Supplementary Material

https://dx.doi.org/10.21037/jtd-22-1199

Table S1 Incidence of LCAL

Ordered by predominant LCAL type, tumor extent

Characteristics	Study		LCAL Cohort					Comparator Cohort			
1st author, reference	Years	Source	n	Dominant type	Tumor extent [a]	Spectrum breadth [b]	Other criteria	n	Setting	Other criteria	Incidence
Shen (4)	15–16	Shanghai	123	Cyst	Lim	Broad	Ad	10,835	Surg	NSCLC	1.1%
Jung (5)	04–17	Seoul	60	Cyst	Lim	Broad	Ad	1971	Surg	Ad	3%
Farooqi (6)	93–09	ELCAP	26	Cyst	Lim	Broad		706	ELCAP	Lg Ca	3.7%
Guo (7)	07–12	Beijing	15	Cyst	Lim	–		3,268	Surg	Lg Ca	0.5%
Fintelman (8)	10–15	Boston	30	Cyst	Mod	Broad		2,599	All [c,d]	NSCLC	1.2%
Kimura (9)	10–14	Kanagawa	12	Cav	Mod	Broad	pI	275	Surg	pI	4.4%
Watanabe (10)	98–07	Tokyo	143	Cav	Mod	Broad	Ad	2,316	Surg	Ad	6.2%
Kunihiro (11)	05–14	Yamaguchi	60	Cav	Mod	Broad	Ad + Sq	426	Surg	Ad+Sq	14%
Shigefuku (12)	05–11	Tokyo	65	Cav	Ext	Broad		1,311	Surg	NSCLC	5%
Chen (13)	09–14	Shanghai	227	Cav	Ext	Broad	pI Ad	2,106	Surg	pIA Ad	10.8%
Byrne (14)	16–18	Vancouver	47	Cav	Ext [e]	Broad		431	Surg [f]	Lg Ca	10.9%
Kojima (15)	93–08	Kanagawa	26	PsCav	Mod	Broad	Ad	1,462	Surg	Ad	1.9%
Utrera (16)	07–17	Vigo, Spain	30	PsCav	–	–	≥2 cm	166	–	Lg Ca	15.3%
Shinohara (17)	07–15	Nagoya	52	Bulla	Mod	Broad		291	Surg	Lg Ca	18%
Hanaoka (18)	76–98	Kyoto	50	Bulla	Ext	–		1,478	Surg	Lg Ca	3.4%
Kaneda (19)	98–08	Mie, Japan	19	Bulla	V Ext	Nar		445	Surg	NSCLC	3.5%

Inclusion criteria: Studies reporting incidence of LCAL within a larger contemporary cohort of patients with lung cancer, involving ≥10 LCAL patients 2000–2022.

Red font highlights study characteristics that may make it an outlier.

[a], categorization of extent of solid component (see Appendix 3); [b], Broad or narrowly configured inclusion criteria. [c], excluded 11% of cases that did not have a prior CT >6 months earlier; [d], 17% non-surgical, 17% wedge only resection; [e], includes pathologic diagnosis of cavity; [f], excluded central cancers; includes patients evaluated for surgery (not all were resected).

Ad, adenocarcinoma; Cav, cavitary; Cyst, cystic; ELCAP, International Early Lung Cancer Action Project (a CT screening collaborative); Ext, extensive; LCAL, lung cancer with air lucency; Lg Ca, lung cancer; Lim, limited; Mod, moderate; Nar, narrow; NSCLC, non-small cell lung cancer; PsCav, Pseudocavitary; pts, patients; Sq, squamous carcinoma; Surg, surgical series (resected cases); V Ext, Very Extensive.

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Table S2 Comparison of LCAL and contemporary lung cancer patients
Ordered by predominant LCAL type, tumor extent

1st Author, reference	years	Source	Inclusion Characteristics			N		Average age		% Men		% Non-smokers		% Adeno		% Squam		% Stage I		% Stage III–IV	
			LCAL dominant type	LCAL tumor extent	Other inclusion (both arms)	LCAL	Comp	LCAL	Comp	LCAL	Comp	LCAL	Comp	LCAL	Comp	LCAL	Comp	LCAL	Comp	LCAL	Comp
Farooqi (6,62)	93–09	ELCAP	Cyst	Lim	Lung Ca	26	484	63	–	50	–	–	–	**92**	71 [a]	4	**14** [a]	81	85	12	–
Fintelman [b] (8)	10–15	Boston	Cyst	Lim	NSCLC	30	2,924	66	65	40	**46**	3	**20**	80	–	13	–	60	–	23	–
Kimura [c] (9)	10–14	Kanagawa	Cav	Mod	pl NSCLC	12	263	67	68	**75**	53	17	**38**	67	**80**	**25**	15	–	–	–	–
Watenabe (10)	98–07	Tokyo	Cav	Mod	Adeno	143	2,173	63	65	**68**	49	34	**54**	–	–	–	–	67 [d]	**76** [d]	**24**	17
Chen [c] (13)	09–14	Shanghai	Cav	Ext	pl Adeno	227	1,879	59	61	**48**	39	93	94	–	–	–	–	–	–	–	–
Byrne (14)	16–18	Vancouver	Cav	Ext	Lung Ca	47	431	69	70	43	43	17	**29**	–	–	–	–	–	–	–	–
Shinohara [c] (17)	07–15	Nagoya	Bulla	Mod	NSCLC	51	239	68	71	**83**	65	10	**25**	50	**68**	**35**	22	65	69	8	**15**
Hanaoka [c] (18)	76–98	Kyoto	Bulla	Ext	NSCLC	50	–	62	62	**98**	71	–	–	42	**53**	26	**34**	**62**	42	12	**43**
Kaneda (19)	98–08	Japan	Bulla	V Ext	Lung Ca	19	445	61	–	100	–	0	–	11	**62**	**47**	33	50	**62**	21	25

Inclusion criteria: all studies 2000–2022 reporting on >10 patients with LCAL as well as a contemporary cohort of lung cancer patients.
Bold indicates >5% higher proportion; Red font highlights study characteristics that may make it an outlier.
[a], only stage I cohort data available; [b], followed for ≥6 months, eventually histologic diagnosis (but only excluded 11% due to limited observation); [c], comparator is non-cystic cancers (i.e., LCAL cases excluded); [d], N0 cases only.
Adeno, adenocarcinoma; Cav, cavitary; Cyst, cystic; Comp, comparator; ELCAP, International Early Lung Cancer Action Project (a CT screening collaborative); Ext, extensive; LCAL, lung cancer with air lucency; Lung Ca, lung cancer; Lim, limited; Mod, moderate; NSCLC, non-small cell lung cancer; Squam, squamous carcinoma; V Ext, very extensive.

