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From randomized trials to the clinic: is it time to implement individual lung-cancer screening in clinical practice? A multidisciplinary statement from French experts on behalf of the french intergroup (IFCT) and the groupe d'Oncologie de langue française (GOLF)

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Background: Despite advances in cancer therapy, mortality is still high except in early-stage tumors, and screening remains a challenge. The randomized National Lung Screening Trial (NLST), comparing annual low-dose computed tomography (LDCT) and chest X-rays, revealed a 20% decrease in lung-cancer-specific mortality. These results raised numerous questions. The French intergroup for thoracic oncology and the French-speaking oncology group convened an expert group to provide a coherent outlook on screening modalities in France.

Methods: A literature review was carried out and transmitted to the expert group, which was divided into three workshops to tackle specific questions, with responses presented in a plenary session. A writing committee drafted this article.

Results: The multidisciplinary group favored individual screening in France, when carried out as outlined in this article and after informing subjects of the benefits and risks. The target population involves subjects aged 55–74 years, who are smokers or have a 30 pack-year smoking history. Subjects should be informed about the benefits of quitting. Screening should involve LDCT scanning with specific modalities. Criteria for CT positivity and management algorithms for positive examinations are given.

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Conclusions: Individual screening requires rigorous assessment and precise research in order to potentially develop a lung-cancer screening policy.

Key words: low-dose CT scan, lung cancer, lung nodule, screening, tobacco

introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Most patients are diagnosed with advanced-stage tumors, precluding curative-intent treatment. Lung-cancer screening is aimed at decreasing lung-cancer-associated mortality and improving prognosis by detection at an early stage, especially stage I, which has the highest long-term survival rates (up to 90%) following surgical resection [1–3]. While lung-cancer screening trials using chest radiography have reported inconsistent findings [4–6], several studies using low-dose computed tomography (LDCT) scans have led to a re-evaluation of screening programs. However, increases in the proportion of stage I cancers and survival rates after diagnosis have not sufficiently demonstrated the efficacy of screening, as these outcomes are subject to bias. Screening benefits can only be demonstrated by comparing specific mortality with and without screening in randomized trials. The randomized, controlled National Lung Screening Trial (NLST) [7] recently demonstrated a reduction in lung-cancer-related and overall mortality of 20.0% [95% confidence interval (CI), 6.8–26.7; $P = 0.004$] and 6.7% (95% CI, 1.2–13.6; $P = 0.02$), respectively, when using LDCT instead of chest radiography. In recent months, these results have received substantial media coverage in the medical and general communities. In routine practice, patients, especially smokers, have increasingly questioned physicians about individual lung-cancer screening.

Given this context, the French intergroup for thoracic oncology [Intergroupe Francophone de Cancérologie Thoracique (IFCT)] and the French-speaking oncology group [Groupe d'Oncologie de Langue Française (GOLF)] invited a group of thoracic oncologists, respiratory specialists, radiologists, surgeons, methodologists, and general practitioners (GPs) to join a multidisciplinary taskforce. Our main objective was to discuss how recent data from lung-cancer screening randomized trials might be implemented on the individual level. Based on available evidence, this article provides physicians and patients with practical information and recommendations for individual lung-cancer screening.

methodology

Following the publication of the NLST [7], the experts of the taskforce were invited to participate in a workshop on 17 February 2012 in Paris, France (supplementary Table S1, available at *Annals of Oncology* online). The taskforce was sponsored by an unrestricted grant from Roche SA France, who played no role in data collection, interpretation, discussion, or manuscript writing. Before the meeting, a core workgroup (FB, EL, BMi, and GZ) undertook a comprehensive literature review, selecting and distributing key publications to the group. It should be emphasized that this is not a systematic review of the literature following usual recommendation for guidelines edition. The following keywords were used for the literature review on the Medline database: 'lung cancer', 'screening', 'randomized, controlled trial', 'nodule', 'CT scan', 'low-dose CT', and 'tobacco'. The bibliography was completed with references to the retrieved articles and with articles suggested by each expert in its proper field.

The core workgroup first listed a number of questions usually asked by patients and colleagues in their daily practice. This list was then sent to the whole group for afterthought. At the meeting, the first plenary session was dedicated to edit the final question list that was approved by showing hands. Each pack of question was then discussed in three workgroups (supplementary Table S2, available at *Annals of Oncology* online) based on available evidence in order to formulate multidisciplinary statements, which were further refined after discussions by the whole group. Finally, this paper was edited by a writing committee (FB, AC, SC, NG, VG, LGr, EL, BMe, BMi, and GZ), and the draft was reviewed and amended by some experts from the taskforce.

to whom should CT screening be proposed?

The NLST results [7] (20% decrease in lung-cancer-specific mortality) appear sufficient to support individual screening. Individual screening may be carried out on a physician's recommendation or at a subject's request once informed of the potential benefits and risks. Participation must be voluntary. To be eligible, subjects must fulfill certain criteria in line with those previously published studies [8–11] (*cf.* Table 1):

- aged between 55 and 74 years;
- at least 30 pack-year tobacco exposure;
- active smoker or quit during the last 15 years;
- no serious progressive disease (history of cancer other than non-melanoma skin cancer or carcinoma *in situ* over the past 5 years[1]; severe co-morbidity, including respiratory insufficiency contraindicating invasive chest examination; prior hemoptysis; unexplained weight loss over 10% over the past 12 months);
- no pulmonary infection over the 12 past weeks;
- accepts repeated scans or additional investigations in the case of abnormal findings;
- accepts considering help to quit smoking (active smokers).

