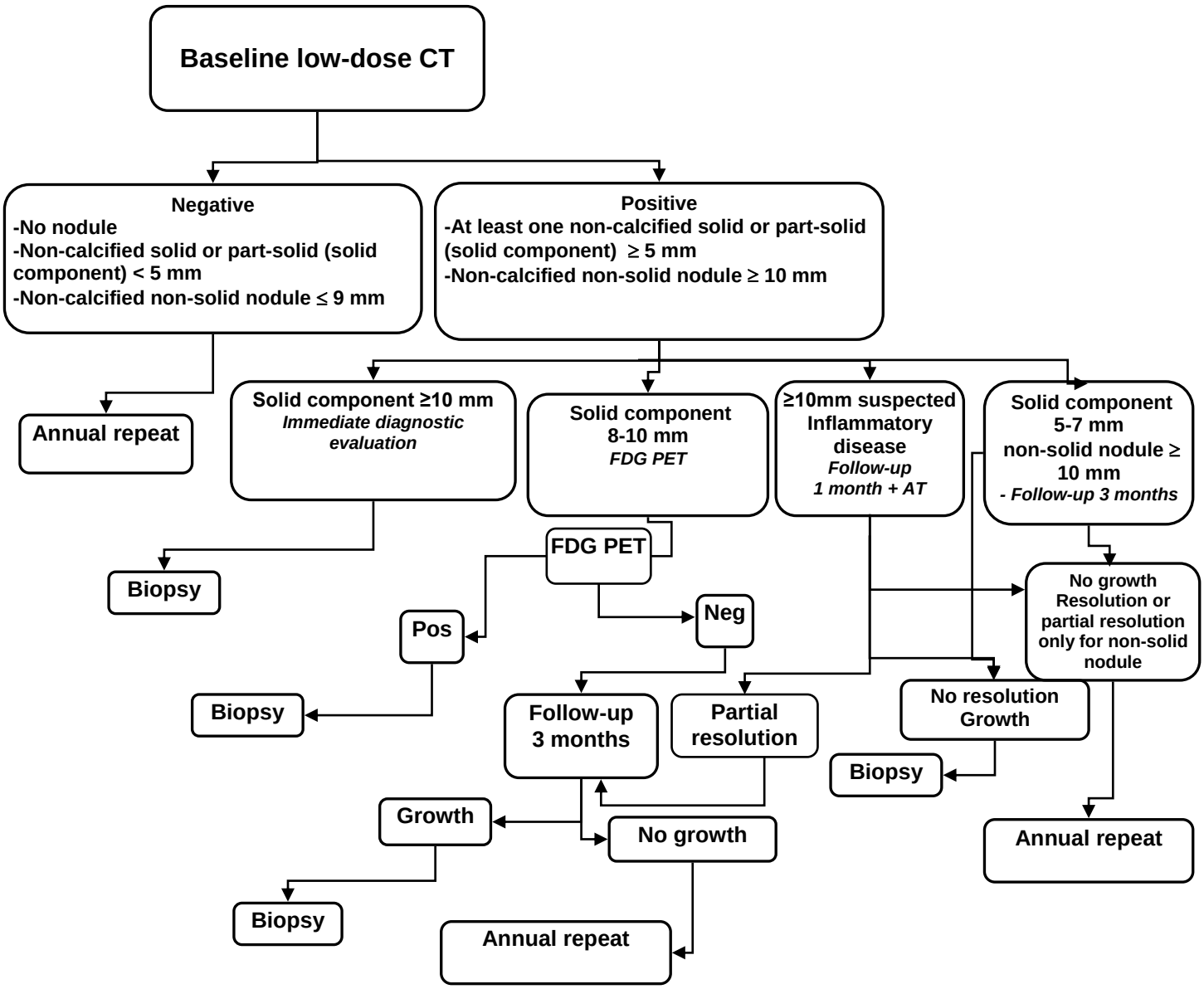
