Editorial

Region specific lung nodule management practice guideline

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Following the recommendation by the United States Preventive Services Task Force (USPSTF) and the final decision on February 5, 2015 by the Centers of Medicare and Medicaid Services (CMS) to cover computed tomography (CT) screening of lung cancer (1-3), CT screening has begun in the United States. Other countries, such as Canada, are planning to implement population based CT screening programs. A large number of lung nodules will be found in addition to incidental lung nodules from diagnostic CTs such as CT coronary angiogram or abdominal CTs. In the US, it was estimated that in an adult population of over 234 million, >1.5 million Americans will be found to have a lung nodule (4). Only ~5% of them will be found to have lung cancer (4). This means a large proportion of patients with lung nodules will have repeat CT imaging studies, PET scans, biopsies or surgery for benign disease with implication in health care resource utilization. For individuals with benign nodules, surveillance provides no benefit, may delay diagnosis of infectious granulomas, incur costs for physician/imaging study visits or suffer from harm of invasive procedures and ionizing radiation. A significant proportion of patients with incidental pulmonary nodules were found to experience clinically significant distress (5). Therefore, it is important to have evidence-based guidelines for timely efficient management of lung nodules—whether screen detected or incidental.

Several professional societies have published guidelines on management of lung nodules such as the Fleischner Society (6,7), the American College of Chest Physicians (ACCP) (8), the National Comprehensive Cancer Network (NCCN) (9), the British Thoracic Society (BTS) (10,11) and the American College of Radiology (12). The European NELSON trial has also published their protocol for management of screen detected lung nodules using volumetric analysis (13,14). These guidelines/protocols differ in the frequency and duration of repeat CT imaging studies, use of PET and the threshold for referral for tissue diagnosis or treatment (*Table 1*) with implication in health care resource utilization and costs as well as potential harms to patients. The major differences in guidelines are related to patient risk assessment and nodule type and size. The recently published clinical practice consensus guidelines for evaluation of pulmonary nodules for patients in Asia (15) have raised important questions in lung nodule management in different regions of the world with different exposures such as outdoor and indoor pollution in addition to tobacco smoking, genetic susceptibility (16) and prevalence of granulomas from infections such as tuberculosis.

Currently, there are at least 20 lung cancer risk prediction models (17,18). The Tammemagi $PLCO_{m2012}$ and $PLCO_{all2014}$ models, the Katki model (both based on the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial and the National Lung Screening Trial (17-20) and the Hoggart European Prospective Investigation into Cancer and Nutrition (EPIC) model (21) are the only models that are based on large prospectively followed population-based samples not limited to people at high risk of lung cancer. These models show high discrimination and calibration in ever smokers. However, these models have ≤3% Asians. Their utility in Asian countries has not been validated. Although outdoor and household air pollution account for an estimated 29% of lung cancer deaths worldwide (22-25) and is a major problem in Asian countries, none of the lung cancer risk prediction models published so far have included outdoor and/or household

Table 1 Management of lung nodules

Guideline	LDCT in 12 months	LDCT in <12 months	PET/CT	Biopsy or surgery
Solid nodules				
Fleischner Society (6)	≤4 mm	>4–8 mm	>8 mm	>8 mm, hypermetabolism or interval growth
ACCP (8)	(I) >4–6 mm if no risk factors; (II) ≤4 mm if one or more lung cancer risk factors	(I) >4–8 mm with lung cancer risk factors or pretest probability <5%; (II) >6–8 mm without lung cancer risk factors; (III) >8 mm if pretest probability <5%	>8 mm with pretest probability 5–65%	>8 mm and (I) pretest probability >10%; (II) interval growth; (III) benign diagnosis requiring treatment suspected or (IV) hypermetabolic on PET
NCCN (9)	>3 to <6 mm; new nodule ≥3 mm	(I) 6–8 mm or (II) solid endobronchial nodule	>8 mm	(I) >8 mm and hypermetabolism or (II) interval growth
BTS (10)	>5 to 6 mm	(I) >6 to 8 mm or >80 to <300 mm^3; (II) >8 or >300 mm^3 if pretest probability <10%	(I) >8 or >300 mm^3 and pretest probability >10%; (II) nodule growth; (III) volume doubling time <400 days	(I) >8 or >300 mm^3 & pretest probability >10% using PET; (II) volume doubling time <400 days; (III) nodule growth
Lung-RADS (12)	(I) <6 mm; (II) new nodule <4 mm	(I) ≥6 to 8 mm; (I) new nodule ≥4 to 8 mm	≥8 mm	≥15 or ≥8 mm with interval growth
NELSON (13)	Benign or nodule <50 mm^3	50–500 mm^3; pleural based 5–10 mm d_{min}		>500 mm^3; pleural based >10 mm d_{min}
NELSON (14) (updated)	(I) No nodule or (II) nodule <50 mm^3	(I) ≥50–500 mm^3 or 5 to 10 mm diameter or (II) VDT 400–600 days		(I) ≥500 or ≥10 mm^3 diameter; (II) interval growth with VDT <400 days
Asia (15)	(I) ≤4 mm & clinical probability >5%; (II) >4 to ≤6 mm & clinical probability <5%	(I) >4 to ≤8 mm & clinical probability >5%; (II) >6 mm & clinical probability <5%	>8 mm & clinical probability 5–60%	>8 mm and (I) clinical probability >5%; (II) interval growth; (III) benign diagnosis requiring specific treatment suspected or (IV) hypermetabolic on PET
Part-solid nodules				
Fleischner Society (7)		Solid component <5 mm	Solid component ≥5 mm or nodule >10 mm	Solid component ≥5 mm and persistent
ACCP (8)		≤15 mm	>15 mm	>15 mm with interval growth or persistent ≥3 months
NCCN (9)	≥ 3 to <6 mm	6–8 mm	>8 mm	(I) >8 mm with interval growth or (II) increased in solid component ≥2 mm
BTS (10)		>5 mm	>5 mm, persistent and pretest probability >10%	Interval growth, enlargement of solid component or persistent with pretest probability >10%
Lung-RADS (12)	<6 mm	≥6 mm & solid component <8 mm, new or growing nodule with solid component <4 mm	Solid component ≥8 mm	Solid component ≥8 mm & malignancy risk ≥15% or hypermetabolic on PET
NELSON (13)	<8 mm and solid component <50 mm^3	Non-solid component ≥8 mm & solid component 50–500 mm^3		Solid component >500 mm^3
Asia (15)		≤8 mm		>8 mm & persistent for ≥3 months