With the help from the attending physician, the prescribing physician should systematically propose helping subjects quit smoking, referring them to health care professionals and suggesting anti-smoking organizations (http://www.tabac-info-service.fr; http://www.ofta-asso.fr; http://cancer.gov/cancertopics/tobacco/smoking). Subjects, particularly those continuing to smoke, should be reminded of the benefits of quitting at each visit.

[1]Screening does not apply to these patients, since they require specific management and monitoring.

Table 1. Comparison of protocol characteristics in the main lung-cancer screening trials

Trial (Country)	*N*	Schedule	CT scan frequency	Duration of screening	CT scan interpretation	Population	Status	Ref
UKLS (UK)	28 000	LDCT versus usual care	Single	No further screening if baseline negative	Double reading	50–75 years, risk >5% of developing lung cancer (questionnaire based on LLP)	Recruiting since September 2011. Preliminary pilot (4200 subjects) results available in 2013. Final results expected in 2016.	[18]
NELSON (NE & BE)	7557	LDCT versus usual care	Y1-Y2-Y4	NA	Double reading	50–75 years, smokers (quit ≤10 years ago) who smoked >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years.	Recruitment completed, final results expected in 2015	[15, 19, 40]
LUSI (DE)	4000	LDCT versus usual care	1/year	Baseline + 4 years	NR	50–69 years, 'heavy smoker'	Recruiting since 2007	[49]
ITALUNG (IT)	3206	LDCT versus usual care	1/year	Baseline + 3 years	Double reading	55–69 years, >20PY, quit <10 years	Recruitment completed, results expected in 2012	[17, 20]
DLCST (DA)	4104	LDCT versus usual care	1/year	Baseline + 4 years	Double reading	50–70 years, >20PY and quit after 50 years and <15 years	Completed, 5-year results published.	[16, 50]
MILD (IT)	4099	Annual LDCT vs biennal LDCT vs usual care	Annual: 1/year, biennial: 2/year	Baseline + 9 years	Double reading, one use automated volume measurement software.	≥49 years ,>20PY, quit <10 years	Completed, 5-years results published.	[25]
COSMOS (IT)	5201	LDCT	1/year	Baseline + 4 years	Double reading for positive only	≥50 years, ≥20PY, quit <10 years	Completed, all round reported.	[12, 13, 14]
DANTE (IT)	2811	LDCT versus usual care	1/year	Baseline + 4 years	Double reading	60–74 years, >20PY	Completed, 3-year results published.	[9]
NLST (US)	53 454	LDCT versus CXR	1/year	Baseline + 2 years	Single reading	55-74 years, >30PY; quit <15 years	Completed and published	[7]
DEPISCAN (FR)	765	LDCT versus CXR	1/year	Baseline + 2 years	Double reading	50–75 years, >15PY; smoking duration >20 years; quit <15 years	Completed and published	[10]
I-ELCAP (EUR, CHI, ISR, JAP, US)*	31 567	LDCT	1/year	Baseline + 1 year	Not in routine, second reading for quality assurance only	>40 years, current or former smoker, never smoker at risk because of exposure to occupational carcinogens or second hand smoking	Completed and published	[1]

CXR, chest radiography; LDCT, low-dose computed tomography; LLP, Liverpool Lung Project; PY, packs per year.

Table 2. Comparison of positive screening test results in the different studies

Study (country)	*N* subjects (CT scan group)	*N* screening CT scans	Positivity criteria for CT screening	*N* positive for CT scan (%/all screening CT scans)	*N* cancers (%/all positive CT screening)	*N* stage 1 (%/all cancers)	Ref
NELSON (BE + NE) (baseline + round 1)	7757	14 846	>500 mm^3–(9.8 mm) or 50–500 and doubling time <400 days	324 (2.2%)	126[a] (38.9%)	88 (69.8%)	[15,19,40]
ITALUNG (IT) (baseline + round 1-3)	1406	5506	Solid ≥5 mm, non-solid ≥10 mm	1045 (18.9%)	38 (3.6%)	NR	[17,20]
DLCST (DA) (baseline + rounds 1–4) 5-year results	2052	9800	≥5 mm	512 (5.2%)	69 (13.5%)	47 (68.1%)	[16,50]
MILD (IT), 5-year results	2376 (A: 1190 – B: 1186)	9477 (A: 5714; B: 3763)	>60 mm^3	NR	59[b] (0.6%) (A: 34 [0.6%]; B: 25 [0.7%])	63%	[25]
COSMOS (IT) (baseline + round 2-5)	5203	23 180	>5 mm	NR	186 (0.8%)	78%[c]	[12,13,14]
DANTE (IT) baseline + 4 rounds) 3-year results (median follow-up = 33 months)	1276	3612	≥10 mm or smaller but showing spiculated margins or focal ground-glass opacities or other relevant abnormalities.	NR[d]	63 (–)	33 (52.4%)	[9]
NLST (US) (baseline + rounds 1–2)	26 722	75 126	≥4 mm	18 146 (24.1%)	649[e] (3.6%)	400[e] (61.6%)	[7]
DEPISCAN (FR) (baseline)	330	336	All NCN	152 (45.2%)	8 (5.3%)	3 (37.5%)	[10]
I-ELCAP (EUR, CHI, ISR, JAP, US)[e] (baseline + round 1)	31 567	59 023	Baseline: ≥5 mm (solid) or ≥8 mm (non-solid), annual: newly identified NCN	5646 (9.6%)	484 (8.6%)	412 (85.1%)	[1]

CT, computed tomography; *N*, number; NCN, non-calcified nodule; NR, not reported; A, annual group; B, biennial group.

