDT for primary lung cancer. A previous review by Geddes et al. in 1979 reported shorter VDTs based on radiographic measurements, with a mean VDT of 102 days for lung cancer, including squamous and adenocarcinoma subtypes at 88 and 161 days, respectively. [35] This finding aligns with previous reviews that lung cancer found by CT had markedly longer VDT compared to chest radiography, especially in adenocarcinoma. [36,37] This variance is largely attributed to CT's superior sensitivity in detecting early-stage lung cancer, including small and subsolid types, typically exhibiting a longer VDT, which is often overlooked by traditional radiography.

Our study also detailed adenocarcinoma's growth variability across nodule types. Solid adenocarcinomas, with a relatively rapid mean VDT of 223 days, exhibit faster growth than part-solid and nonsolid, which have VDTs of 536 and 863 days, respectively. Subsolid adenocarcinomas, predominantly found in Asian populations, typically mark the initial phase of tumor development. [32,33] They begin as ground-glass opacities, with tumor cells proliferating along the surface of intact alveolar walls without stromal or vascular invasion, and progress to increased consolidation as they gradually fill the alveolar spaces—a process known as lepidic growth. [38,39] During this transition, the growth rates evolve, reflecting the morphological changes as the tumor

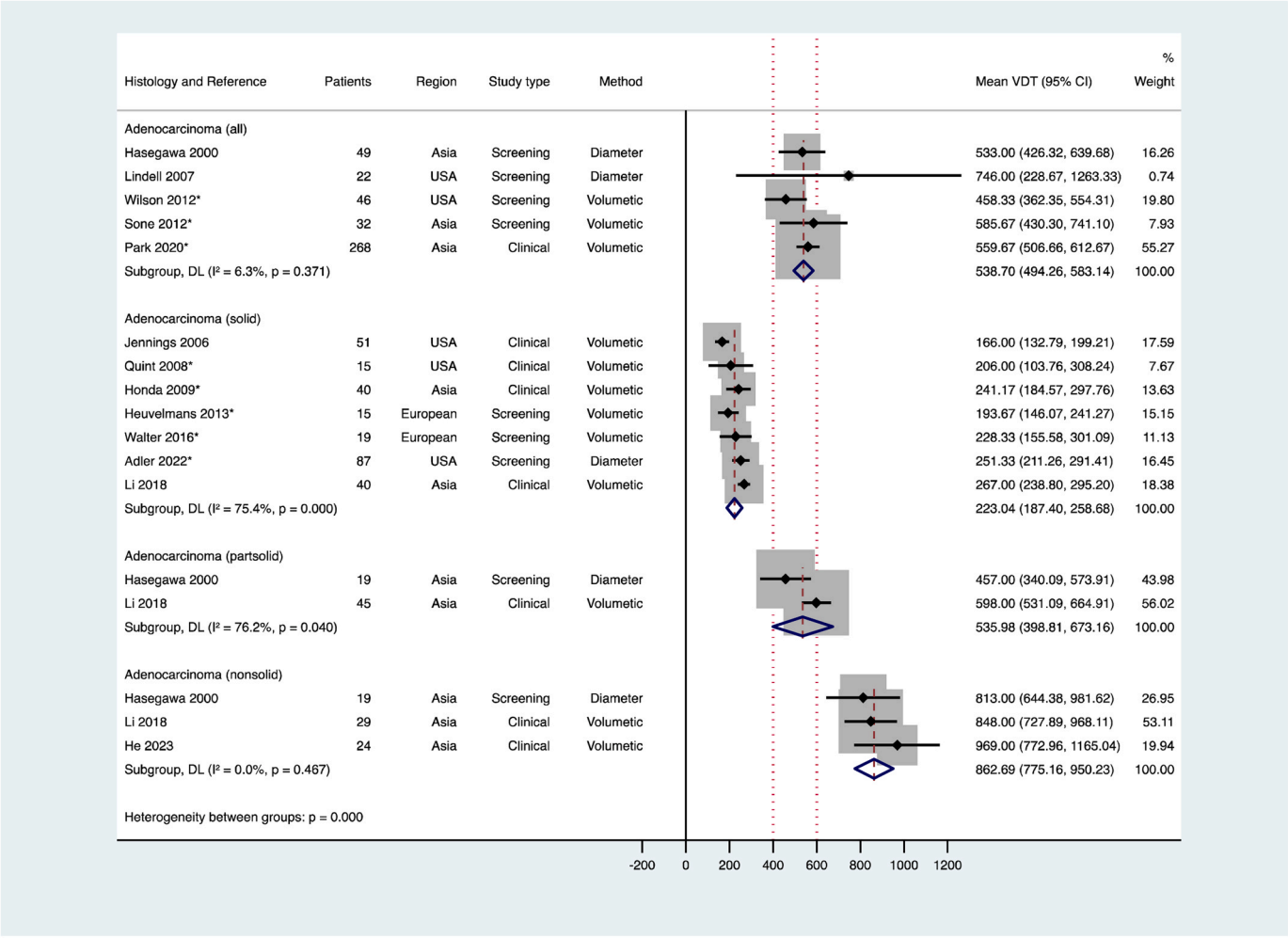

Fig. 2. (*continued*).

Table 2a
Distribution of lung cancer growth rates.

Study	Patients	Male	Adeno	Solid		Indolent lung cancer		
					Rapid growth VDT≤ 400d	Slow growth VDT> 400d	Shrinkage VDT < 0d	Total VDT> 400 or < 0d
author year	*n*	*%*	*%*	*%*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Lindell 2007[52]	48	37.5	64.6	52.1	16 (33.3)	13 (27.1)		13 (27.1)
Honda 2009[16]	51	68.6	78.4	100.0	35 (68.6)	11 (21.6)	5 (9.8)	16 (31.4)
Mikita 2012[26]	34	61.8	58.8	100.0	25 (73.5)	9 (26.5)		9 (26.5)
Veronesi 2012[17]	120	70.0	74.2		89 (74.2)	31 (25.8)		31 (25.8)