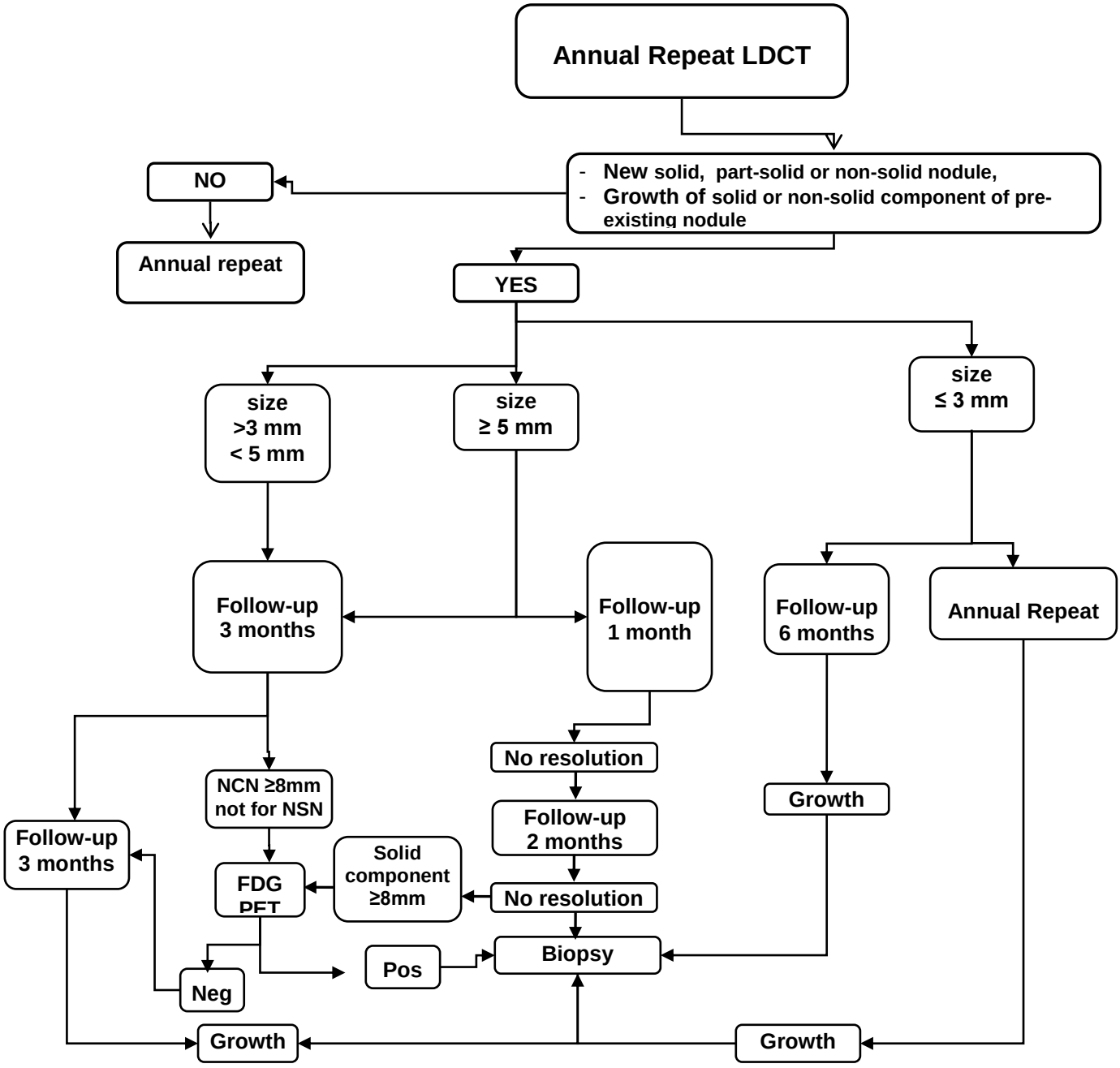
SUPPLEMENTARY APPENDIX: Section 1