[a]Some are positive after being first indeterminate and after rescanning at 3 months.

[b]Include 49 CT-detected lung cancers.

[c]Include all initial stages.

[d]A total of 351 patients had a positive CT scan during the considered screening period.

[e]Lung cancer diagnosed following a CT screening only. In contrast, the total number of patients with cancer diagnosed in the CT group is 1060 (5.8%) and the number of corresponding stage 1 is 520 (49%).

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how to inform subjects about screening?

Subjects wishing to undergo LDCT scans for cancer screening should receive detailed information, notably about the risks of detecting abnormalities (Table 2) and the probability of complementary examinations or surgical procedures leading to the diagnosis of malignant or benign conditions (one-third of cases). In the NLST, for over 17 000 positive examinations, 457 invasive procedures (surgery, bronchoscopy, and needle puncture) were carried out in subjects not diagnosed with a malignancy (2.6% 'useless' investigations). Of these, 413 (90.4%) were completed without any complications, while major complications occurred in 44 (0.24%). By comparison, in COSMOS (an Italian cohort study with 5201 subjects incorporating TEP scan in nodule management) 13 useless surgeries were carried out after baseline and first round screening accounting for 0.13% of all positive screening CT scan [12–14]. In the NELSON study [15] (incorporating volume doubling time of the nodule in its management), 324 of the 7557 participating subjects had a positive CT screening after two rounds. From those, 162 underwent useless examinations, mainly with an invasive procedure (1.1% of all screening CT scan—follow-up scan at 3 months for indeterminate nodule excluded).

Subjects must be reminded of the risk of diagnosing tumors that would probably never have led to clinical symptoms (over diagnosis risk) or impacted survival (rare indolent forms). Finally, physicians should mention the radiation exposure risks related to repeated scanning, including evaluation of positive screening, even at low doses. During this information session, subjects should be reminded that quitting smoking is always beneficial, regardless of age and tobacco exposure, and that screening only makes sense when combined with smoking cessation. Information should be provided orally and accompanied by written documents.

Health care professionals involved in screening, namely GPs, radiologists, and pulmonologists, should also receive written information reminding the target population of screening its expected benefits, notably in terms of cancer-specific and overall mortality reduction, and its risks. Moreover, these professionals should be aware that repeated examinations may detect lesions whose management requires referral to specialists, such as pulmonologists, radiologists, surgeons, and pathologists. Finally, chronic obstructive pulmonary disease should be investigated in all subjects even if the scan is normal, in the case of respiratory symptom or symptoms reported by screening participants. [9, 16–20].

what is the optimal follow-up duration and screening interval?

Little prospective data are available regarding the optimal follow-up duration. However, the New York's ELCAP cohort was compared with another cohort of smoker with no screening intervention (CARET). In this paper, it appears clearly that discontinuation of screening is associated with an increase of lung-cancer mortality rate [21]. Veronesi *et al.* showed that the lung-cancer detection rate among a long duration annual screening cohort was stable over time [22, 23]. Overall, a minimum of three scans carried out 1 year apart seems advisable, as in the NLST protocol [7]. Finally, considering that (collective) screening programs only make sense on an ongoing basis [24], carrying out LDCT scans annually appears justified, especially compared with other cancer screening programs, such as breast or colon cancer, although the optimal frequency remains undetermined. Continued screening seems all the more relevant since in all screening studies, cancers were detected at each round. The benefits of continued screening in patients over 75 years of age (having undergone at least three initial scans) and subjects with over 15 years' smoking abstinence are not known.

The optimal interval between two rounds of CT is unknown. The MILD trial compares an annual schedule versus a biennial schedule. Ground-glass opacities were not considered in this study until a solid component appears. Although the paper reports intermediate and underpowered results, the cumulative incidence of lung cancer increases in the annual group but without any shift to higher stage in the biennial arm [25]. The mortality rate seems higher in the annual than in the biennial arm, although nonsignificant. Moreover, there was no difference in the number of lung cancers detected from CT screening in each arm. Another approach might be to propose a personalized screening interval according to the individual risk factors and radiological findings at baseline CT. This model if validated will allow us to save costs and radiation exposure by increasing the screening interval in low-risk population [26].

what are the technical screening modalities?

Screening modalities include technical recommendations on how LDCT scan should be carried out according to the 230 available literature, and recommendations on CT reading and interpretation [8, 15, 27–37]. The patient should be supine, with the arms above the head. A multi-detector row CT scanner should be used without contrast medium injection. Acquisition is performed in volumetric mode, during apnea at the end of the inspiration, from the apices to the pleural recesses. Native slice thickness should be $\leq$1.25mm with a 30% overlap reconstruction, allowing for volumetric analysis [8, 15, 27, 28]. The examination is then reconstructed with two reconstruction algorithms (i.e. soft tissues and high-resolution).

