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Large cell carcinoma of the lung: LDCT features and survival in screen-detected cases

Abstract

Purpose. To investigate the early radiological features and survival of Large Cell Carcinoma (LCC) cases diagnosed in low-dose computed tomography (LDCT) screening trials.

Methods. Two radiologists jointly reviewed the radiological features of screen-detected LCCs observed in NLST, ITALUNG and LUSI trials between 2002 and 2016, comprising a total of 29,744 subjects who underwent 3-5 annual screening LDCT examinations. Survival or causes of death were established according to the mortality registries extending more than 12 years since randomization.

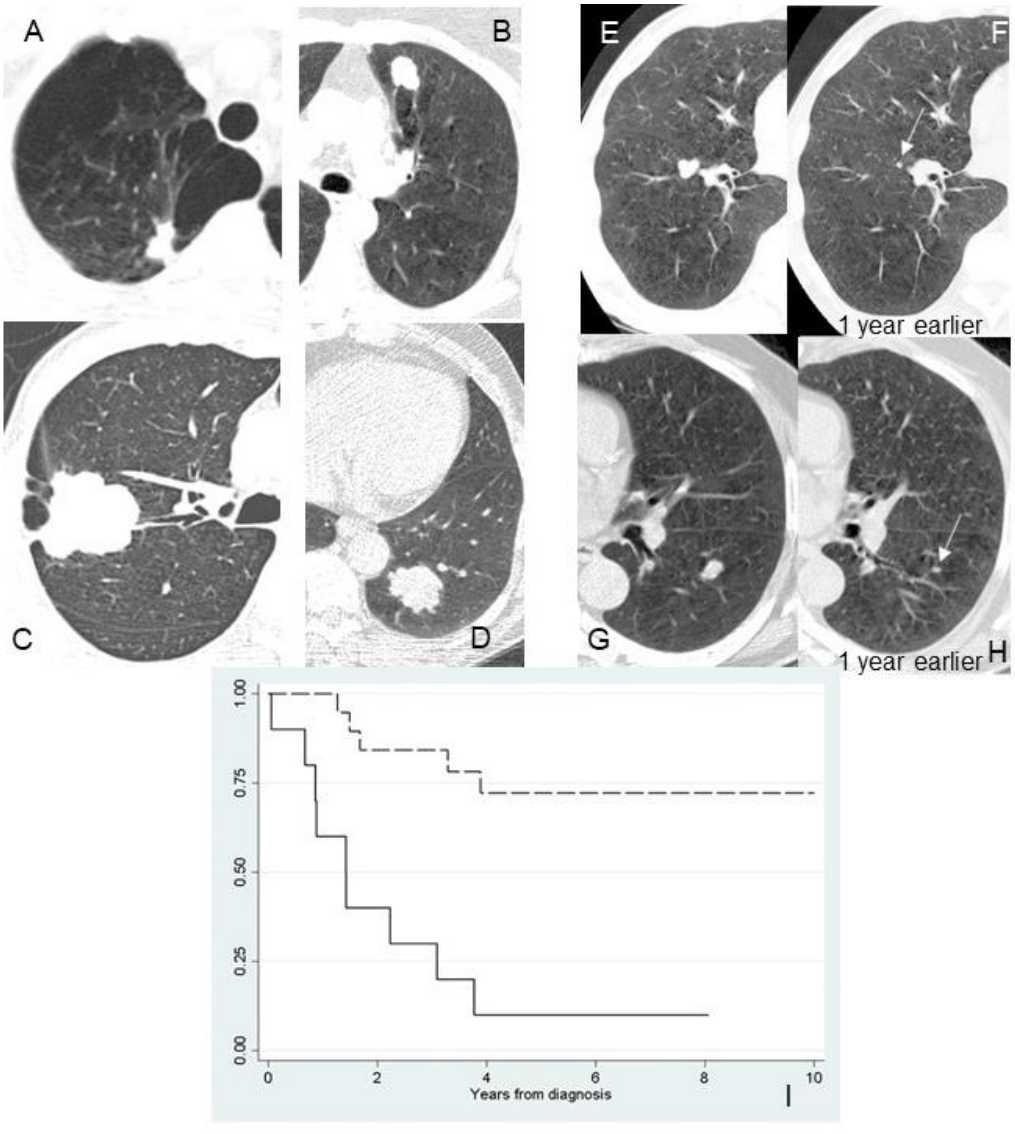
Results. LCC was diagnosed in 30 (4%) of 750 subjects with screen-detected lung cancer (LC). Fifteen LCCs were prevalent, and 15 incident LC cases, whereas 3 additional LCCs occurred as interval cancers during the screening period. LDCT images were available for 29 cases of screen-detected LCC, and in 28 showed a single, peripheral, and well-defined solid nodule or mass with regularly smooth (39%), lobulated (43%) or spiculated (18%) margins. One case presented as hilar mass. In 9 incident LCCs, smaller solid nodules were identified in prior LDCT examinations, allowing to calculate a mean Volume Doubling Time (VDT) of 98.7±47.8 days. The overall five-years survival was 53%, with a significant (p=0.0001) difference between stage I-II (75% alive) and stage III-IV (10% alive).