Wilson 2012[18]	63	50.8	73.0		33 (52.4)	30 (47.6)		30 (47.6)
Koike 2014[22]	71	70.6	90.1	46.5	36 (50.7)	23 (32.4)	12 (16.9)	35 (49.4)
Mackintosh 2014[19]	46	54.3	78.3	100.0	33 (71.7)	9 (19.6)	4 (8.7)	13 (28.3)
Karita 2023[59]	560	61.3	75.0		360 (64.3)	200 (35.7)		200 (35.7)
Total	**993**	**61.2**	**78.3**		**627 (63.1)**	**326 (32.8)**	**21 (2.1)**	**347 (34.9)**

The distribution of lung cancer growth rates is categorized into rapid growth (VDT≤400 days), slow growth (VDT>400 days), and shrinkage (VDT<0 days), as observed across various studies. The latter two categories are collectively referred to as indolent lung cancer, defined as VDT> 400 or < 0 days. Blank cells indicate that information was not provided in the studies. VDT, volume doubling time; d, days.

progresses from a noninvasive state towards an invasive state. [40–42].

In subgroup analyses, regional differences were noted, with solid adenocarcinomas in Asia showing longer VDT compared to non-Asian regions (262 vs 207 days, $p < 0.001$). This variation may be due to genetic factors, as approximately one-third of lung cancer patients in East Asia are never smokers, and no major environmental risk factors have been identified in these populations, suggesting a genetic predisposition. [43] EGFR mutations are more prevalent in Asians (40–55 %) compared to Caucasians (15–25 %), [44] while KRAS mutations, more common in smokers, are less frequent in Asians (5–11 %) than in Western populations (20–26 %). [45] These genetic differences could influence the growth rates of lung cancer across regions.

No significant differences were found in VDT outcomes between measurement methods (volumetric vs. diameter). This consistency across measurement methods is likely due to the inclusion of studies that measured VDT for pathologically confirmed lung cancers, where the mean/median tumor diameters were generally greater than 10 mm, and most often around 20 mm. At these sizes, measurements are more

Table 2b
Distribution of lung cancer growth rates by histology.