There is no consensus on low-dose scanning. To avoid variability, voltage was not limited, but dose-length product[2] (DLP) had an upper limit of 150 mGy.cm for an adult of average weight (70 kg) [29], with adjustment according to weight [30]. The DLP should appear on the imaging report. Ultra-low-dose scanning is not recommended, so as to avoid altering image quality. Noise level reduction software may be used.

CT reading should be performed on workstation using native slices in the axial plane and multi-planar reconstruction. Five to eight millimeters maximum-intensity-projection (MIP)

[2]According to the French Institute for Radioprotection and Nuclear Safety (IRSN), dose length product (DLP) is the basic dosimetric quantity in CT. The DLP is equal to the product of length and the CT dose index volume, which is the mean absorbed dose delivered to each slice, taking into account previous and subsequent slices.

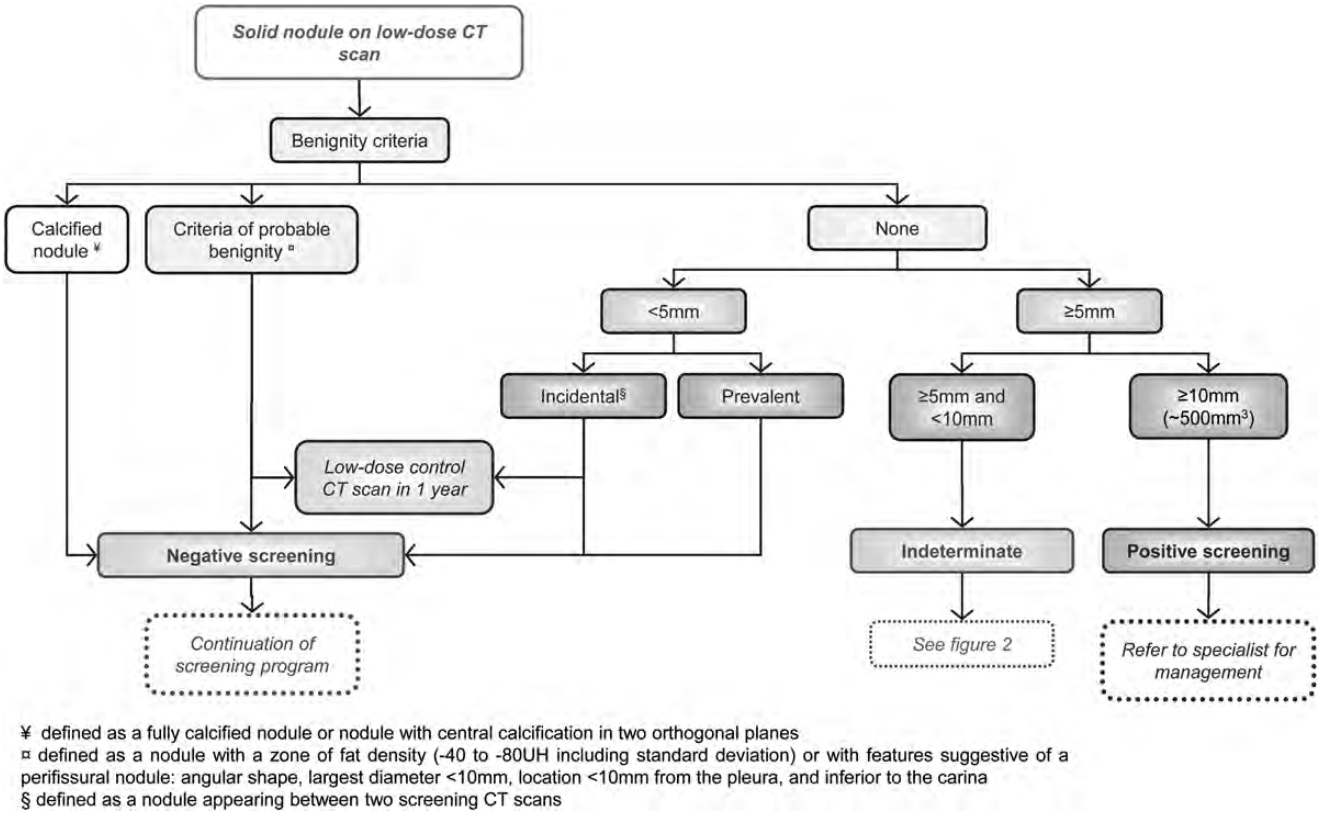

Figure 1. Management algorithm for the interpretation of scans showing a solid nodule.

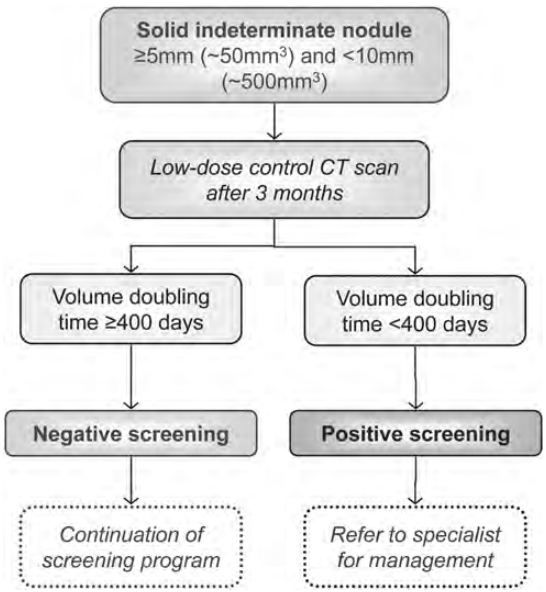

Figure 2. Management of solid indeterminate nodules.

slabs should be analyzed for improving the detection of pulmonary nodules. Currently, computer-assisted diagnosis is not recommended in this indication [31]. Software that measures nodule volume is necessary for follow-up [15]. As regards individual scanning, a systematic second reading is not justified [32, 33].