Conclusions. LCC is a fast-growing neoplasm that can escape detection by annual LDCT screening. LCC typically presents as a single solid peripheral nodule or mass, often with lobulated margins, and exhibits a short VDT. The 5-year survival reflects the stage at diagnosis.

Keywords: ITALUNG; large cell carcinoma; low dose CT; Lung cancer; LUSI; NLST; screening; survival

Graphical abstract

Large Cell Carcinoma (LCC) observed in low-dose computed tomography (LDCT) screening trials typically presented as a single solid peripheral nodule or mass, often with lobulated margins (panels A-D), and exhibited a fast growth (panels E-F and G-H). The 5-year survival (panel I) reflected the stage at diagnosis and was fair (15/20 alive) for stage I-II (dashed line) and poor (1/10 alive) (continuous line) for stage III-IV.



Highlights

- LDCT screening enables the definition of early radiological features of LCC
- LCC was diagnosed in 30 (4%) of 750 subjects with LDCT screen-detected lung cances
- LCC appeared as a peripheral solid nodule/mass often (43%) with lobulated margins
- 5 years after diagnosis, 5/20 stage I-II and 9/10 stage III-IV subjects had died of LCC
- Survival of screen-detected LCC depends on the stage at diagnosis

Introduction

Worldwide, lung cancer (LC) is the second most frequent neoplasm after female breast cancer, but the first cause of mortality due to neoplasm, accounting for about 2.2 million cases and 1.8 million deaths in 2020 [1]. In particular, despite some improvement following molecular characterization and target therapy [2], the overall five-year survival rate of LC is only 20.5% [3]. The main histological types of LC include adenocarcinoma, squamous-cell carcinoma, and small-cell lung cancer.

The 2015 and 2021 World Health Organization classifications of lung tumors identify large cell carcinoma (LCC) as a distinct histotype in resection specimens, defined by lack of glandular, squamous or neuroendocrine differentiation on morphology or immunostaining [4, 5]. LCC accounted for 1.3% of LC in the National Cancer Institute Surveillance, Epidemiology, and End Results Cancer Statistics Review, 2012–2016 [6].

Screening of LC with Low-Dose Computed Tomography (LDCT) decreases LC mortality [7], is now being recommended for 50-80 years old subjects with a long-term smoking history in the US [8], and provides an opportunity to examine early radiological features of LCC on LDCT, and its prognosis in the case of pre-symptomatic detection and treatment.

We reviewed LDCT features and survival in 30 screen-detected LCCs observed in three randomized clinical trials (RCT) of LC screening, namely the National Lung Screening Trial (NLST) [9], the ITALUNG trial [10] and the LUng cancer Screening and Intervention (LUSI) trial [11], that were performed between 2002 and 2016 before the introduction of immunohistochemistry characterization of LCC.

Materials and Methods

The three studies constituting the base for this investigation were registered RCT (NLST: NCT00047385; ITALUNG: NCT02777996; LUSI: SRCTN30604390). Overall, they involved 29,744 smokers and former smokers who were allocated to the active screening arms with LDCT and 30,348 smokers and former smokers who were allocated to the control arms receiving three annual single-view posteroanterior chest radiography in NLST [9] or usual care (no screening) in ITALUNG and LUSI [10, 11]. The enrolment criteria of the three trials were similar [9-11] and included age between 55 and 69 (ITALUNG and LUSI) or 74 (NLST) years and a history of long-term smoking (NLST: 30 pack-years; ITALUNG: 20 pack-years; LUSI: either 25 years' smoking duration plus minimum of 18.75 pack-years, or 30 years' duration combined with at least 15 pack-years). Former smokers were eligible only if they had stopped smoking less than 10 (ITALUNG and LUSI) or 15 (NLST) years ago.