Table S3 Diagnostic evaluation and clinical management

Clinical scenario	Diagnostic approach	Justification
Thin-walled irregular cyst with new or progressing small solid component	• Surgical biopsy and / or resection • ± CT needle aspiration/wash	• High likelihood of lung cancer, outcomes good if treated when only small solid component • High FN rate for needle aspiration and low chance of specific benign diagnosis • PET unlikely to detect the primary lesion or find occult metastases
Cavitary lesion that is persistent, progressing, or otherwise suspicious for lung cancer	• CT needle aspiration / wash • Bronchoscopy, surgical biopsy • ± PET	• Likelihood of specific diagnosis (but negative results warrants further intervention) • PET likely positive at primary site regardless of etiology (but may be useful for distant stage evaluation
Pseudocavitary appearance in a solid / consolidated lesion	• PET; if negative → surveillance for ≥2 years • PET; if positive → tissue biopsy	• Major differential is scar vs active lesion; larger size suggests low PET FN rate
Regional bulla/emphysema with progressing or larger adjoining solid nodule	• Surgical biopsy and / or resection • ± CT needle aspiration/wash • ± PET	• High likelihood of lung cancer • High FN rate for needle aspiration and low chance of specific benign diagnosis • PET can corroborate presumptive cancer diagnosis in larger lesions and provide stage assessment

CT, computed tomography; FN, false negative rate; PET, positron emission tomography.

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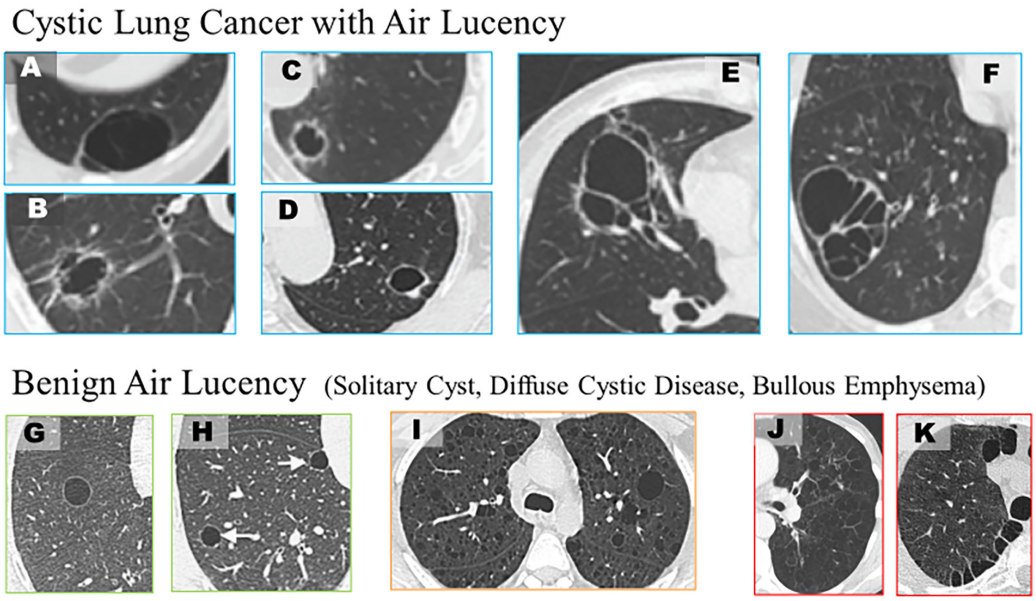

Figure S1 Representative CT images of cystic LCAL.

Representative examples of appearance of cystic LCAL. Cystic LCAL with (A) irregular thin wall; (B) surrounding GG; (C) slightly thicker wall; (D) nodule (this patient had a destructive L4 spine metastasis); (E,F) septations / multiloculation. Examples of benign causes of air lucency shown for comparison (such benign causes are not the focus of this review): (G,H) isolated round cyst; (I) lymphangioleiomyomatosis (LAM); (J,K) Emphysema and Bullae.

Images reproduced with permission from: (A-F) Deng, *Onc Lett* 2018 (24); (G,H) Araki, *Thorax* 2015 (45); (I) Gillott, *Semin Roentgenol* 2015 (63); (J) Sheard, *Radiographics* 2018 (64); (K) from clinical experience.

GG, ground glass; LCAL, lung cancer with air lucency.

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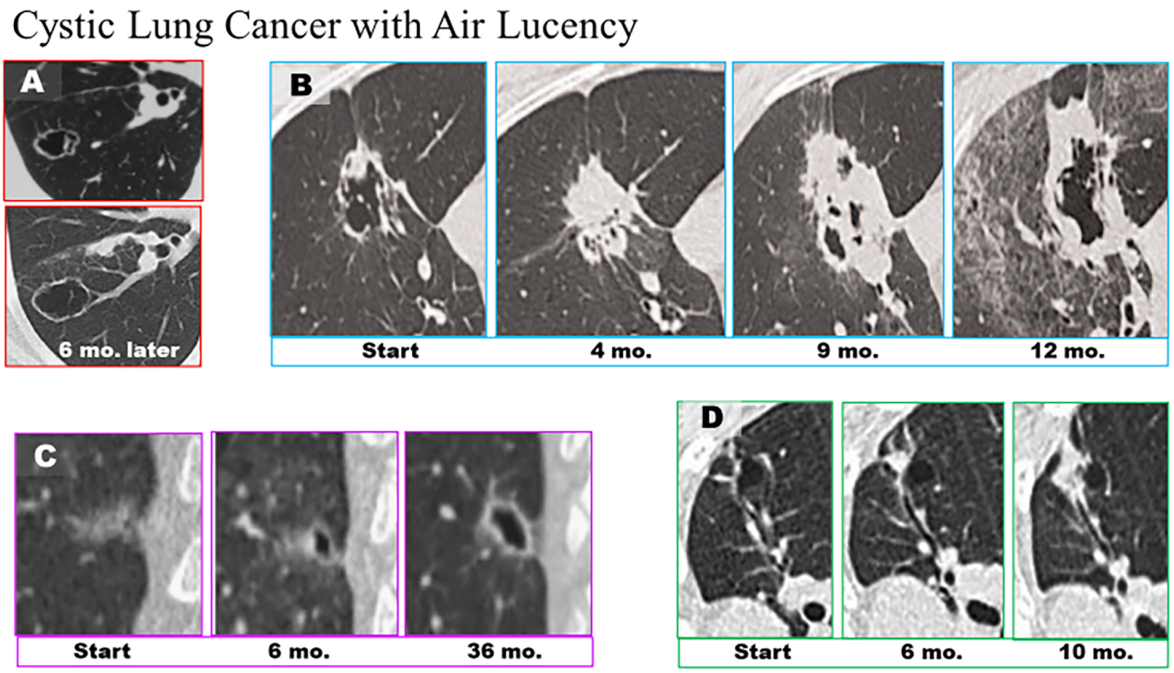

Figure S2 Representative CT images of progression of cystic LCAL.