Interpretation of these examinations should ideally be undertaken by radiologists who specialize in thoracic imaging or have undergone specific training. Two-dimensional measurement of nodules should be obtained on axial images using lung parenchyma window settings (window level of −600 to −700 HU, window around 1500 UH), while volumetric measurement should be performed using images obtained with a standard reconstruction algorithm. When available, previous chest scans must be systematically reviewed. The screening scan should first be interpreted alone and then in comparison with all prior CT scans, including the oldest, in order to assess abnormality change. Each non-calcified nodule must be characterized as prevalent (discovered at first screening) or incidental (appearing between two examinations). Every detected abnormality must be described and detailed in the report, as should nodule characteristics, notably anatomical position (lateralization, lobe, segment), slice number, dimension (largest axial transverse diameter and volumetric measurement), contour characteristics (regular, spiculated, poorly defined, and indeterminate), doubling time in the case of previous examinations, and attenuation (solid, part-solid, or pure ground-glass nodules). The native slices should be stored on a CD-ROM in DICOM format along with the native slices. Subjects are invited to undergo repeated examinations in the same center or, failing that, to present the CD-ROM of the previous CT examination.

All French centers with CT scanner equipments able to respond to the technical and organizational constraints described above should be able to perform lung cancer screening CT scans.

Radiation protection in diagnostic radiography requires setting an upper DLP limit. In the NLST, the mean dose was

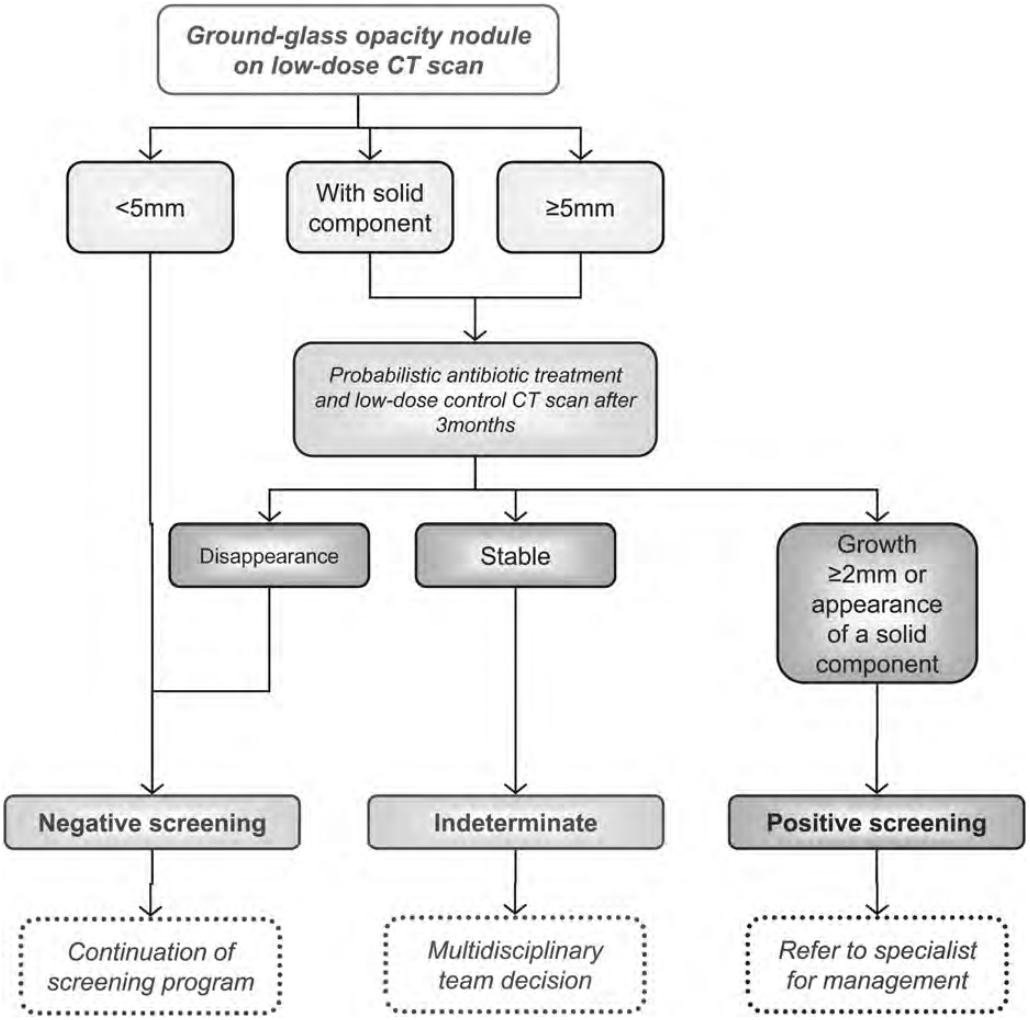

Figure 3. Management of ground-glass opacity nodule.