Subjects in the active arm of screening received 3 (NLST), 4 (ITALUNG), or 5 (LUSI) annual LDCT examinations [9-11]. Active screening spanned between 2002 and 2007 and involved 26,309 subjects in the 33 centers of the NLST [12], between 2004 and 2010 and involved 1,406 subjects in the 3 centers of ITALUNG [13], and between 2007 and 2016 and involved 2,029 subjects in the single center of the LUSI [14].

The study PIs of ITALUNG (blinded for review) and LUSI (blinded for review) had access to ITALUNG and LUSI data, including clinical information and all LDCT images. For the NLST cases, two of us (blinded for review) applied for and were granted access to the clinical data and images of all the 1,086 NLST participants who received a diagnosis of LC in the LDCT arm. In particular, the data included participants' initial LDCT and up to two annual repeat LDCTs when available.

All participants had signed an institutional review board (IRB)–approved informed consent form to participate in the trials.

For the present investigation, we selected all cases of LCC that have been diagnosed with histological confirmation in the active arms of the three trials. The screen-detected LCC cases were classified as prevalent, if they were diagnosed within 1 year of baseline LDCT, or incident, if they were diagnosed thereafter within the screening period. Cases of LCC that were not screen-detected during the screening period or were diagnosed within a year after the last screening participation were labeled as interval LCC cases.

Two radiologists with experience in LC screening (blinded for review) reviewed in consensus the following radiological features of the screen-detected LCCs in the available LDCT examinations: site (lobar distribution), size (mean diameter), density (solid, mixed, non-solid, cavitation, cysts), lesion margins (regularly smooth, lobulated or spiculated –"corona maligna") and of significant emphysema defined as an extension >5% of centrilobular emphysema and corresponding to moderate, confluent and advanced emphysema according to the Fleischner Society visual scoring of emphysema on CT [15].

For incident cancers visible in two or more LDCT examinations, the volume doubling time (VDT) was measured in the first and last available LDCT examinations showing the malignant nodule based on the maximum and perpendicular diameters, according to Hasegawa et al. [16].

Tumour staging at diagnosis was extracted from the databases, whereas survival or cause of death were obtained by link to mortality registries, which extended for more than 12 years (median 12.5 years in NLST, median 13.5 years in ITALUNG and median 12.1 years in LUSI) in the three trials [17-19].

Results

Overall, LCC was diagnosed in 30 (4%) of 750 subjects with screen-detected LC. Fifteen LCCs were prevalent and 15 incident LC cases, whereas 3 LCCs occurred as interval cancers during the screening period. In the ITALUNG, one prevalent case of LCC (2.6%) out of 38 screen-detected LCs was observed (Fig. 1). In the LUSI, one incident case of LCC (1.5%) was observed in the 3rd screening round among a total of 63 screen-detected LC cases. In the NLST, 28 (14 prevalent and 14 incident) cases of LCC (4.3%) out of 649 screen-detected LC cases, were observed, and 3 additional LCC cases were diagnosed as interval cancers.

Table 1 reports demographic characteristics, LC risk factors, tumour pulmonary lobe distribution, and (in 29 cases) radiological features in the 30 subjects with screen-detected LCC. The LCCs were observed

in 17 men and 13 women with a mean age 61.5 years. Eighteen were current and 12 were former smokers. Their mean pack-years were 63.2±31.1. One subject reported exposure to asbestos. LCC was localized to the upper lobes in 19 (64%) subjects and lower lobes in 11 (36%).

A review of LDCT images was possible in 29 of 30 cases since they could not be retrieved in 1 NLST case. In the last LDCT before diagnosis, LCC appeared as a single peripheral solid well-defined lesion in 28 cases, with regularly smooth (n=11, 39%), lobulated (n= 12, 43%) (Fig. 2) or spiculated ("corona maligna") (n=5, 18%) margins. No associated cysts or internal cavitation were present. One prevalent case presented as a hilar mass with airway occlusion and atelectasis (Fig. 2). One incident LCC appeared as a non-solid nodule which became solid the next year. In other 9 incident LCCs, smaller solid nodules could be retrospectively identified in prior LDCT examinations (Fig. 2). This allowed to calculate a mean tumor VDT of 98.7±47.8 (mean ± standard deviation) days. Emphysema was observed in 6 (21%) of 29 subjects.