Study	Patients	Solid		Indolent lung cancer		
			Rapid growth VDT≤ 400	Slow growth VDT> 400d	Shrinkage VDT < 0d	Total VDT> 400 or < 0d
author year	*n*	*%*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Adenocarcinoma						
Lindell 2007[52]	31	35.2	18 (58.1)	13 (41.9)		13 (38.2)
Honda 2009[16]	40	100.0	24 (60.0)	11 (27.5)	5 (12.5)	11 (40.0)
Wilson 2012[18]	46		20 (43.5)	26 (56.5)		26 (56.5)
Sone 2012[60]	32	13.3	4 (12.5)	25 (78.1)	3 (9.4)	25 (87.5)
Mackintosh 2014[19]	36	100.0	24 (66.7)	9 (25.0)	3 (8.3)	9 (33.3)
Park 2020[63]	269	37.2	101 (37.5)	168 (62.5)		168 (62.7)
Tan 2021[24]	407	41.0	77 (18.9)	330 (81.1)		330 (81.1)
Total	**861**		**268 (31.1)**	**582 (67.6)**	**11 (1.3)**	**593 (68.9)**
Squamous cell carcinoma						
Lindell 2007[52]	8	85.7	8 (100.0)	0 (0.0)		0 (0.0)
Honda 2009[16]	11	100.0	11 (100.0)	0 (0.0)		0 (0.0)
Wilson 2012[18]	8		7 (87.5)	1 (12.5)		1 (12.4)
Mackintosh 2014[19]	6	100.0	6 (100.0)	0 (0.0)		0 (0.0)
Total	**33**		**32 (97.0)**	**1 (3.0)**		**1 (3.0)**
Small cell lung cancer						
Lindell 2007[52]	3	100.0	3 (100.0)	0 (0.0)		0 (0.0)
Jiang 2023[27]	27	100.0	27 (100.0)	0 (0.0)		0 (0.0)
Total	**30**	**100.0**	**30 (100.0)**	**0 (0.0)**		**0 (0.0)**
Other lung cancer						
Lindell 2007[52]	6	83.3	6 (100.0)	0 (0.0)		0 (0.0)
Wilson 2012[18]	9		6 (66.7)	3 (33.3)		3 (33.3)
Mackintosh 2014[19]	4	100.0	3 (75.0)	0 (0.0)	1 (25.0)	0 (25.0)
Total	**19**		**15 (78.9)**	**3 (15.8)**	**1 (5.3)**	**4 (21.1)**

The distribution of lung cancer growth rates is categorized into rapid growth (VDT≤400 days), slow growth (VDT>400 days), and shrinkage (VDT<0 days), as observed across various studies. The latter two categories are collectively referred to as indolent lung cancer, defined as VDT> 400 or < 0 days. Blank cells indicate that information was not provided in the studies. VDT, volume doubling time; d, days.

Table 3
Factors correlated with lung cancer growth rates.

Study	Patient factors				Lung cancer factors			
author year	Sex	Age	Smoking history	Pack-years	Histology	TNM Stage	Size	Solidity
All lung cancer								
Hasegawa 2000[6]	NC		↑		↓ (Adeno)		NC	↑
Jennings 2006[29]		↓			NC			
Quint 2008[53]					NC		NC	
Honda 2009[16]					↓ (Adeno)			
Mikita 2012[26]	NC	NC	↑		NC		NC	
Veronesi 2012[17]	↑ (male)	NC		NC	↓ (Adeno)	↑		
Wilson 2012[18]	NC	NC		NC	↓ (Adeno)	NC		
Koike 2014[22]								↑
Mackintosh 2014[19]	NC		↑	NC	↓ (Adeno)	NC		
Nakamura 2014[21]	↑ (male)	NC	↑			↑	↑	
Adler 2022[28]			NC					
Nakahashi 2022[20]	NC	NC	NC		↓ (Adeno)	↑	↑	
Adenocarcinoma								
Li 2018[23]								↑
de Margerie-Mellon 2020[25]	NC	↑	NC	NC			↑	
Tan 2021[24]	NC	NC	NC				↑	↑
Small cell lung cancer								
Jiang 2023[27]	NC	NC	NC				NC	

The studies are grouped by the histology type investigated (all lung cancer types or specific histological subtypes). ↑ represents factors or characteristics that were positively associated with lung cancer growth rates. ↓ represents factors or characteristics that were negatively associated with lung cancer growth rates. NC (No Correlation) represents factors or characteristics that lack a significant correlation with growth rates. Blank cells indicate that information was not provided in the studies. Adeno, adenocarcinoma.

reliable as larger tumors are less susceptible to errors. However, for subcentimeter lung cancer and indeterminate nodules, particularly those with volumes of 100–300 mm^3 as defined by the NELSON study, traditional diameter measurements might lack the sensitivity and accuracy of assessing tumor volume and growth rate compared to the semi-automatic volumetric method. [14,46,47].