1.5 mSv [7]. Mean natural radiation exposure in France is 3.7 mSv per year [34], while a chest X-ray carries a dose of 0.05 mSv [35]. Patients need to be informed that screening CT scan is equivalent to less than 6 months' natural radiation exposure or 50 chest X-rays. The risk of developing radiation-induced cancers should not be understated. However, in screening, this risk is low, impacting very little on the magnitude of survival benefit [36]. Recently, the ITALUNG study team published follow-up results for doses given during the trial. For the entire study duration (initial scan followed by annual scans for 4 years), the mean individual cumulative dose ranged from 6.2 mSv to 6.8 mSv. Overall, 77.4% of the radiation dose was linked to CT screening, and the remaining 22.6% to other examinations due to positive results. The individual dose effectively delivered by screening scans was low in this study [37].

what is positive screening?

Only nodules and masses observed in screening results are considered. Other radiological abnormalities on CT should be referred for specific management. With multiple nodules, the appropriate strategy is that suited to the most suspicious nodule.

solid nodules

The solid nodule size is determined by measuring largest diameter. Volumetric measurements are also used, particularly for comparison.

The management algorithm proposed for solid nodules detected on CT is presented in Figure 1.

The characteristics of CT-detected nodules allow examination results to be classified into three categories: positive (abnormality requiring further exploration), indeterminate (abnormality justifying a control CT scan), and negative (no abnormalities or abnormality not requiring specific follow-up besides annual screening).

Examinations are considered negative when:

- The nodule is entirely calcified or shows central calcification on two orthogonal reformations, regardless of size (calcified nodule) [38];
- The nodule size is <5 mm. If there is an incidental nodule (not found on previous low-dose scanning), a low-dose control scan is carried out 1 year later;
- The criteria for 'probably benign' nodules are:
  - fat attenuation (−40 to −120 Hounsfield units, standard deviation included) within the nodule;

- characteristics suggestive of intrapulmonary lymph nodes: nodules <10 mm with angular shape at a distance of <10 mm from the pleura and situated below the carina [39].

The technical difficulty of measuring small nodule attenuation, coupled with the limited data on intrapulmonary nodes, supports characterizing such nodules as probably benign and repeating the low-dose scan after 1 year.

Examinations are considered indeterminate when the greatest nodule diameter is between 5 and 10 mm (approximate volume of 50–500 mm^3), justifying a low-dose control CT scan after 3 months (cf. Figure 2). The working group supported the follow-up proposed in the NELSON study [40]. The CT reading is subsequently based on doubling time estimations using volumetric measurements:

- If the doubling time is ≥400 days, the test is negative. A CT scan is systematically carried out 1 year after initial examination.
- If the doubling time is <400 days (~25% volume increase), the test is positive, and the subject is referred to a specialist.

Examinations are considered positive when either:

- at least one solid nodule of >10 mm at largest diameter (approximate volume 500 mm^3); or
- initially indeterminate, but the 3month-CT follow-up demonstrates that the nodule doubling time is <400 days.

ground-glass nodules (pure ground-glass and part-solid)

Volumetric measurement is poorly suited to ground-glass nodules [41]. These are, therefore, monitored using one-dimensional largest-diameter measurements. Pure ground-glass nodules of <5 mm in diameter require no specific follow-up (it is negative screening and screening continues annually) as they are highly correlated with localized atypical adenomatous hyperplasia [41] which is a premalignant lesion of adenocarcinoma with a long doubling time of 988 ± 470 days as showed by Takashima et al. [42]. Ground-glass nodules with solid components and pure ground-glass nodules of ≥5 mm in diameter require probabilistic antibiotic treatment and a new scan after 3 months (Figure 3). After 3 months, management can vary:

- For resolving nodules, the test is negative and screening resumes without modification.
- If the nodule size increases by at least 2 mm or if a solid component appears, the test is positive, and the subject is referred to a specialist [43].
- If a pure ground-glass nodule is stable, the test is indeterminate, and management is subjected to multidisciplinary discussion.

how should positive subjects be investigated?

histology

As far as screening in particular is concerned, conventional bronchofiberscopy is low-performing in anatomic pathology diagnoses, with 13.5% sensitivity and a negative predictive value of 47.6% [44]. Accordingly, negative examinations are not cause to discontinue investigation. New methods of fibroscopic sampling are being developed (radial endoscopic ultrasound, electromagnetic navigation), although their place in diagnosis after screening has yet to be defined. Transthoracic puncture has excellent sensitivity and specificity in pulmonary parenchymal nodules. However, this examination includes an approximately 20% risk of pneumothorax with a minority of cases requiring drainage [43]. Nonetheless, its being negative does not totally exclude a cancer diagnosis.

positron emission tomography (PET)

For screening populations at high risk of cancer, PET is irrelevant. The absence of hyper-metabolic nodule activity upon examination is insufficient to conclude benignity. PET's negative predictive value is only 81% [45]. That said PET must be performed in staging work-ups or before locoregional treatment, as recommended, when cancer is diagnosed or suspected. Other investigations, particularly cerebral imagery, should also be conducted according to current recommendations [43].

therapeutic and diagnostic options of solid nodules

The following two strategies are proposed:

- immediate surgical excision following pre-therapeutic assessment with no contraindications, for diagnostic and potentially therapeutic purposes, especially when malignity is highly probable. Subjects must be fully informed of the risk of "useless" excision of a benign nodule;
- initially obtaining anatomic pathology evidence by transthoracic puncture as explained above. Subjects must be fully informed of the risk of false-negative histology (invasive cancer with negative puncture). The surgical excision of confirmed malignant nodules would then be the same as in the previous strategy.