Table 2 reports the stage and LC mortality in the 30 screen-detected LCC cases. There were 20 (66%) stage I-II and 10 (33%) stage III-IV at diagnosis. After 5 years of diagnosis, 14/30(47%) subjects had died of LC, 5/20 in stage I-II and 9/10 in stage III-IV. The overall 5-year survival was 53%, with a significant (Log-rank test, p=0.0001) difference between stage I-II (75% alive) and stage III-IV (10% alive) (Fig. 3).

Discussion

According to Travis [20], LCC diagnosis can be made in the case of a poorly differentiated non–small cell carcinoma that lacks glandular or squamous differentiation by morphology or immunostaining (negative to TTF-1 and p40 to exclude glandular or squamous differentiation, respectively) (Fig.1). In this restrictive sense, LCC is ultimately a diagnosis of exclusion that applies to LC with large cytoplasm/nucleus and no immune-marker consistent with adenocarcinoma or squamous cell carcinoma. Moreover, diagnosis of LCC requires a resection specimen and cannot be made on small biopsy or cytological samples [20]. Application of these criteria accounts for the progressive decrease of the frequency of LCC, from the 9% of LC in the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) monograph for 1983 to 1987 [21] to the 1.3% of LC in the SEER document for 2012–2016 [6]. Some pathologists, based on the above trend, have even anticipated the ultimate extinction of LCC as a diagnostic entity [22, 23]. However, LCC is still recognized in the 2021 WHO Classification of Lung Tumors [5], and a subdivision has been made on the basis of immunohistochemistry results among LCC- adenocarcinoma (LCC-AD), LCC-squamous cell carcinoma (LCC-SqCC), or LCC- marker-null (LCC-Null) tumors (Fig.1) [24, 25]. In accordance with the 2015 and 2021 WHO Classification of Lung Tumors, the term LCC in a restrict sense should probably refer only to the marker-null LCC subtype [4, 5].

Admittedly, the diagnoses of the screen-detected LCCs reviewed here were made between 2002 (NLST) and 2013 (the incident case of LUSI), when immunohistochemistry analysis had no established role of in the assessment of these tumors. For this reason, we considered here the category of LCC in a large sense,

including not only LCC-Null tumors (Fig.1), but presumably also a relevant and undefined percentage of LCC-AD and LCC-SqCC tumors. However, so far, the possible clinical benefit for the patient's treatment of sub-classification through immunohistochemistry of LCC [4, 20, 26] with the possibility of mutations detection and target therapy have not established [26]. In particular, no significant difference in disease specific survival among the LCC-AD, LCC-SqCC, and LCC-Null subgroups was reported [24], only LCC-Null tumors being associated with a significantly worse prognosis when compared to all other more common LC histotypes as adenocarcinoma and squamous cell carcinoma [24, 25]. Therefore, we feel that a reappraisal of the LDCT features and survival in screen-detected immune-marker undefined LCC might be still worth doing. In fact, on the one hand, the LDCT features of screen-detected LCCs has not been described so far, and may help radiologists in suspecting these uncommon LCs. On the other hand, prognostic profile of immune-marker undefined LCC cases may represent a valuable benchmark for assessment of the likely beneficial effects of immune-marker characterization.

The average 4% frequency (range 1.5-4.3%) of LCC among all (screen-detected or interval) LC in the three LDCT trials we considered is in the middle between the 9-1.3% range of the SEER series related to clinically presenting cases [6, 21], but lower than the 11.6% frequency observed in the NELSON LC screening trial [27], confirming that LCC is a rare LC.

The distribution among prevalent, incident and interval cancers of the screen-detected LCCs we evaluated indicates an aggressive tumor type. In particular, LCC was the second more frequent histotype, after Small Cell Cancer (SCC), presenting as an interval cancer in both the NLST (3/30:10%) [9] and in the NELSON (6/27:22%) [27] trials.