Flow chart of management of Non Calcific Nodules (NCN) in ITALUNG RCT. Baseline and Repeated LDCT screening.





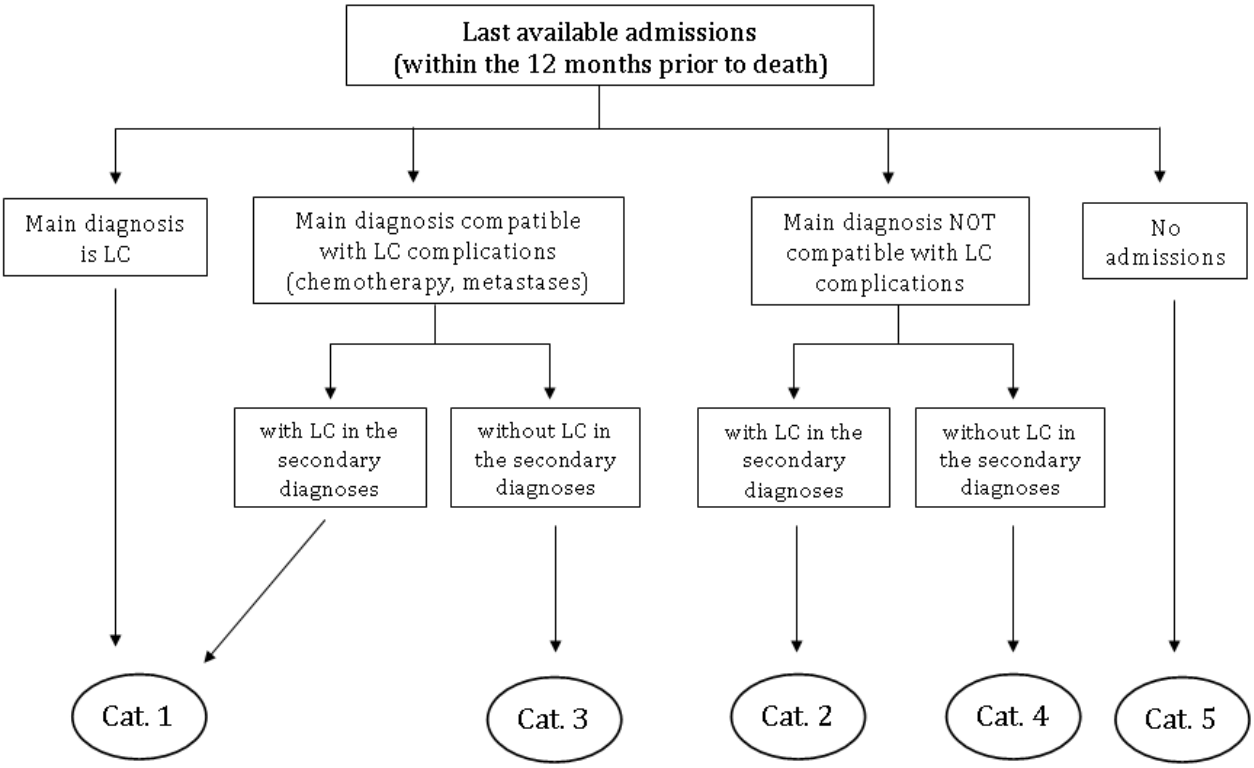
SUPPLEMENTARY APPENDIX: Section 2: CAUSE OF DEATH REVIEW

During the follow-up, 335 deaths were observed among subjects enrolled in the ITALUNG trial. A classification algorithm, defined on the basis of the classification of hospital discharge notes and death certificates, was used to identify 31 cases (9.3%) for cause-of-death review (Table 1).

Definition of the algorithm

Firstly, all deaths were linked to hospital discharge records using admissions which had occurred only in the 12 months prior to death. The last available admissions were classified to one of 5 categories depending on whether the main and secondary diagnoses were lung cancer (LC), compatible with LC complications (chemotherapy, radiotherapy and metastases) or not compatible with LC complications, as described in Figure 1.

Figure 1.
Flow chart of hospital discharge notes categories.



Secondly, all death certificates were retrieved and classified to one of 5 categories depending on the death certificate code (LC or other than LC) and on all the causes reported in the certificate, as described in Figure 2.

Figure 2.
Flow chart of deaths certificates categories.

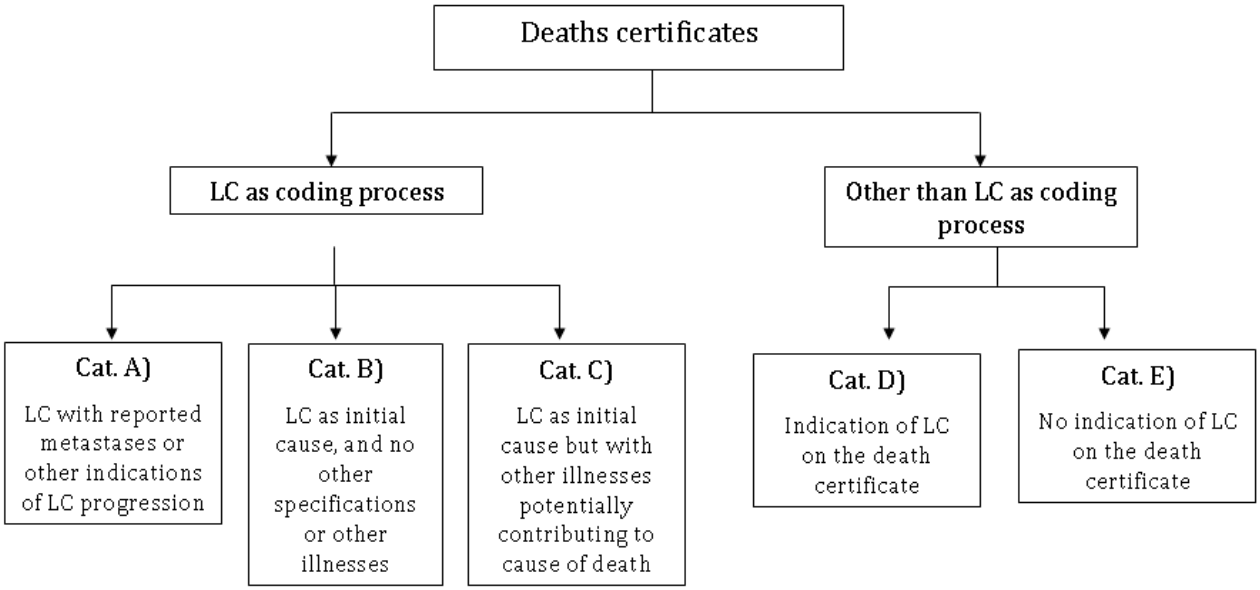


Table 1. Classification algorithm (number of deaths)