Our review confirmed the existence of indolent lung cancer in 34.9 % of cases, particularly in 68.9 % of adenocarcinomas. Indolent lung cancer is generally associated with a more favorable prognosis [17, 29] but raises concerns about overdiagnosis and overtreatment. The COSMOS study highlighted the potential overlap between an indolent fraction and an overdiagnosed fraction. [17] Consequently, individuals with indolent tumors may benefit from a tailored approach, such as active surveillance, delaying invasive treatments until there's clear evidence of tumor progression. [48].

The correlated factors analyses underscore that histology is the primary determinant of lung cancer growth rates. This critical insight allows clinicians to estimate the likely histological type of lung cancer based on VDT evaluation, providing a valuable tool for preliminary diagnoses when biopsy results are not immediately available.

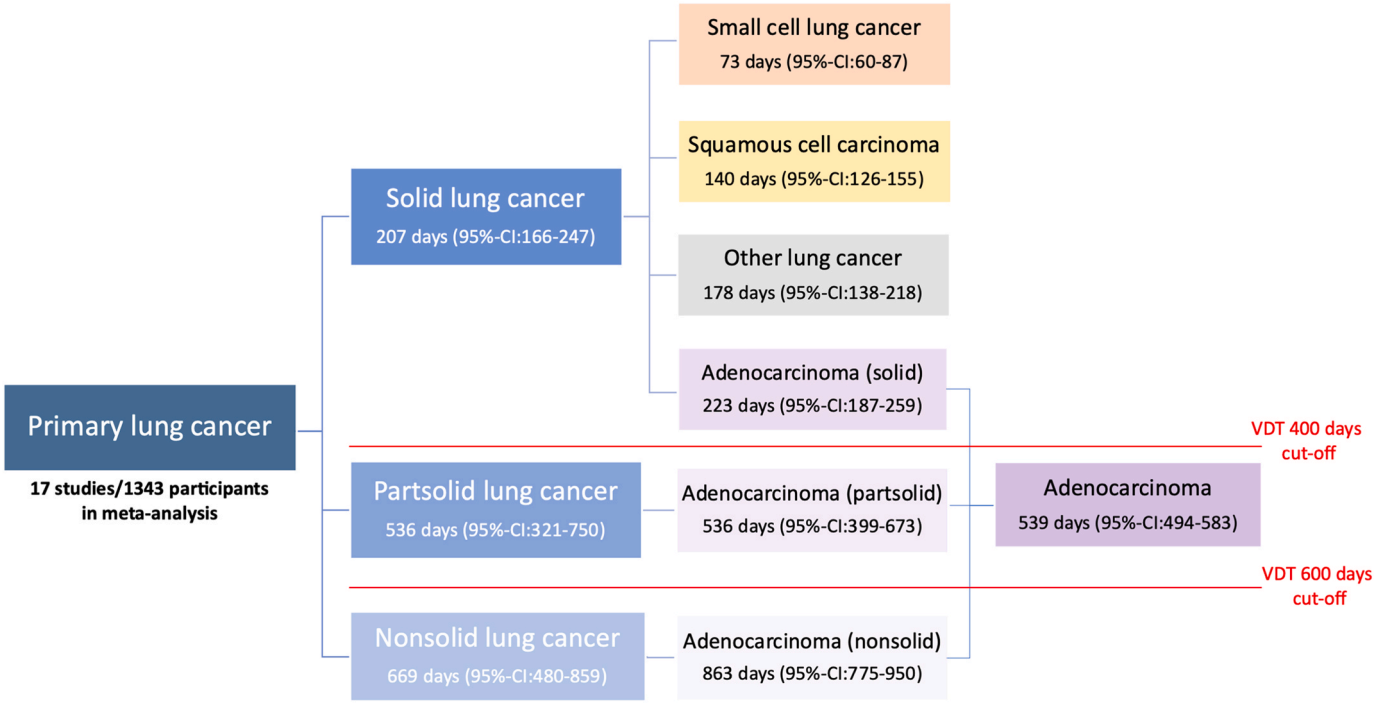

Fig. 3. Overview of pooled mean volume doubling time of lung cancer by nodule type and histology. Pooled mean volume doubling time (VDT) is presented in days with 95 % confidence interval (CI) from the meta-analysis. Red dashed lines represent reference VDTs of 400 and 600 days.

Table 4
Lung cancer growth estimation over time based on pooled mean VDT from initial volumes of 100–300 mm^3 .