Until now the CT or LDCT features of LCC have not been addressed. In 29 screen-detected LCCs we observed substantially homogeneous LDCT features consistent with an aggressive tumor type that remarkably match the radiological features outlined in chest X-rays studies of screening or clinically detected LCCs performed in Japan [28-30]. These include: the singularity of the lesion (as opposed to adenocarcinomas which may be multicentric) [31]; its largely predominant peripheral location (as opposed to SCC and squamous cell carcinoma) [32]; its well-defined and often lobulated margins, reflecting expansive tumor growth; lack of internal cavitation (as seen in squamous cell carcinoma) [33] or of associated cystic components (as commonly seen in adenocarcinomas) [34]; and, finally, the short VDT. In particular, the mean VDT in 9 of our LDCT screen-detected LCCs (98 days) falls in the middle between the mean VDT of 67 and 134 days, respectively, calculated (in overall 23 LCC cases) in two screening chest X-rays studies in Japan [28, 29]. The shorter VDT of LCC appears a possibly characterizing feature as compared to other more frequent peripheral screen-detected LCs that show longer mean or median VDT, e.g., in the range of 177-1140 days for adenocarcinomas [16, 28, 29, 35, 36] and of 115-160 days for squamous cell carcinomas [16, 28, 29, 35].

Based on the radiological presentation of a peripheral single solid, well-defined lesion and with a short VDT, the main differential diagnosis of LCC appears to be early-stage SCS (limited disease) [37] that accounts for 30% of the SCC, the remainder of SCC presenting as extensive stage disease with overt hilar or mediastinal masses [38]. A possible subtle, differential radiological aspect might be the irregular, non-nodular shape of early-stage SCC, which was described presenting as “small spindle or pyramidal”, as well as ”vermiform, pine-cone-like or tandem-like” lesions, reflecting spread along the bronchial walls [37]. While we did not observe such non-nodular shapes in any screen-detected LCC case, the VDT we measured (mean 98 days) and that of and early-stage SCC (mean 84 days) [37] is similar.

The overall 5-year survival in our 30 subjects with screen-detected LCC was 53%, with a marked difference between stage I-II (75% alive) and stage III-IV (10% alive). These data are in line with studies of clinically symptomatic LCC without [39] or with immunohistochemistry characterization [24, 25, 40]. This prognostic profile may represent a valuable benchmark for assessment of the impact of immune-marker characterization, molecular genetic mutations and targeted therapy, that is currently indicated for advanced stage LCC cases [24, 25, 40].

We recognize the following limitations of our study. First, we performed a retrospective, multi-center investigation, which may imply that pathologists have some heterogeneity in diagnosing LCC. However, the histological features of LCC are well-established [5, 20]; all the diagnoses of the LCC reported here were made on tissue specimens following invasive procedures including thoracotomy, thoracoscopy, mediastinotomy or mediastinoscopy; and the frequency of LCC diagnosis in the active screening arm of the three trials was similarly very low. Second, except than for the single case observed in ITALUNG, we have no information about possible immunohistochemistry tests and sub-classification of the LCC in our cases. Third, no detailed information about therapy in NLST cases of LCC is available. Still, execution of state-of-the-art (namely without target therapy in advanced stages) treatment was confirmed in all subjects and included surgical excision for the early stages.

In conclusion, our study indicates that, in line with its histological features of an undifferentiated tumor and with the experience of chest X-rays screening, LCC is a fast-growing neoplasm that can escape detection by annual LDCT screening. LCC typically presents in screening LDCT as a single peripheral solid nodule or mass, often with lobulated margins, and without cavitation or associated cysts, but with a short VDT. The prognosis substantially reflects the stage at diagnosis.

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'Declaration of Generative AI and AI-assisted technologies in the writing process'.

No AI or AI-assisted technologies were used in preparing this manuscript.

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Legends

Fig.1 A-D). A prevalent screen-detected LCC in ITALUNG appears as a mass lesion with lobulated margins in the left lower lobe (A). Ematoxylin and Eosin stain (original magnification 20X) (B) shows an undifferentiated non-small cell carcinoma without glandular and squamous differentiation. The negative staining for TTF1 (C) and p40 (D) allows diagnosis of large cell carcinoma with marker-null phenotype.