	Hospital discharge note category				
Death certificate category:	**1)** Main diagnosis LC	**2)** Secondary diagnosis LC	**3)** Main diagnosis compatible with LC	**4)** LC not mentioned	**5)** No admission
A) LC, metastases	LC (n=35)	LC (n=10)	LC (n=4)	Review (n=4)	LC (n=0)
B) LC, no other illnesses	LC (n=9)	LC (n=6)	Review (n=0)	Review (n=3)	Review (n=1)
C) LC, other illnesses	LC (n=15)	Review (n=6)	Review (n=0)	Review (n=7)	Review (n=0)
D) Other than LC, with indication of LC	Review (n=1)	Review (n=2)	Review (n=0)	Review (n=4)	Review (n=0)
E) Other than LC, without indication of LC	Review (n=2)	Review (n=1)	No LC (n=26)	No LC (n=158)	No LC (n=41)

Note : the 31 subjects reviewed by the cause of deaths panel of experts are those in the cells marked 'Review'.

<u>Review of the cause of death</u>

Finally, a panel of experts (AB, AC and CG) was convened to review, blind to the study arm, the 31 subjects resulting from the algorithm. The following information was available to the panel:

- LC features from cancer registries (date of incidence, staging and therapy when available);

- All available admission data from computerized hospital discharge notes (admission and discharge date, admitting department and hospital, main and other diagnosis, modality of discharge);
- The DC form or similar documentation, showing all illnesses recorded on DC;
- Presence of other cancers (date of incidence, staging, and therapy).

Two experts (AB and AC) reviewed each case independently and the review was assumed to be complete when the two experts expressed the same opinion. In the event of disagreement, cases were discussed with the third expert (CG).

The review confirmed the original cause of death in 28 out of 31 cases (90%). Three cases originally classified as 'died of cause other than LC' were re-classified as 'died of LC'.

SUPPLEMENTARY APPENDIX: Section 3

Surgery, stage and histological type of lung cancers by detection mode in the active group (n=67)

	Screen-detected (n=38)	Clinically detected among screened (n=25)	Clinically detected among unscreened (n=4)
Surgery			
Resected	31 (82%)	4 (16%)	0 (0%)
Not Resected	7 (18%)	21 (84%)	4 (100%)
Stage*			
I	23 (61%)	1 (4%)	0 (0%)
II	5 (13%)	0 (0%)	0 (0%)
III	4 (11%)	5 (20%)	0 (0%)
IV	6 (16%)	16 (64%)	2 (50%)
Unknown	0 (0%)	3 (12%)	2 (50%)
Histological type			
Adenocarcinoma	23 (61%)	6 (24%)	0 (0%)
Squamous-cell carcinoma	7 (18%)	7 (28%)	0 (0%)
Small cell lung cancers	3 (8%)	5 (20%)	2 (50%)
Carcinoid	2 (5%)	0 (0%)	0 (0%)
Non-small cell carcinoma**	1 (3%)	2 (8%)	0 (0%)
Unclassified	2 (5%)	5 (20%)	2 (50%)

* Pathological or clinical

** This category includes 2 non-small cell carcinomas, not other specified and 1 adenosquamous carcinomas,

SUPPLEMENTARY APPENDIX: Section 4: LIST OF ADVERSE EVENTS

List of 12 subjects deceased within 60 days after an invasive diagnostic procedure:

Group	Invasive diagnostic procedure	Date of the invasive diagnostic procedure	Date of death	Cause of death	Days from the invasive procedure to death	Detection mode
Active	Surgery	01/02/2006	02/02/2006	C34	1	Screen-detected
Active	Exploratory thoracotomy	12/05/2006	19/05/2006	C34	7	Screen-detected
Active	FNAC	06/09/2006	29/09/2006	C34	23	Clinical
Active	Biopsy	08/07/2010	27/08/2010	C34	50	Clinical
Active	Biopsy	09/02/2011	18/03/2011	C34	37	Clinical
Active	Surgery	12/09/2013	26/09/2013	C34	14	Clinical
Control	FNAC	20/01/2009	09/02/2009	C34	20	Clinical
Control	Surgery	10/06/2010	03/07/2010	C34	23	Clinical
Control	Surgery	18/11/2010	28/12/2010	C34	40	Clinical
Control	FNAC	24/01/2011	28/01/2011	J84	4	Clinical
Control	Biopsy	22/08/2013	05/09/2013	C34	14	Clinical
Control	Bronchoscopy	06/09/2012	24/10/2012	C34	48	Clinical