Representative examples of progression of cystic LCAL. (A) Enlarging thin-walled cyst; note new density after 6 months centrally near fissure; (B) rapid progression of a solid nodule in a cystic LCAL over 12 months; (C) slower progression of a cystic LCAL with surrounding GG over 3 years; (D) rapid progression of a solid nodule in a cystic LCAL over 10 months.

Images reproduced with permission from: (A) Guo *et al.*, *Asia-Pac JCO* 2016 (7); (B) Zhang *et al.*, *Medicine* 2019 (25); (C) Jung *et al.*, *Ann Surg Onc* 2020 (5); (D) Tan *et al.*, *Radiol* 2019 (20).

GG, ground glass; LCAL, lung cancer with air lucency; mo., months.

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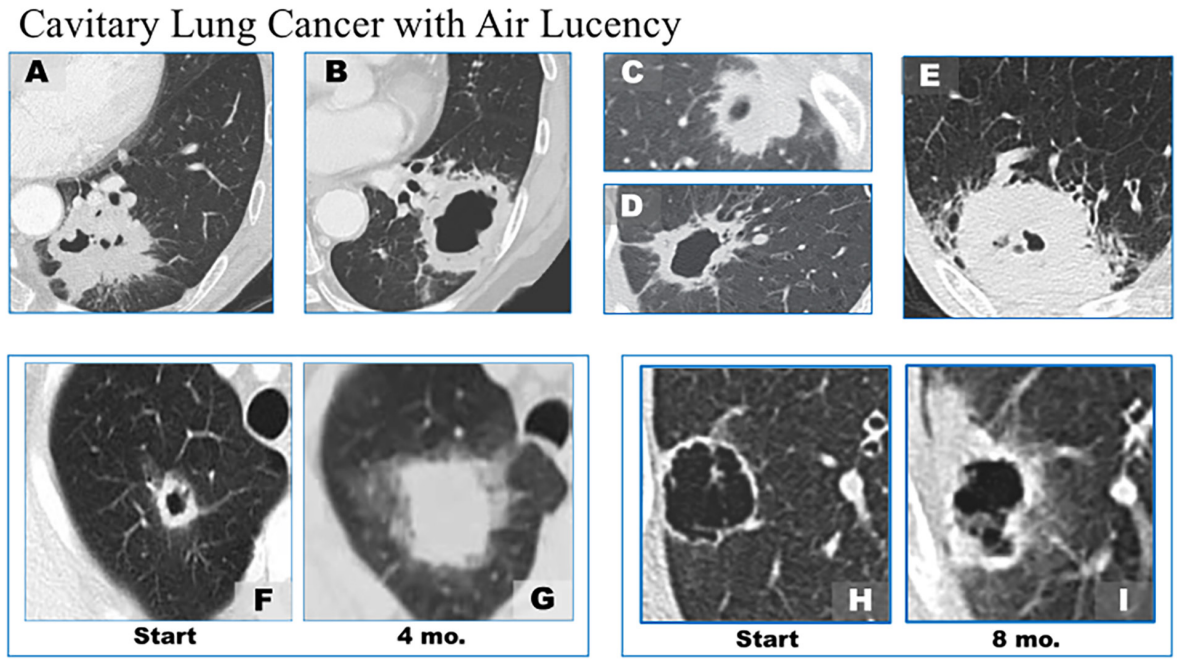

Figure S3 Representative CT images of cavitary LCAL.

Representative examples of appearance and progression of cavitary LCAL. Reproduced with permission from: (A,B) Watanabe, *Ann Th Surg* 2015 (10); (C,D) Shigefuku, *J Thor Dis* 2018 (12); (E) Kunihiro, *Clin Radiol* 2016 (11); (F,G) Byrne, *J Thorac Imaging* 2021 (14); (H,I) Mascalchi, *J Comput Assist Tomogr* 2015 (28).

LCAL, lung cancer with air lucency; mo., months.

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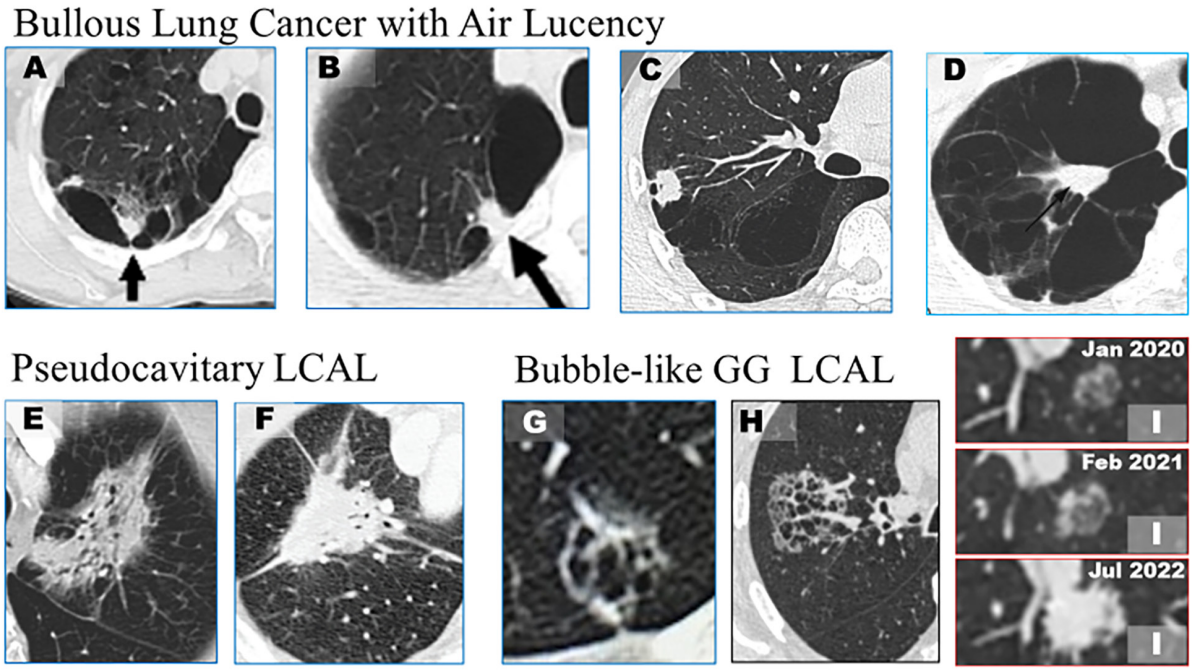

Figure S4 Representative CT images of bullous, pseudocavitary and bubble-like GG LCAL.