Fig. 2 A-H. LDCT presentations of screen-detected LCC. Prevalent LCCs (A-D) appear as single solid nodular or mass lesions with lobulated margins in the right (A; NLST id. 204878) and left (B; NLST id. 108420) upper lobes, and in the right (C; NLST id. 207286) lower lobe. One prevalent LCC presents with an atelectasis of the left inferior lobe (*) associated with stenosis and occlusion of the left central airway (D; NLST id. 207431). One incident LCC appears as a solid nodule with lobulated margins in left lower lobe (E; NLST id. 100658) that was retrospectively attributed to a small solid round nodule (arrow) in the LDCT obtained one year earlier (F), when it had not been further investigated due to its small size. One incident LCC appears as a solid nodule with lobulated margins in the right lower lobe (G; NLST id. 127302) that was retrospectively attributed to a small solid round nodule (arrow) in the LDCT obtained one year earlier (H), when it had not been further investigated due to its small size.

Fig. 3. Kaplan-Meier survival curve since diagnosis in the 30 screen-detected LCC stratified by stage at diagnosis (dashed line for stages I-II) (solid line for stages III-IV). Log-rank test chi-square=15.62, p=0.0001.

Table 1. Demographic characteristics, risk profile and LDCT features in 30 screen-detected LCC of the lung

	ITALUNG	LUSI	NLST	Total
	n=1	n=1	n=28	n=30
Age (yrs at randomization) Mean ± sd	60	65	61.5 ± 5.1	61.5 ± 50
Gender				
Male (n,%)	1	1	17	19 (63%)
Smoking status				
Current	1	0	17	18 (60%)
Former	0	1	11	12 (40%)
Pack-years				
mean ± sd	63	62.7	63.2 ±32.3	63.2 ± 31.1
Exposure to asbestos				
No	1	1	27	29 (97%)
Yes	0	0	1	1 (3%)
Site				
RUL	0	1	14	15 (50%)
RLL	0	0	4	4 (14%)
LUL	0	0	6	6 (18%)
LLL	1	0	4	5 (18%)
Size at last LDCT				n=29 ^
Mean diameter (mm)	35	11	15.7	16.2
Density at last LDCT ^				n=29^
Solid	1	1	27	29/29 (100%)
Margins at last LDCT ^*				n=28^*
regularly smooth		1	10	11/28 (39%)
lobulated			12	12/28 (43%)
spiculated	1		4	5/28 (18%)
Empyhsema at LDCT #				n=29^
Yes	0	0	6	6/29 (21%)
Volume Doubling Time				n=9
mean ± sd (days)	NA	NA	98.7 ±47.8	98.7 ± 47.8

^ LDCT images could not be retrieved in one case of NLST; * one NLST case presented as hilar mass with airway occlusion and atelectasis; # defined as an extension of centrilobular emphysema >5% of lung parenchyma

sd= standard deviation

Table 2. Stage and LC mortality in 30 screen-detected LCC of the lung

	ITALUNG	LUSI	NLST	Total
	n=1	n=1	n=28	n=30
Stage I			18	18
IA			14	14
IB			4	4
Stage II	1		1	2
IIA	1			1
IIB			1	1
Stage III		1	5	6
IIIA		1	4	5
IIIB			1	1
Stage IV			4	4
LC death	1	0	13	14

Fig.1

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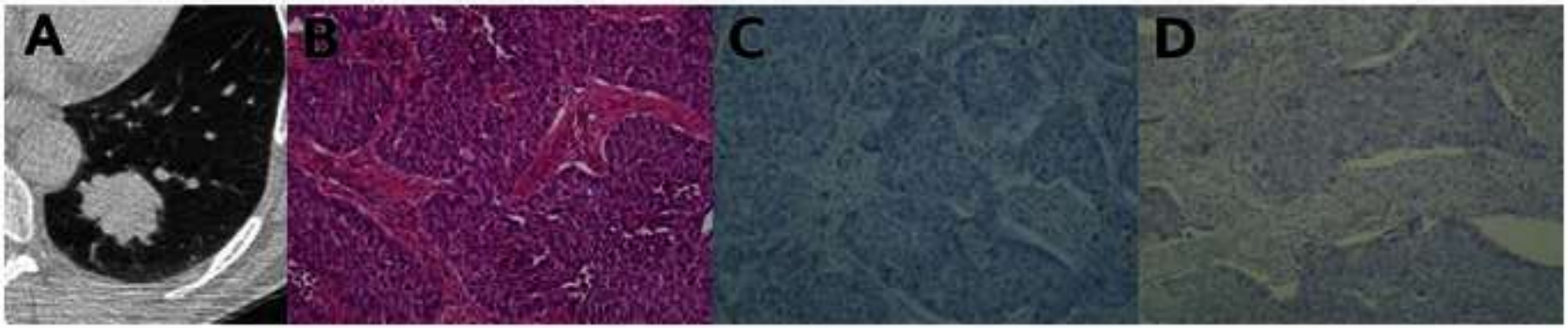

