Screening for Lung cancer in Malaysia: Are we there yet?

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BACKGROUND

The recently published (New England Journal of Medicine August 2011) preliminary results of the multi center randomized North American National Lung Cancer Screening Trial (NLCST) demonstrated for the first time a significant reduction in disease specific mortality with screening for lung cancer with spiral computed tomography (CT). The landmark findings of this trial mandates serious consideration for instituting lung cancer screening here in Malaysia, where disease prevalence is high, resection rates low and outcomes poor due to a majority of patients presenting with advanced disease. This commentary reviews the key evidence for screening and discusses the relative merits of screening for lung cancer in Malaysia.

INTRODUCTION

Lung cancer is overall the third commonest cancer in Malaysia, the commonest tumour to afflict males and the most common cause of cancer deaths accounting for 19.8% of all medically certified cancer related mortality in this country [1,2]. There is a curious ethnic variation; the age-standardised incidence of lung cancer amongst the Chinese race is two-fold that of the non-Chinese regardless of gender [1]. The precise reason for this observation is uncertain but smoking volume and a genetic predisposition to cancer may be partly responsible. Approximately 88 % of cases are histologically classified as non-small cell lung cancer (NSCLC) in keeping with global trends [3]. With the exception of few cases of limited stage disease, small cell lung cancer (SCLC) has a poor prognosis as most patients already have advanced disseminated disease due to early subclinical mediastinal or distant metastasis at initial presentation.

Cigarette smoking is a major aetiological risk factor and 92% of Malaysian male lung cancer patients have a significant smoking history [3]. The smoking prevalence in Malaysia is exceptionally high with almost 50% of all adult males being smokers [4]. The morbidity and therapy of smoking induced lung cancer accounts for approximately 440 million ringgit annually and thus a major economic burden on our personal and national healthcare finances [5].

Early stage (I, II and even selected IIIa) disease is amenable to curative surgery which affords the best prognosis in terms of a cure and long term disease free survival. However in Malaysia, most cases are diagnosed too late with either locally advanced tumours or distant metastasis, precluding surgical resection. Over 75% of lung cancer cases are stage III or IV at diagnosis, and these patients can only be offered palliative but not inexpensive therapy [6]. Surgical resection rates in Malaysia are dismally low (8%) in comparison with resection rates of Western Europe or North America (20%) [7-8]. Diagnosis and resection rates have been shown to improve with increased availability of specialist thoracic surgeons and their presence at multi disciplinary lung cancer meetings. In the UK, the overall resection rate for NSCLC increased from 14.2% to 20.7% in just 1 year (2008-09) with more surgeons available [9]. Other commonly cited reasons for low resection rates include advanced inoperable disease at diagnosis, patient refusal or prohibitive co-morbidities.

The natural history of lung cancer and its high prevalence in Malaysia mandates serious consideration for disease screening on clinical and health economic grounds. The goal of screening is to detect the disease at an early pre-clinical stage in "at risk" individuals thereby facilitating early effective intervention. Screening must be cost effective, affordable, reproducible and reliable. A high sensitivity and a high specificity is ideal. Screening must be safe, widely available and must be for a disease that can be treated effectively.

Historical attempts at screening for lung cancer have included surveillance with sputum cytology and chest radiography (CXR). A detailed analysis of four historical randomised clinical trials (RCT) of lung cancer screening with dual sputum cytology and CXR failed to demonstrate any survival benefit [10-12]. Disease specific mortality (DSM) refers to the number of persons who die from the cancer, relative to the number screened and is a frequently cited parameter for cancer screening. Although data from these trials showed the stage of NSCLC was lower and resection rates higher in screened subjects with an improved 5-year survival of 35% compared to controls, additional analysis showed the DSM was 3.2 per 1000 person-years and not improved by screening [10-12]. In short, although screening did improve survival, it did not appear to improve the DSM.

Another study, the Mayo Lung Cancer Project, screened individuals with dual CXR and sputum cytology at four monthly intervals for six years, detecting more early stage (I and II) cancers and a better 5-year survival however again no significant differences were observed in lung cancer mortality between screened and unscreened subjects at a mean follow-up of 20 years [13]. The shift in stage distribution and improved 5-year survival was attributed to lead-time bias, length-biased sampling and over-diagnosis. Lead time refers to the time interval between detection of a disease usually based on a new criteria or test (eg. spiral CT) and its normal clinical presentation and diagnosis with traditional criteria (eg. CXR).

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Lead time bias refers to bias that occurs when two tests for the disease are compared and one test diagnoses the disease earlier; thus it may appear that this test prolongs survival but in actual fact there is no effect on the outcome of the disease. Length-biased sampling, a more complex concept is a statistical artifact that occurs in survival analysis when the probability of including an individual observational unit in a sample is related to its survival time. Over diagnosis refers to lung tumours that would not lead to an individual's death because of its slow growth rate and competing age-related risks for death. In short, the negative implications of these historical studies hampered progress in the field of lung cancer screening for the next 20 years.