Representative examples of appearance and progression of bullous, pseudocavitary and bubble-like GG LCAL. Images reproduced with permission from: (A,B) Kaneda, *Interact Cardiovasc Thorac Surg* 2010 (19); (C) Shinohara, *J Thorac Dis* 2018 (17); (D) Maki, *J Comput Assist Tomogr* 2006 (65); (E) Tailor, *J Thorac Imaging* 2015 (66); (F) Saito, *J Comput Assist Tomogr* 2009 (32); (G) Haider, *Clin Imaging* 2019 (27); (H) clinical experience; lesion increased slightly in size and density over 4 years; (I) clinical experience; lesion increased slightly in size 2019, 2020, 2021, solid component increased rapidly from 2021 to July 2022.

Feb, February; GG, ground glass; LCAL, lung cancer with air lucency; Jan, January; Jul, July.

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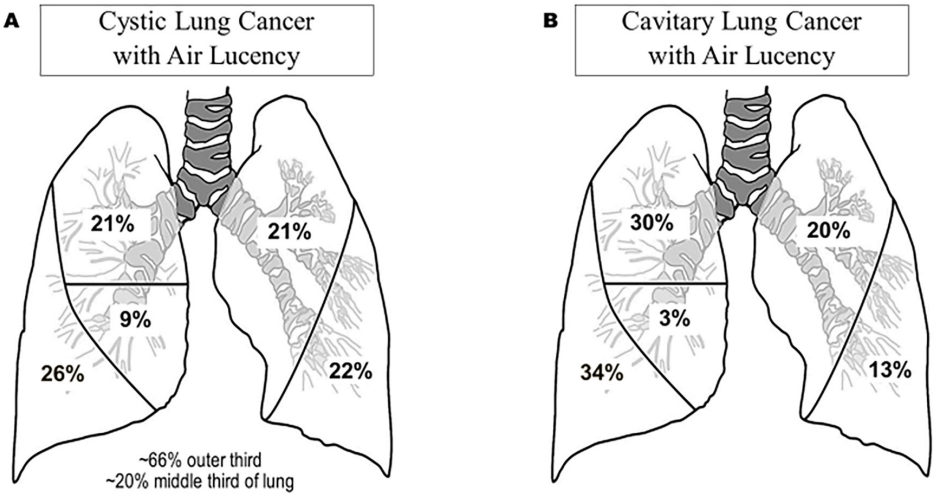

Figure S5 Lobar distribution of LCAL.

Lobar distribution in studies reporting this data (A) among predominantly cystic LCAL and (B) predominantly cavitary LCAL. Insufficient data is available on bullous and pseudocavitary LCAL.

References for cystic LCAL (4,6-8,20,22-24,26,27,29) peripheral location (4,20) and cavitary LCAL (11,14,28).

LCAL, lung cancer with air lucency.

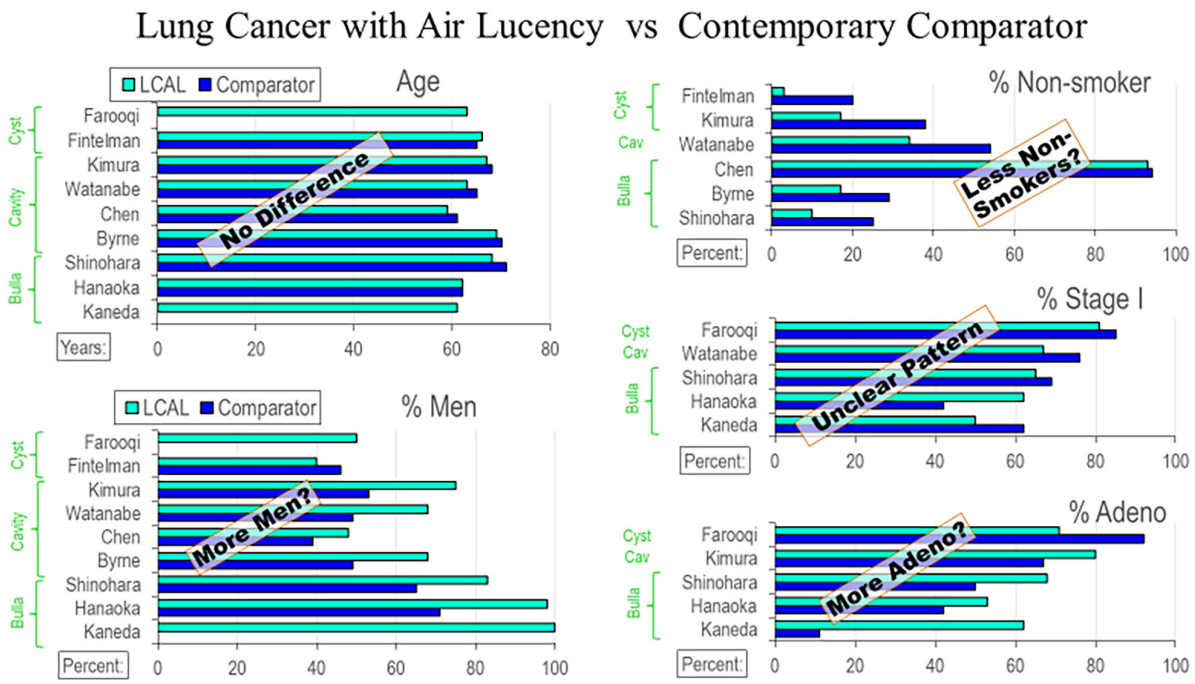

Figure S6 Comparison of LCAL and contemporary lung cancer patients.

Graphic depiction of studies in Table S2. Data from all studies reporting on LCAL as well as a contemporary comparison cohort of lung cancer patients.