Fig.2

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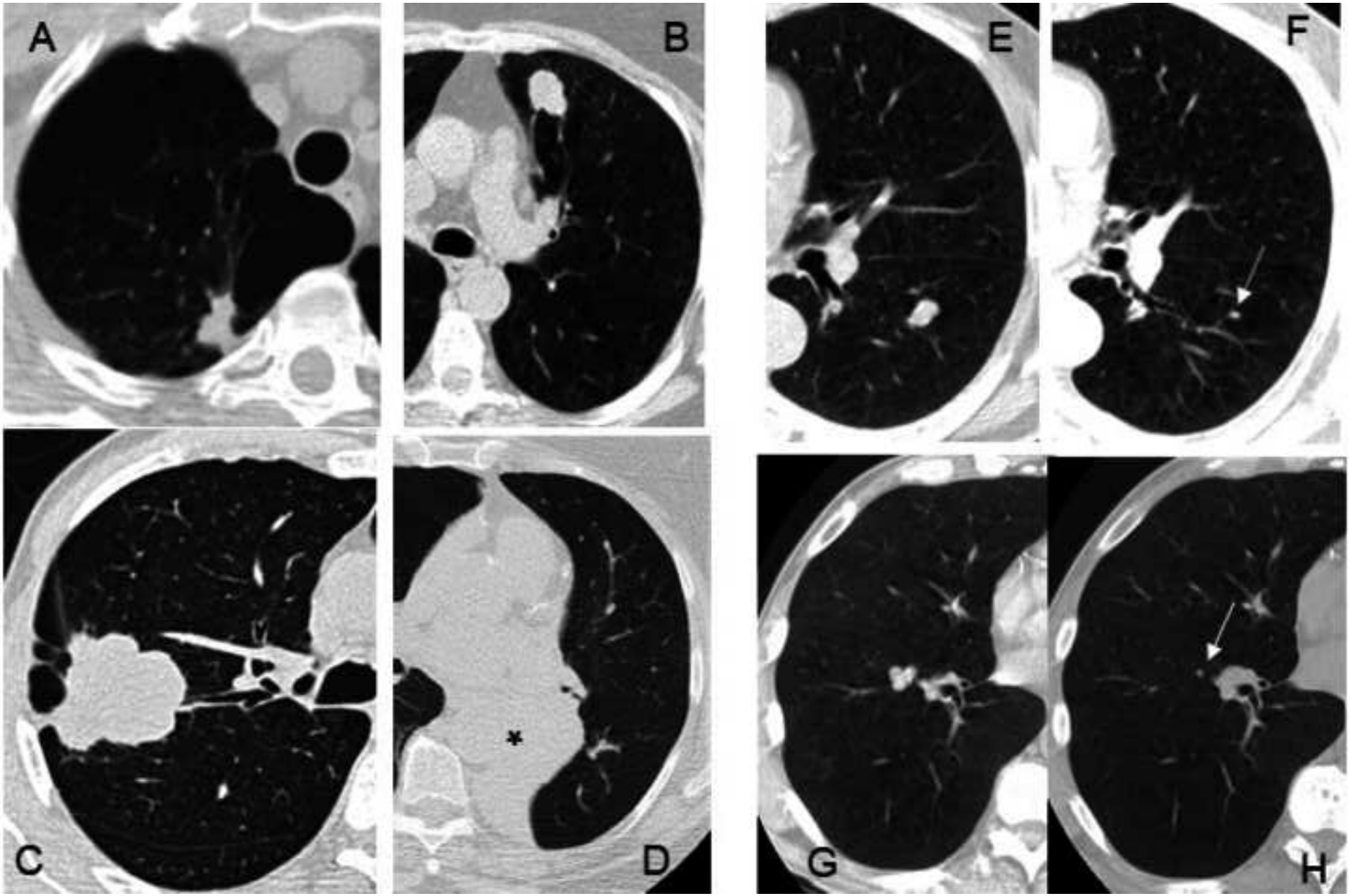