The choice between these two options should be made at a multidisciplinary meeting after informing the subject and taking into account the individual benefits and risks of each strategy.

therapeutic and diagnostic options of pure ground-glass nodules

For positive pure ground-glass nodules, diagnosis cannot be confirmed by biopsy [46]. Similarly, the value of extemporaneous examination to distinguish *in situ* from invasive adenocarcinomas is not proven. Diagnostic strategy therefore involves surgical resection. However, the risk of synchronous or metachronous multifocal lesions is high, entailing minimal surgical resection. Peripheral pure ground-glass nodules in particular should be considered for sublobar resection [47].

For indeterminate pure ground-glass nodules, the probability of *in situ* or minimally invasive adenocarcinoma (CT cannot differentiate) is high (over 75%), which may lead to surgical resection. However, given these tumors' usually show slow

growth, annual follow-up CTs for at least 5 years may be considered as an alternative [41].

surgery

Recommendations differ depending on nodule type, i.e., pure ground-glass or solid:

- Tumor ≥2 cm: the preferred techniques are lobectomy and complete mediastinal lymph node dissection performed according to recommendations (48);
- Tumor <2 cm and full nodule: the standard is lobectomy and complete mediastinal lymph node dissection, although anatomic segmentectomy with node resection is an option;
- Tumor <2 cm with pure ground-glass opacity: atypical resection is initially recommended. The definitive anatomic pathology analysis (invasive lepidic adenocarcinoma or *in situ* carcinoma) will determine subsequent surgical management.

The use of video-assisted thoracoscopic surgery is encouraged, as this therapeutic option is recognized in national recommendations for surgical practice in the treatment of early-stage lung cancer.

discussion

Our group's results support the implementation of individual screening in France after informing the subject of the benefits and risks and in accordance with the conditions detailed in this article. Subjects should be between 55 and 74 years, smoke at least 30 pack-years and voluntarily agree to participate in the screening. They should be given information about quitting smoking, the main elements of which have already been formalized. Screening should be carried out using a LDCT scan according to specific technical modalities. Positivity criteria and management algorithms for positive tests are detailed in this article.

The responses currently given by French physicians to individual requests for screening are diverse. While some accept prescribing CT scans, usually standard and non-low-dose scans (although no specific rules have been established), others refuse because no national program has yet been implemented.

The members of this working group considered that the magnitude of the benefit observed in the NLST was such that it was not possible to refuse subjects who requested individual screening spontaneously, and that it even appeared acceptable to propose it. Theoretically, the NLST is the only prospective randomized study to have observed this benefit, and it would be valuable to confirm the efficacy of screening in another study. However, this comparative randomized study with high statistical power gave the highest level of evidence, and the trial was well conducted. Still, this study presents some methodological features which could be discussed. First, there is no true control arm considering the non-interventional arm is annual chest X-ray. However, the randomized PLCO study, recently carried out on >150 000 individuals showed that annual screening with chest radiograph did not reduce lung-cancer mortality compared with no screening, the so-called bona fide control arm [6]. Second, attention should be paid to the fact that the results of the NLST trial were prematurely reported, according to the recommendations of the independent data and safety monitoring committee. So it could carry a risk of over-emphasizing the true benefit of intervention. However, as mentioned in the seminal paper, 'the efficacy boundary for the primary end-point had been crossed, and that there was no evidence of unforeseen screening effects that warranted acting contrary to the trial's prespecified monitoring plan' [7]. Finally, the NLST trial included a high proportion of former smokers (around 50% in each arm) comparatively with other randomized study (around 25 to 40%). So it could be a recruiting bias as former smokers have better life expectancy than current smokers. However, this high proportion is well balanced in both the arms and cannot explain the observed significant differences. It could be interesting to perform a sub-group analysis which would explore whether the benefit of screening is similar in current or former smokers. Moreover, the NLST results are consolidated by a number of nonrandomized trials, which have evaluated the mortality benefit using statistical models and showing positive results [21, 23]. On the other hand, several randomized studies are currently ongoing (see Table 1) but most will probably lack power to confirm the follow-up results obtained in the NLST study [20, 25, 40, 49, 50]. From those, two have recently reported no benefit of CT screening on lung-cancer mortality, although they both obviously lack of power [25, 50]. Indeed, the primary objective of the DLCST trial [16, 50] was to assess a 25% difference in lung-cancer specific mortality. The trial was statistically powered to highlight this difference in addition with the NELSON study effective and 10 years after randomization. The 5ive-year results of DLCST alone reported a significant higher rate of cancer in the screening group and a nonsignificant higher lung-cancer and global mortality rate in this arm but with evident lack of power. The Italian MILD study [25] also shows (5-year results) a higher mortality rate (both lung cancer specific and global) in the screening groups. Nonetheless, this trial suffers from limitations due to the lack of comparability between groups and differential attrition bias. In addition, initially powered for detecting a 30% difference in lung-cancer mortality, 10 000 participants were needed for a 10-year period of screening. Unfortunately, only 4104 peoples were recruited.