Advances in diagnostic imaging technology with the advent of rapid, single breath, low radiation-dose helical CT (spiral CT) renewed interest in screening for NSCLC. Spiral CT is vastly superior to CXR in detection of asymptomatic early and potentially curable NSCLC. The Early Lung Cancer Action Project (ELCAP) screened 1,000 asymptomatic smokers (age > 60 years) with a 10 pack-year history, and stage I tumours were detected six times more frequently with CT imaging over conventional CXR. However spiral CT also detected more benign nodules (20.6% Vs 6.1%) [14]. The question arises whether prevalence data on CT scanning represents a true stage shift enabling detection of NSCLC at an earlier stage or if it represents detection of small biologically insignificant tumours that will not affect the overall DSM, the so called lead-time and length time bias. Only a RCT with long term follow-up can address this issue.
Recently published preliminary results from the contemporary National Lung Cancer Screening Trial (NLCST) (August 2002-April 2004) demonstrated for the first time, a mortality risk reduction from lung cancer with spiral CT scanning. The NLCST is a pan-North American multi center prospective RCT that evaluated 53,454 current or former heavy smokers (aged 55-74 years) who were randomized to either three annual low-dose CT scans or CXRs. The NLCST showed 20% fewer cancer deaths among trial participants screened with spiral CT compared with those screened with CXR (a relative risk reduction of 20% 95% CI: 6.8-26.7 p=0.004), and a 6.7% decrease in all-cause mortality in the group screened with spiral CT [15]. A substantial portion of this lower mortality rate was attributable to lung cancer.

The Case for screening

There is no question that the earlier a lung cancer is diagnosed and treated, the better the patient's chance of survival. Historical limitations with diagnostic technology meant by the time a lung cancer became clinically detectable, the disease was already in the late stages of its natural course and only a couple of doublings away from reaching a lethal tumour burden. Biologically even an early NSCLC (size < 1 cm) (clinical stage 1A) would have undergone many divisions and already contain 10^8 cells by the time it reaches a 5 mm size [16]. Studies have shown tumour size to be a significant predictor of long term survival even within early stage 1A cancers [17]. Furthermore, in Malaysia, significant delays in the diagnosis of lung cancer have been documented with the median patient delay being 60 days and median doctor delay 33 days[18].

In the USA, the number of deaths from lung cancer exceeds the total combined number of deaths from the next three most common malignancies; namely breast, colorectal and prostate cancer. Routine screening is recommended and practiced in selected population for these cancers and all three cancers have shown a 10-15% reduction in mortality in the last two decades [19].

Lung cancer lends itself towards screening due to the lengthy pre-clinical phase of the disease. Screening "at risk" individuals affords the best chance of detecting the cancer at an early treatable stage and hence offers the best chance of a cure. Despite this intuitive appeal however, based on the historical RCTs, screening for lung cancer has not previously been shown to decrease overall DSM. Even more contemporary diagnostic studies which confirmed the superior sensitivity of spiral CT scanning over CXR did not clearly demonstrate clearly any survival benefit with screening [14, 20-23]. The NLCST findings has changed all this and merits serious consideration for a local screening programme.

Globally the incidence of the adenocarcinoma subtype of NSCLC is increasing relative to squamous cell carcinoma (SCC). Adenocarcinoma tends to be more peripheral and screening has been shown to be more effective for this tumour subtype perhaps due to its apparent slower growth [24]. There is growing evidence that it frequently originates as atypical adenomatous hyperplasia progressing through an intermediate carcinoma in-situ (CIS) phase before the eventual bronchioalveolar carcinoma (BAC) phase with solid or non-solid nodules, that if detected early enough can be safely treated with a limited lung sparing surgical resection. Such resections may be accomplished with a minimally invasive video-assisted thoracoscopic (VATS) approach with a very low incidence of local recurrence and excellent disease free survival. This may translate into less post-operative pain, earlier mobilization, shorter hospital stay and thus less cost.
Our East Asian neighbours Japan, have a long pedigree of successful regional population-based or clinic-based lung cancer screening programmes. Several Japanese case control studies have demonstrated a significant reduction in the smoking-adjusted odds ratio of death from lung cancer between screened and unscreened populations (OR 0.40-0.54) 0-12 months before diagnosis [24-28]. However the data has been interpreted with caution due to its retrospective nature and possible publication bias.

In short, prior to the landmark NLCST findings, most historical and contemporary data was non-randomised or equivocal regarding the benefit of screening in terms of mortality reduction.

The Case against screening

There is no doubt that prevention is better than screening to reduce the burden of lung cancer and some might argue resources and efforts should be prioritized for preventative strategies instead, but this will only address a future generation. Even if all cigarette smokers were to quit smoking today it would take 20 years before the resulting decrease in mortality from lung cancer becomes evident [29]. Lung cancer screening does not compete or contradict efforts to promote smoking cessation.