Adeno, adenocarcinoma; Cav, cavitary; LCAL, lung cancer with air lucency

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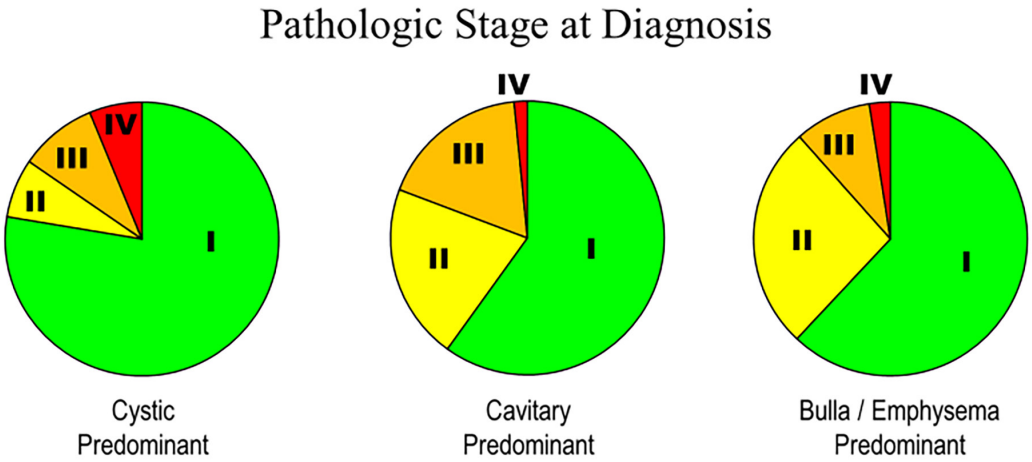

Figure S7 Average reported stage distribution among studies by predominant LCAL type.
Average reported stage involves more higher stages in studies involving cavitary or bullous vs cystic LCAL. Details of data is taken from the individual studies reported in Appendix 3 Table A; references are as listed in Table A. Insufficient data is available on pseudocavitary LCAL. LCAL, lung cancer with air lucency.

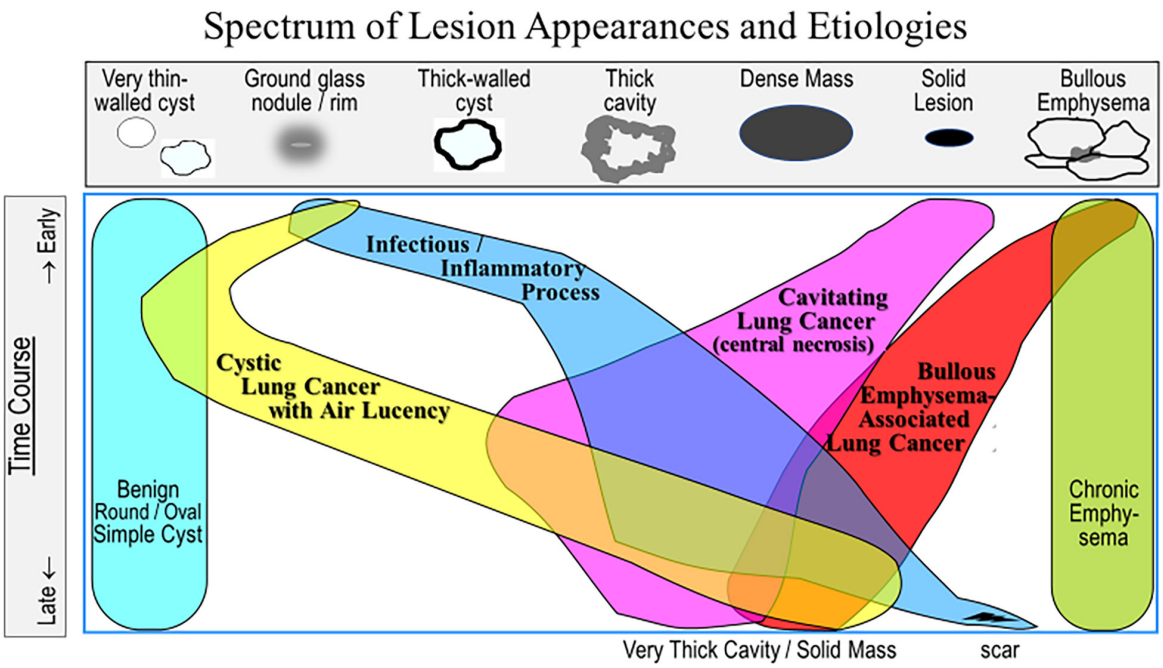

Figure S8 Schematic of overlap of imaging appearances and disease processes over time.
Schematic depiction of imaging appearance during the course of disease of various entities associated with an air lucency. This schematic is based on what is known about the imaging behavior of some lesions (e.g., simple benign cyst, emphysema, cystic lung cancer with air lucency, subacute inflammatory conditions) and presumed behavior of other lesions (e.g., cavitating lung cancer, bullous emphysema-associated lung cancer).