Table 1 (*continued*)

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Guideline	LDCT in 12 months	LDCT in <12 months	PET/CT	Biopsy or surgery
Non-solid nodules				
Fleischner Society (7)		>5 mm		>10 mm with interval growth or increased attenuation
ACCP (8)	>5 mm	Consider if >10 mm		>10 mm and persistent, interval growth or development of solid component
NCCN (9)	≤5 mm	>5–10 mm		>10 mm and persistent, interval growth or development of a solid component
BTS (10)		>5 mm		Interval growth >2 mm in maximum diameter or development of solid component
Lung-RADS (12)	<20 mm	≥20 mm		
NELSON (13)	<8 mm	≥8 mm d_{mean}		
Asia (15)	>5 mm			

LDCT, low dose computed tomography; CT, computed tomography; ACCP, American College of Chest Physicians; NCCN, National Comprehensive Cancer Network; BTS, British Thoracic Society.

pollution as one of the risk variables. Lung cancer risk prediction model that evaluate and consider these factors need to be developed and validated in Asian patients to define lung cancer risk more accurately.

Due to a much higher prevalence of granuloma from tuberculosis in many Asian countries, higher outdoor and indoor pollution exposures, high incidence of adenocarcinoma in female non-smokers and anecdotal evidence of the emergence of malignancy in stable nodules after many years of stability, the proposed Asian guideline (15) differs from the ACCP guideline (8) by incorporating clinical judgement of lung cancer risk, lesser reliance on PET imaging, longer surveillance of nodules (≥3 years even for solid nodules) and greater use of non-surgical biopsy for diagnosis. As discussed above, there is no validated lung cancer risk prediction model that has included air pollution exposures or genetic profile as risk variables. Physicians' perception of lung cancer risk may vary. Individual lung cancer risk is not the same as lung nodule malignancy risk although some of the lung nodule malignancy risk prediction tools such as the Pan-Canadian lung nodule malignancy risk calculator take into account age, sex, family history of lung cancer and emphysema in addition to nodule type, size, spiculation and location (26). The accuracy of the PanCan model has been validated in other non-Asian countries (27,28). However, the utility of the PanCan model needs to be validated in Asia. An integrated model such as the PanCan model has advantages over those recommended in current guidelines as it incorporates nodule type in the risk assessment and action thresholds for further investigation. It is difficult to remember different size and follow-up criteria for solid, part-solid and non-solid nodules. Observer variations in nodule size measurement can affect nodule classification and management especially with manual measurement of smaller nodules (29). Repeat CT scanning introduces yet another variable with different size criteria for new nodules (9,12) and different interval growth criteria (*Table 2*).

The Asia Guideline (15) points to knowledge gaps in lung nodule management that needs to be addressed in future studies such as a better model of lung cancer risk that includes outdoor and indoor pollution exposures as well as genetic susceptibility. Further research is also needed in lung nodule characterization especially for nodules ≤10 mm as the likelihood of cancer is not the same as likelihood of biologically aggressive cancer that grows rapidly or with high metastatic potential. Rapid non-invasive diagnosis of infectious granuloma is also needed to facilitate treatment.

Table 2 Interval nodule growth criteria for serial CT

Guideline	Solid nodule	Part-solid	Non-solid
NCCN	Nodule <15 mm: increase in mean diameter by ≥2 mm; nodules ≥15 mm: increase in mean diameter ≥15%	Increase in mean diameter of nodule or solid component by ≥2 mm	Development of solid component or becomes solid
BTS (10)	≥25% volume change (significant using 2D measurements not defined)	≥2 mm increase in maximum diameter of nodule or solid component	≥2 mm increase in maximum diameter of nodule or development of a solid component
Lung-RADS	≥1.5 mm increase in diameter	≥1.5 mm increase in diameter of solid core	Becomes part-solid or solid
NELSON (13,14)	≥25% volume change if nodule 50–500 mm^3 with volume doubling time <600 days	Not defined	Not defined
Asia (15)	Not defined	Not defined	Not defined

CT, computed tomography; NCCN, National Comprehensive Cancer Network; BTS, British Thoracic Society.

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Footnote

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