Lung cancer type		VDT	3 month follow-up		1 year follow-up		2 year follow-up	
		(days)	Folds	Volume (mm^3)	Folds	Volume (mm^3)	Folds	Volume (mm^3)
Solid		**207**	1.35	135 –406	**3.39**	**339 –1018**	11.52	1152 –3457
	Adenocarcinoma	**223**	1.32	132 –397	**3.11**	**311 –933**	9.67	967 –2900
	Squamous cell carcinoma	**140**	1.56	156 –468	**6.07**	**607 –1822**	36.90	3690 –11069
	Small cell lung cancer	**73**	**2.34**	**234 –702**	31.45	3145 –9434	988.82	98882 –296647
	Other lung cancer	**178**	1.42	142 –426	**4.15**	**415 –1245**	17.23	1723 –5169
Part-solid		**536**	1.12	112 –337	1.60	160 –481	**2.57**	**257 –772**
Nonsolid		**669**	1.10	110 –329	1.46	146 –438	**2.13**	**213 –639**

This estimation started from initial tumor volumes of 100-300 mm^3 (as defined for indeterminate nodules by the NELSON study). VDT refers to the pooled mean VDT derived from our meta-analysis. Folds represent the fold increase in tumor volume over the initial volume. Folds= $2^{\text{Time interval/VDT}}$. Volume provides the range of tumor volumes measured at the end of each period. Volume=Initial volume (100-300 mm^3) × Folds. Bold numbers highlight significant and timely volume changes over the specified periods. VDT, volume doubling time.

Furthermore, tumor characteristics such as size, solidity, and clinical stage significantly correlate with growth rates, which facilitates effective risk stratification and monitoring. While studies show that smokers tend to have faster lung cancer growth rates, no direct correlation has been found between pack-years and growth rate. Adler et al showed that smokers exhibit shorter VDT than non-smokers (226 vs 373 days, $p = 0.001$), yet this difference became insignificant in multivariable analyses after adjusting for sex, age, and histology ($p = 0.06$). [28] This suggests that although smoking substantially influences the risk and histology of lung cancer, promoting more aggressive types like squamous cell and small cell lung cancers, [49–51], it does not directly accelerate tumor growth within individual histological subtypes.

Our review identifies several limitations in the current literature on VDT evaluation in lung cancer. Our meta-analysis showed significant heterogeneity among studies, despite our attempts to address it through subgroup analyses. Additionally, our inclusion criteria inherently omit a subset of patients with more aggressive cancer who were immediately referred without follow-up scans that would permit VDT calculation. We also assumed VDT is constant, overlooking the potential dynamic changes in cancers like adenocarcinomas, where increasing solidity may accelerate growth rates. Furthermore, we did not account for technical factors such as voxel size, reconstruction kernel, and software package variability, which could introduce some variability in VDT measurements. Future research needs to focus on understanding the variability and dynamics of VDT, improving the understanding of lung cancer progression to enhance screening, diagnostic, and treatment decisions.

5. Conclusion

In conclusion, this systematic review demonstrates significant variability in lung cancer VDT across different nodule types and histologies, underscoring the need for tailored screening and management strategies. Our study validates the use of a 400-day VDT threshold for clinical referrals, particularly for solid nodules. For subsolid nodules, we propose more lenient VDT cut-offs—600 days for part-solid and 800 days for nonsolid nodules—warranting closer CT follow-up. Biennial screening is supported for subsolid nodules, with extended follow-up up to at least five years. Key predictors of growth rate including histology, size, solidity, and smoking history, are crucial for tailoring early intervention strategies.

Contributors

BJ, DH, MAH, and MO developed the concept and designed the study. BJ and DH conducted systematic searches and collected the data. BJ did the statistical analysis. BJ and DH verified the data. HJK, MAH, and MO supervised the study. BJ, DH, and MAH wrote the original draft. All authors had full access to raw data. All authors wrote, reviewed, and edited the Article and approved the final version. The corresponding author (MAH and MO) had the final responsibility to submit for publication.

Ethics approval

Not applicable.

Data sharing

All articles in this Article are available from Pubmed, Embase, and Web of Science.

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CRediT authorship contribution statement

Mario Silva: Writing – review & editing. **Jan-Willem C Gratama:** Writing – review & editing. **Marleen Vonder:** Writing – review & editing. **Harriet Lancaster:** Writing – review & editing, Conceptualization. **Matthijs Oudkerk:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Marjolein A Heuvelmans:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Harry J de Koning:** Writing – review & editing, Supervision. **John K Field:** Writing – review & editing. **Carlijn M van der Aalst:** Writing – review & editing, Supervision, Methodology. **Daiwei Han:** Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Beibei Jiang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114339.

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