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Appendices

Appendix 1 PICO Questions

Primary Study questions, PICO format (Population, intervention, comparator, outcomes)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
1. Are cystic, cavitary, bullous, pseudocavitary and bubble-like GG LCAL different entities?		
Population	Patients with LCAL	Not LCAL
Interventions	Cystic, *cavitary, bullous, pseudocavitary and bubble-like GG LCAL*	
Comparators	Cystic, *cavitary, bullous, pseudocavitary and bubble-like GG LCAL*	
Outcomes	Demographic aspects, risk factors, histologic / genetic aspects	
Study Design	Systematic reviews, observational studies [a]	<10 cases
2. Are LCAL a different entity from traditional NSCLC?		
Population	Patients with NSCLC or LCAL	Not NSCLC, not LCAL
Interventions	Patients with LCAL	
Comparators	Patients with NSCLC	
Outcomes	Demographic aspects, risk factors, histologic/ genetic aspects assessed in contemporary cohorts and identified in similar settings	
Study Design	Systematic reviews, observational studies [a]	<10 cases
3. What is the natural history of LCAL?		
Population	Patients with LCAL	Not LCAL, observation <6 mo.
Interventions	No treatment	
Comparators	Not applicable	
Outcomes	Stability, progression, stage shift over time	
Study Design	Systematic reviews, observational studies [a]	<10 cases
4. Which characteristics are best to differentiate benign from malignant lesions with air lucency?		
Population	Patients with lesions with air lucency	Lack of definitive diagnosis
Intervention	LCAL	
Comparators	Benign lesions with air lucency	
Outcomes	Sensitivity, specificity, FN, FP rates of clinical / imaging characteristics	
Study Design	Systematic reviews, observational studies [a]	<10 cases
5. How reliable are diagnostic tests (and how common are complications)?		
Population	Patients with lesions with air lucency	Lack of data on any of the outcomes
Interventions	PET, CT guided biopsy, bronchoscopy	
Comparators	Not applicable	
Outcomes	Sensitivity, specificity, FN, FP rates for LCAL or for specific benign diagnoses; rate of complications	
Study Design	Systematic reviews, observational studies [a]	<10 cases
6. Which characteristics identify the need for intervention (before stage progression or worsening outcomes ensue)?		
Population	Patients with LCAL	Lack of data on any of the outcomes
Interventions	Imaging / Clinical Characteristics	
Comparators	Not applicable	
Outcomes	Stage, Survival	
Study Design	RCT, NRC, systematic reviews, observational studies	<10 cases
7. What are the long-term outcomes of surgical treatment of LCAL?		
Population	Patients with LCAL	Lack of data on any of the outcomes
Interventions	Surgical resection	
Comparators	Not applicable	
Outcomes	Overall survival, recurrence	
Study Design	RCT, NRC, systematic reviews, observational studies	<10 cases
8. What are the outcomes of non-surgical treatment of LCAL?		
Population	Patients with LCAL	Lack of data on any of the outcomes
Interventions	Radiotherapy, systemic therapy (± surgery)	
Comparators	Not applicable	
Outcomes	Response, Overall survival recurrence	
Study Design	RCT, NRC, systematic reviews, observational studies	<10 cases

[a], Randomized controlled trials are not applicable for this question.

FN, false negative; FP, false positive; LCAL, lung cancer with air lucency, mo, months; NRC, non-randomized comparison; RCT, randomized controlled trial; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracic surgery.

No formal study protocol was written beyond the PICO questions. This systematic review was not registered as such.

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Appendix 2 Search Strategy, Results and Approach to Data Analysis and Synthesis

Descriptive summary

None of the authors have any relevant conflicts of interest. There was no funding source for this study. No formal study protocol was written beyond the PICO questions and search strategy (details in Appendix 1). The systematic search was not formally registered.

A formal systematic literature search was conducted in PubMed and EMBASE according to the details provided below. Titles were reviewed by 2 authors. Based on further review of abstracts, studies were selected for full review and read by ≥2 authors. All study types were eligible. Review articles were read in full, but only included if they reported relevant patient data. All studies were included that contained information relevant to the patients, outcomes and interventions outlined in Appendix-1. We selected studies published in the years 2000–2022 with ≥10 LCAL cases for data abstraction. Case reports were included only if they provided unique relevant data. Studies addressing lung abscesses or multi-cystic lung diseases (e.g., lymphangioleiomyomatosis, lymphocytic interstitial pneumonia, Langerhans cell histiocytosis) were excluded.

A formal assessment of study quality or certainty (risk of bias) table was not created; because all studies consist of case series all are categorized as low-level evidence. However, we used a scale to categorize low-level evidence (67) in order to transparently represent the basis for statements and conclusions.

Data was abstracted by 1 reviewer. Because the topic is not well-defined and studies involve retrospective case series, many details of patient characteristics, interventions and outcomes were variably and often vaguely defined (e.g., CT parameters, observation intervals, resection extent, stage definition). Therefore, quantitative summary calculations were deemed inappropriate. Instead, attention was given to highlighting uncertainties, limitations, and relevant differences in the results sections in order to promote transparency and appropriate interpretation and application of the results. All panelists were involved in reviewing the papers and assessing uncertainties and differences; consensus among panelists was required that the assessment was transparently represented. No method of data imputation was used.

A quantitative meta-analysis was deemed inappropriate due to limitations in the source data: the data comes from case series, patient characteristics and inclusion criteria are incompletely defined, most studies include at least some degree of a mixture of what seem to be distinct entities and there is ambiguity regarding many outcomes (e.g., how size is measured, unspecified time intervals). Instead, we sought to summarize pertinent characteristics of the studies so that comparison of results across studies could be made with consideration of differences in the patients, tumors and settings involved.

We undertook a categorization of the studies (described in Appendix 3) in order to facilitate interpretation of an aggregate of the data. Each panelist was asked to independently assess the studies in Table A; the categorization represents a consensus among all panelists.

Based on the review of available data on natural history, progression, interventions and outcomes, we developed a clinical guide to patient management. The proposals seek to balance avoiding unnecessary intervention against consequential delays in addressing a lung cancer. The proposed protocol for observation, criteria for intervention and approach to management represents the consensus of all panelists.

PubMed Search

Filters: 2000–2022, journal article
Date of Last Formal Search: 10-30-2022
Search string:
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Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "neoplasm"[All Fields]) OR "lung neoplasm"[All Fields]) OR ("adenocarcinoma of lung"[MeSH Terms] OR ("adenocarcinoma"[All Fields] AND "lung"[All Fields]) OR "adenocarcinoma of lung"[All Fields] OR ("lung"[All Fields] AND "adenocarcinoma"[All Fields]) OR "lung adenocarcinoma"[All Fields]) OR "lung neoplasms"[MeSH Terms])) AND (("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields])))

EMBASE Search

Date of Last Formal Search: 10-28-2022
Search string:
Embase <1974 to 2022 October 28>

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2	(bubble-like or bulla).af.	5184
3	(lung neoplasms or lung cancer or lung neoplasm or lung cancers).af.	388320
4	lung adenocarcinoma.af.	57645
5	3 or 4	410149
6	1 or 2	286281
7	3 and 4 and 6	377
8	limit 7 to yr="2000 - 2022"	358