A shift to detection of early-stage cancers however, does not necessarily translate into a survival benefit hence the question arises whether prevalence data on CT scanning represents a true stage shift enabling detection of NSCLC at an earlier stage or if it represents detection of small biologically insignificant tumours that may not affect the overall DSM, the so called lead-time bias, length time bias and overdiagnosis effect.

A national screening programme will undoubtly be costly but much expenditure can be offset or subsidized with revenues generated from taxation on cigarettes, and partial reimbursement from insurance providers. Published studies evaluating the cost effectiveness of CT screening for lung cancer are conflicting and equivocal, but what is not in doubt is the need to target screening of only individuals of the highest risk to make screening cost-effective. Our collective challenge is to identify that high risk group here in Malaysia. Wisnikesky et al demonstrated with incorporation of the ELCAP data into a decision analysis model, the incremental cost-effectiveness ratio of a single baseline low dose CT was USD$ 2,500 per year of life saved, and screening would be expected to increase survival by 0.1 years at an incremental cost of approximately USD$290 [30]. Whether such analyses can be easily and reliably extrapolated to our local population remains undetermined.

It is crucial we have sufficient well trained specialists (radiologists, respiratory physicians, pathologists, oncologists and thoracic surgeons) to offer and execute an effective screening programme and importantly we must recognize that lung cancer screening is a process and not a single test. Dedicated chest radiologists with 'expertise' in characterizing nodules and providing appropriate recommendations for follow-up is essential. Currently Malaysia has approximately 170 radiology specialists with over a third in the public sector (Ministry of Health hospitals) but it is difficult to ascertain how many or few are dedicated thoracic radiologists. Equally, it is likely that more thoracic surgeons and pulmonologists will become necessary and thoughtful recruitment of high caliber trainees and expansion of accredited structured training programmes must be undertaken without delay or compromising quality.

Other considerations include the possible harms of screening with spiral CT although the radiation dose is low and similar to that of a mammogram and the availability of screening technology. Nodule detection is determined by thickness of the collimation (slices) of the CT scan. Historical data (up to 2001) from the College of Radiology, Academy of Medicine Malaysia suggests facilities are unlikely to be a rate limiting factor as at least 28 institutions were equipped with a spiral or multi-slice CT scanner, equitably distributed geographically nationwide over a decade ago [31]. CT imaging however is suboptimal for very central tumours which may require adjunctive bronchoscopic assessment.

Appropriate management of a false positive or false negative result is another important issue. False positives carry a real risk of harm. Earlier studies with spiral CT did not show impressive positive predictive values with 90-92% of "positive" CT scans eventually proving non-cancerous [14,23]. Hence patients may be exposed to unnecessary radiation, anxiety and inherit the risks of invasive diagnostic procedures to confirm or exclude a suspicious lesion. A false negative result can be minimized with appropriate surveillance but care must be taken to ensure patients are not subjected to unnecessary radiation with long term follow-up. The indeterminate solitary pulmonary nodule (SPN) will also require appropriate monitoring. In short, any screening protocol must include obtaining a detailed informed consent from each individual subject who should be fully aware of the benefits, limitations, potential risks and costs of being screened.

Concluding remarks

Lung cancer is a major and costly health concern and the leading cause of cancer related death in this country. Due to the long latency phase of lung cancer, smoking cessation will have minimal impact for many decades. Early stage disease has a superior prognosis with an improved chance of a curative surgical resection. Despite the high disease prevalence, resection rates remain disappointingly low here in Malaysia as the majority of patients present with advanced unresectable disease.

The natural history of this disease coupled with the safety and widespread availability of low dose spiral CT scanning suggests screening should be feasible in this country. The NLCST provides compelling (albeit level 2A/B) evidence and a sound scientific basis for screening for this disease perhaps initially in the context of a local trial [15]. A well executed and comprehensive screening programme may potentially save many lives and billions of ringgit in the long term although admittedly evaluating cost-effectiveness is not straight forward.

A pilot study targeting a smaller "at risk" select population based on local epidemiology of the disease should be undertaken to determine precisely who should be screened. For example, all individuals over the age of 50 years and with a significant smoking history (> 20 pack year history) could be invited to participate. In contrast to the West, lung cancer here is diagnosed at an earlier age in 'never smokers' (mean 54.7 years Vs 61.6 years smokers) [3]. Overall, the mean age at which lung cancer is diagnosed in Malaysia is 60.1 years with peak age of distribution in the 7th decade. Hence whilst largely an arbitrary choice it is intuitive to consider commencing screening at a slightly earlier age, given the lengthy pre-clinical phase of lung cancer. The incidence of diagnosed lung cancer in Malaysian patients aged less than 40 years of age is relatively low at approximately 6.2% [32]. Hence screening at a younger age is likely to reduce the diagnostic yield, increase false positives and thus reduce the specificity and positive predictive value of CT imaging, leading to unnecessary interventions. It is imperative however that appropriate clear guidelines and quality assurance programs are established, by a dedicated multi disciplinary interest group prior to embarking on a screening programme.

The case for lung cancer screening in Malaysia is persuasive; decision time is now.

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