The implementation of individual screening is only conceivable if a large amount of information is given to prescribing physicians. In fact, the difference between the trials and routine clinical practice lies in the sharing of information and individual discussion of the risks and benefits (among other things) [51]. This information is not currently available. A survey conducted in the United States showed that physicians sometimes poorly interpret the findings of clinical trials on screening. This observation justifies expert work to explain these results and help transpose them into practice [52]. The working group of the International Association for Study on Lung Cancer recently provided a summary of the literature, but this offered few solutions to individual requests, particularly in a European health system [28]. More recently, experts from the American National Comprehensive Cancer Network (NCCN) published their recommendations for

clinical practice [53]. As in our group, they proposed implementing individual screening for at-risk subjects. Investigators of ongoing European lung-cancer screening trials were more cautious in their statement, underlying that 'several questions need to be answered in the near future, before considering implementation of low-dose CT screening for lung cancer' [54]. The authors from a recent systematic literature review concluded that 'there are substantial uncertainties regarding how to translate that conclusion into clinical practice' [55]. Nevertheless, our work is therefore part of an overall effort to propose the standardization and organization of screening and its consequences in a different geographical and social context to that in which the NLST was conducted. Indeed, the populations and health care systems of North America and Europe are different. It is also a question of transposing the conditions that yield certain trial results into actual clinical practice [56].

The benefit of screening in terms of mortality is thus demonstrated in an American population subjected to some selection based mostly on motivation to participate in a long-term clinical trial, and including current or former smokers aged between 55 and 74 years and consuming at least 30 pack-years. It would evidently be hazardous to extrapolate these results to another population, and thus, to the population targeted by screening, outside the setting of a clinical trial. Adherence to screening is essential. In the NLST, compliance with repeated examinations was excellent (95%) [7]. In contrast, in the Italian DANTE study with 2811 subjects [9], the adherence rate for the third scan was only 44% (20% for the fourth). In the French DEPISCAN study with 765 subjects, 19% of included patients were not compliant [10]. However, this was a prospective controlled study, suggesting that in 'real life' even greater deviations could be observed. These findings are in line with the observations made in France in relation to organized breast cancer screening, in which the patients' participation rate is sometimes low [57, 58]. One of the factors favorably influencing adherence to screening programs is higher socioeconomic level. In both the NLST and DEPISCAN trials (data not published), subjects largely came from affluent segments of the population, [10, 59], whereas the low socio-economic level is a known risk factor in lung cancer [60].

Data from Table 1 show that the studies published on screening are heterogeneous in terms of subject selection, particularly with regards to the level of tobacco intoxication. Selecting participants for the screening program is crucial for increasing its cost-effectiveness. In this way, several models have been proposed, whereas only one has been built on a screening population. In their paper, Maisonneuve et al. showed that the use of a mathematical model (taking into account the presence of nodule, nodule characteristics and the presence of emphysema) seems suitable for selecting a higher risk population [26]. Another original approach is used in the UKLS study [18]. This study uses the Liverpool Lung project questionnaire [61] to calculate the risk of lung cancer related to tobacco use, but also to personal and family cancer history, professional exposure, and pneumonia history. Nevertheless, the NLST study was the only randomized study which clearly demonstrates any benefit in terms of mortality, and thus for the moment, any possible screening policy should follow these inclusion criteria. Finally, NCCN guidelines recommend to select individuals at risk according several criteria including tobacco history and also other exposure to carcinogen such as occupational or second hand smoking [53].

Any individual or collective policies for lung-cancer screening must be accompanied by an anti-smoking program in order to be effective, including from a medico-economic point of view [62]. It is certain that screening visits offer a valuable opportunity to address complete and permanent smoking cessation [63, 64]. For this reason, our working group drafted information aimed at GPs and people wishing to participate in a screening program.

Our proposals are based on expert's advice. However, many questions remain unresolved. It is, therefore, necessary to rapidly develop clinical research programs in this field. First, our group was unanimously in favor of a rigorous evaluation and follow-up of these proposals' implementation, of lung-cancer incidence, and of positive subjects' change in time. Overdiagnosis (i.e. cancers discovered by screening which would not have led to clinical symptoms during the patient's lifetime) must be studied, as must the real efficacy of screening in terms of specific and overall mortality, and finally the frequency and results of examinations conducted after positive screening.

Five other themes based on currently unresolved issues were identified as priorities by our group: (i) medico-economic evaluation of individual screening in the French health care system is essential in order to calculate the cost-benefit ratio of screening, and this evaluation must include compliance and smoking cessation, possibly in relation to subjects' sociodemographic characteristics. (ii) The frequency and optimal duration of screening need to be studied. (iii) The value of CT scan double-reading and computer-aided nodule diagnosis should be evaluated, since such software does not seem efficient when used for the initial reading [31]. Furthermore, breast cancer screening programs with systematic double reading have shown that this practice is cost-effective [65, 66]. However, the NLST did not include systematic CT double reading [67], and the value of this practice was challenged in the NELSON study [33]. (iv) Studying benignity criteria for intra-thoracic nodules may reduce unnecessary investigations. These criteria are based on retrospective data from a small series of 234 nodules in 98 subjects [39]. (v) Finally, it would be useful to evaluate other screening techniques. The discovery of a plasma microRNA signature predictive of malignity appears promising [68, 69]. All future studies should, therefore, take plasma biomarkers into account.

In conclusion, lung-cancer screening using LDCT scans was shown to substantially decrease lung-cancer-specific mortality [7]. These data deserve recognition and justify the work at hand, which will need to be updated with findings from other ongoing trials.

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