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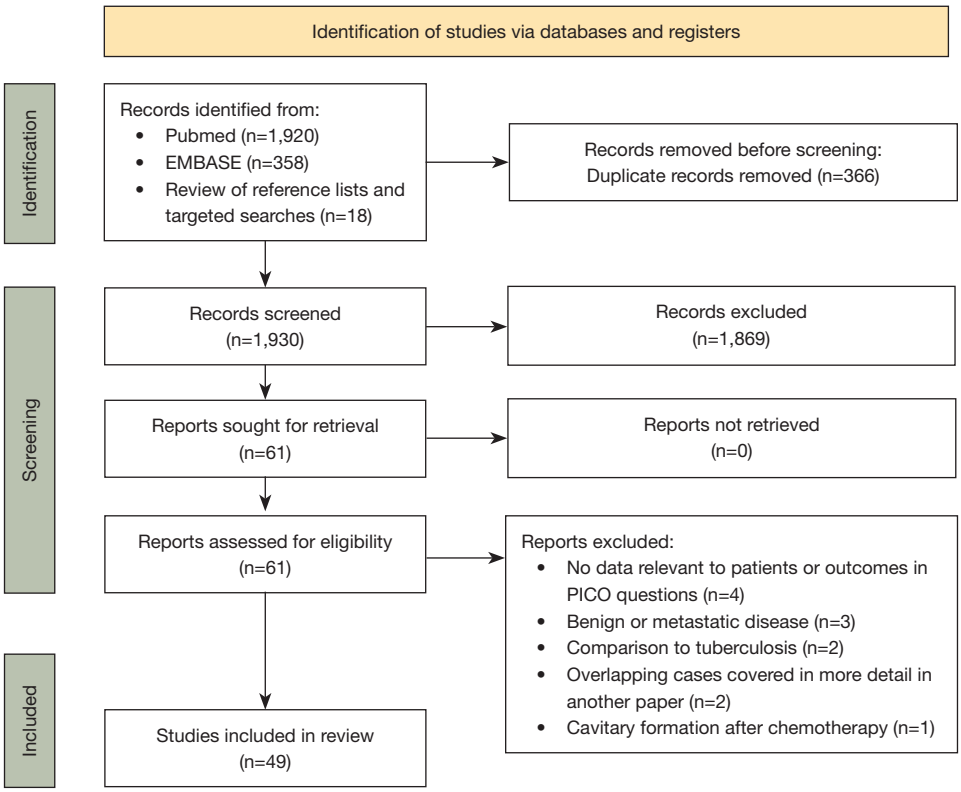
Results



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Appendix 3 Categorization of Tumors in LCAL Studies

Studies of LCAL have used various terms, including lung cancers associated with cystic airspaces, cavities, and bullous emphysema. The formal definition of a cyst is a lucency within normal lung parenchyma with a well-demarcated interface (of variable thickness, usually <2 mm); a cavity is a lucency within an area of pulmonary consolidation, mass or nodule; a bulla is a focal lucency >1 cm sharply demarcated by a thin wall ≤1 mm, typically associated with adjacent emphysematous changes (2). However, the terms are often used loosely (interchangeably) in studies of LCAL.

Additional terms associated with LCAL are pseudocavitation and bubble-like appearance. Pseudocavitation is defined as small (usually <1 cm) oval or round areas of low attenuation within a region of consolidation, mass or nodule, representing spared parenchyma, normal or ectatic bronchi, or focal emphysema rather than cavitation (2). Bubble-like appearance is not formally defined; it is often used in the setting of a ground glass (GG) nodule, but sometimes in the context of a solid mass or dense area of consolidation (i.e., what is defined as pseudocavitation). We think it is best to distinguish between mostly GG and mostly solid lesions with small lucencies. Therefore, we use the term "bubble-like GG" to specifically describe a GG nodule with small air lucencies and pseudocavitation for mostly solid lesions with small air lucencies.

Additionally, reports have included a variable spectrum of tumor extent. Some studies have used narrowly-defined inclusion criteria—e.g., only thin-walled lesions (often defined as ≤4 mm thick), or extensive tumors (i.e., ≥15 mm or completely solid but previously having a cystic/cavitary appearance)—but most have defined inclusion broadly or ambiguously. Does the extent of the solid components of included tumors in studies reflect degrees of progression of a single type of lung cancer or distinct entities?

To facilitate interpretation of data from studies that have included a varying spectrum of lesions, we categorized studies based on (I) whether they predominantly included cystic, cavitary, pseudocavitary or bullous LCAL, and (II) by the extent of a solid component (limited, moderate, extensive) and (III) whether narrow or broad inclusion criteria were used. This is summarized in Table A [predominantly cystic (4-8,20,22-27,29), predominantly cavitary (9-14,21,28), predominantly pseudocavitary (15,16,66), predominantly bullous (17-19)]. We included bubble-like GG LCAL together with cystic LCAL for several reasons: there is no clear distinction between a bubble-like GG and a multi-cystic thin-walled lesion, and studies reporting patient characteristics, progression or outcomes focused on bubble-like GG LCAL are lacking.

To categorize reported studies, we sought consensus among the writing panel, using various pieces of information: the terms used in reports, whether and how they were defined, the description of lesions and images provided, and a quantitative or qualitative assessment of the proportions of thin-, thick-walled, nodular or solid lesions. Additionally, some studies used other inclusion/exclusion criteria (e.g., only adenocarcinoma or stage pI) that warrant consideration when comparing to other studies. We recognize that the categorization is inexact and somewhat subjective but hope that it adds to the interpretation of the published literature. Studies generally appear to report tumor characteristics present at the time of diagnosis (resection), although cases may be included based on appearance at an earlier time.

Table A leads to several conclusions. There are differences in the tumors among studies predominantly focused on cystic, cavitary and bulla-associated lung cancers—suggesting these are not simply different presentations or states of progression of a single entity. There is a progression in the proportion of smoke-exposed individuals and the proportion of squamous carcinomas and other histotypes. A striking proportion of men and smoking is apparent in studies involving predominantly bullous LCAL. These differences by predominant LCAL type are manifest across studies involving similar settings and populations—arguing against confounding due to baseline population characteristics (e.g., demographics, smoking prevalence) in the geographic region or time period of a study. Insufficient data is available regrading pseudocavitary LCAL to draw firm conclusions.

Clear definition of distinct entities is not possible from this analysis of literature on LCAL; most studies appear to involve a mixture of potential distinct entities. A speculative hypothesis is that adenocarcinoma associated with cystic airspaces, cavitary squamous carcinomas, and "traditional" solid lung cancers arising within an area of bullous emphysema are distinct entities. Acquiring evidence confirming or disproving this hypothesis is difficult because of overlap in imaging appearance, especially across a spectrum of progression. However, overlap is not limited exclusively to late phases of progression; several studies show examples of squamous carcinoma associated with thin-walled cystic lesions (17,20,24,26-28) and adenocarcinomas associated with thick-walled cavities with a shaggy interior border (10,25).

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We conclude that an awareness that studies involving LCAL likely include a mixture of entities is crucial for interpretation of an aggregation of the published literature. To promote this awareness, we have included the categorization by predominant imaging category and solid component extent within evidence tables in the main paper.