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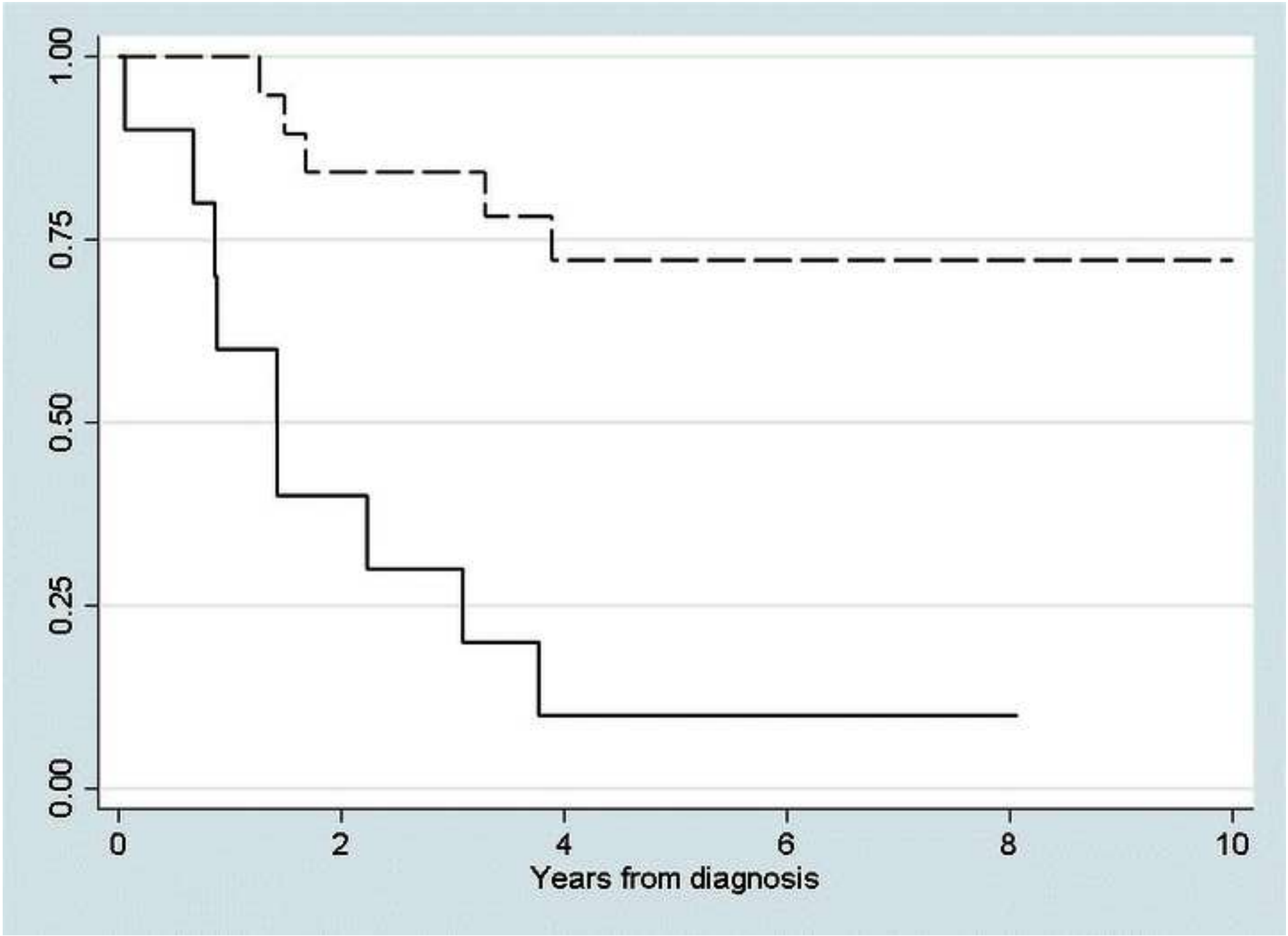
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