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Table A Categorization of studies

Ordered by description of lesion, tumor extent, breadth of spectrum

1st author year, reference	Setting			Categorization			% of cases				Range		Histology %				Patients			Stage %, (6th/7th Ed)			
	Years	Source	n	Tumor extent[a]	Breadth of spectrum[b]	Other	Thin wall (<4 mm)	Nodule	Thick (4–15 mm)	Solid or >15 mm	Smallest solid size (mm)	Largest solid size (mm)	Adeno	Ad-Squam	Squam	Other	Av Age	% Men	% non-smoker	I	II	III	IV
Cystic air lucency																							
Xue[c] 2012 (22)	06–11	Beijing	18	V Lim	V Nar		All	–	–	–	–	–	100	0	0	0	58	67	89	83	6	0	12
Qi 2015 (23)	08–12	Shandong	16	Lim	Nar		+++	++	+	–	–	10	100	0	0	0	52	75	–	71	0	21	7
Deng 2018 (24)	06–17	Beijing	45	Lim	Nar		+++	++	–	–	1	–	93	0	7	0	55	71	73	–	–	–	–
Shen[d] 2019 (4)	15–16	Shanghai	123	Lim	Broad	Ad	20	45	30	5	–	–	–[e]	–[e]	–[e]	–[e]	60	67	–	91	1	8	0
Jung 2020 (5)	04–17	Seoul	60	Lim	Broad	Ad	17	55	28	–	0	–	–[e]	–[e]	–[e]	–[e]	–	73	–	87	3	10	0
Farooqi 2012 (6)	93–09	I-ELCAP	26	Lim	Broad		20	75		5	1	16	92	0	4	4	63	50	–	–	7	11	0
Zhang 2019 (25)	15–18	Beijing	65	Lim	Broad		++	++	++	+	1	–	92	0	6	2	–	68	62	–	–	–	–
Tan[c] 2019 (20)	11–17	Beijing	106	Lim	–		–	–	–	–	–	–	87	4	8	1	59	65	54	63	11	10	15
Guo 2016 (7)	07–12	Beijing	15	Lim	–		–	–	–	–	–	–	73	7	13	7	58	80	–	69	15	7	7
Fintelmann[f] 2017 (8)	10–15	Boston	30	Mod	Broad		0	57	33	10	–	–	80	0	13	7	66	40	3	60	17	7	17
Pan 2020 (26)	17–20	Zhoushan	35	Mod	Broad		+	++	++	++	–	–	86	3	11	0	61	66	–	–	–	–	–
Haider 2019 (27)	–	Canada	11	Mod	Broad		+	++	++	++	–	–	82	0	18	0	63	18	0	64	27	9	0
Yu 2015 (29)	05–13	Dalian	31	Ext	Broad		–	++++	+	++++	12	50	90	-	6	3	56	58	–	–	–	–	–
Average													89	1	8	2	59	61	47	74	10	9	6
Cavity																							
Kimura 2017 (9)	10–14	Kanagawa	12	Mod	Broad	pl	++	++	++	–	–	–	67	–	25	8	67	75	17	–	–	–	–
Watanabe 2015 (10)	98–07	Tokyo	132	Mod	Broad	Ad	+	++	+++	++	1	18	–[e]	–[e]	–[e]	–[e]	63	68	34	59	18	21	3
Kunihiro 2016 (11)	05–14	Yamaguchi	60	Mod	Broad		–	–	+++	–	–	–	–	–	–	–	69	63	28	82	13	3	1
Chen 2019 (13)	09–14	Shanghai	227	Ext	Broad	pl Ad	–	++	+++	+++	–	–	–[e]	–[e]	–[e]	–[e]	59	48	93	–	–	–	–
Ma 2022 (21)	10–19	Shanghai	384	Ext	Broad		8	42	29	++	–	–	69	–	30	1	58	66	88	58	22	20	0
Byrne 2021 (14)	16–18	Vancouver	47	Ext[g]	Broad		++	++	+++	+++	–	–	76	2	20	2	69	43	17	–	–	–	–
Shigefuku 2018 (12)	05–11	Tokyo	65	Ext	Broad		12	51		37	-	–	–	0	28	8	66	74	11	58	31	11	0
Mascalchi 2015 (28)	–	Italy	24	Ext	Broad		8	50		38	1	67	71	0	29	0	71	71	0	50	13	17	21
Average													69	1	26	4	65	64	36	61	19	14	5
Pseudocavity																							
Kojima 2010 (15)	93–08	Kanagawa	26	Mod	Broad	Ad	–	–	++	++++	–	–	–[e]	–[e]	–[e]	–[e]	68	27	69	88	8	4	0
Utrera Pérez 2019 (16)	07–17	Vigo, Spain	30	–	–	≥2 cm	–	–	–	–	–	–	73	–	23	3	–	–	–	–	–	–	–
Tailor 2015 (66)	00–09	Seattle	23	–	–		–	–	–	–	–	–	83	–	–	–	–	–	–	58	16	21	5
Average													–	–	–	–	–	–	–	–	–	–	–
Bulla/emphysema																							
Shinohara 2018 (17)	07–15	Nagoya	52	Mod	Broad		Few	71		Few	0	35	50	–	36	14	68	83	10	65	27	8	0
Hanaoka 2002 (18)	76–98	Kyoto	50	Ext	–		–	–	–	–	–	–	–	–	26	32	62	98	–	62	26	6	6
Kaneda 2010 (19)	98–08	Mie, Japan	19	V Ext	Nar		0	0	+++	+++	10	80	10	21	45	24	61	100	0	52	26	21	0
Average													34	7	36	23	64	94	3	60	26	12	2

Inclusion criteria: Studies 2000–2022 with >10 cases of LCAL on CT imaging. One study was excluded (Nambu *et al.*) (68) due to limited information and inclusion of mostly lesions with air bronchograms. Red font highlights study characteristics that may make it an outlier.

Ad or Adeno, adenocarcinoma; Ad-Squam, adenosquamous carcinoma; Ext, extensive; I-ELCAP, International Early Lung Cancer Action Project (a CT screening cohort); LCAL, lung cancer with air lucency; Lim, limited; Mod, moderate; Nar, narrow; Squam, squamous carcinoma; V, very;

[a], categorization of extent of solid component; [b], Broad or narrowly configured inclusion criteria; [c], patients with >1 lesions excluded; [d], excluded cavitary tumors; [e], not applicable (only adenocarcinoma); [f], Excluded if <6 months of observation; [g], includes pathologic diagnosis of cavity.

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