New Applications of Bronchoscopic Techniques

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Lung cancer screening: has there been any progress? Computed tomography and autofluorescence bronchoscopy

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Purpose of review

Advances in imaging technologies are currently being explored in the attempt to reduce lung cancer morbidity and mortality by achieving stage shift. We reviewed recent important publications on lung cancer screening.

Recent findings

Autofluorescence bronchoscopy has established its important role in the intervention of early central airway lesions. Multidetector computed tomography (CT) and CT–positron emission tomography may facilitate diagnosis of early parenchymal lung lesions. Practical implications of screening are reaching far beyond early diagnostic efforts *per se* as lead-time, length-time, overdiagnosis biases combined with low specificity of screening tests undermine its cost-effectiveness in the era of healthcare budget constraints.

Summary

Advanced imaging technologies may allow early detection and prudent intervention in some individuals that harbour asymptomatic early lung cancer, but disproportional expenses may be required to sieve out many more individuals at risk to attain stage shift. Confounding co-morbidities and practical hurdles may reduce screening's efficacy as it is plausible that for the majority of smokers, lung cancer may not be the ultimate cause of suffering since 90% of them will not develop lung cancer. This fact remains true despite increased use of noninvasive and minimally invasive technologies for the maximum preservation of quality of life irrespective of whether early intervention is a success or failure.

Keywords

autofluorescence bronchoscopy, CT, lung cancer, PET, screening

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Abbreviations

COPD chronic obstructive pulmonary disease
CT computed tomography

1070-5287

Introduction

The impetus to intervene in individuals with lung cancer is fully comprehensible as clinically advanced disease is associated with high morbidity and fatality. Despite advances made in therapeutics, for example improved chemoradiotherapeutic regimens and use of targeted treatment such as tyrosine-kinase inhibitors, prolongation of an individual's survival by several months without achieving significant stage shift is futile [1]. Lung cancer mortality can be significantly reduced if all individuals harboring early cancers are timely detected to enable less invasive treatments such as stereotactic body radiotherapy (SBRT), bronchoscopic treatment or video-assisted thoracoscopic resection to preserve maximally the quality of life since they are in the asymptomatic phase.

Screening implies detection of clones of malignant cells in the preclinical phase and is based on the premise that without intervention or if intervention fails, these lesions will lead to crippling morbidity or fatal outcome for the individuals concerned. Moreover, screening should be able to predict with accuracy outcome of these preneoplastic lesions, and alert clinicians to those that harbour malignant potential in the chronic and dynamic process of carcinogenesis. Early intervention in these asymptomatic individuals must not result in unacceptable morbidity or mortality but allows its implementation at reasonable cost. Thus, screening can only be cost-effective if the majority at risk have a high likelihood to suffer and die from lung cancer. Factors influencing survival, however, are indeed too many and varied to permit prediction in advance, apart from the fact that only a low percentage of heavy smokers (10%) would ultimately develop lung cancer thereby making nationwide implementation of screening by health authorities analogous to vaccination of children against endemic diseases a colossal task [1,2]. Many comprehensive and excellent reviews have been published on the topic of lung cancer screening [3•,4,5,6•,7,8], and we, the authors, would like to add that our views may be biased since we are interventional pulmonologists. We attempt, however, to offer a different perspective to a controversial topic that is based on few available observational screening studies and even fewer randomized population trials.

Rationale for lung cancer screening

Lung cancer portends fatality with a dismal 5-year survival rate of 15%. The impetus to prevent, interrupt or delay

lung cancer progression in individuals at risk by timely detection whilst in the preclinical asymptomatic phase is obvious from the clinical standpoint. Precise identification of the individuals at risk who may benefit most from screening, however, is the first hurdle to overcome.

Black [3•] discussed the importance of detecting lung cancer prior to the onset of metastasis (critical point), and how tests with variable sensitivities could cause lead time, length and overdiagnosis biases. Detection of clinically irrelevant cases because they were benign or slow growing, and overshadowed by suffering and death from attendant co-morbidity could undermine screening efforts [9]. Screening at regular intervals, which leads to overdetection of biologically benign cancers whilst more aggressive interval tumors remain incurable at the time of diagnosis, could result in fallacious improvement in outcome. Thus, cautious interpretation of a high cure rate achieved after treatment of screen-detected cancers is necessary as overdiagnosis with long lead time might belie the fallacious perception. Results from observational studies can therefore be biased by the number of 'clinically irrelevant' cancers that are detected early, which by themselves lead to a significant reduction in disease specific mortality. Randomizing screen-detected cancers to early treatment versus expectant management could potentially jeopardize the stage shift advantage and lead to treatment delay beyond the disease critical point [3•].

A recent systematic review indicated that in reality many screening studies lack a comparator group and will be not able to answer whether screening is effective or not. Judging from the few studies that have been included, the follow-up has been relatively short to derive conclusions about disease specific and total mortality rates [10]. Early data have also demonstrated extremely low incidence (0.1–1%) and prevalence (0.4–3.2%) rates of lung cancer, and, based on a prevalence of 3.2%, an enormous number of individuals at risk (31 249 persons at risk) would have to be screened in order to detect one early lung cancer.

Bach and co-workers [11•] cautioned about the current premise that deadly lung cancers can be detected early with more advanced computed tomography (CT) imaging technologies. Based on their calculations of observed lung cancer deaths reported in three longitudinal studies against the expected number of cases, by means of prediction models that take into account estimated probability and conditional probability, for example in screening chronic obstructive pulmonary disease (COPD) individuals, no reduction in advanced lung cancer cases or in the number of deaths was observed. This underscores an important concept that a reduction in cancer mortality may be masked by significant overdiagnosis that can persist and even increase in the following years due to overrepresentation of relatively benign tumours. Indeed, lead, length and overdiagnosis biases should not be trivialized in our critical appraisal of screening effectiveness; rather, the premise that all lung cancers if left untreated are fatal requires confirmation with well designed longitudinal randomized controlled trials targeting the population at risk [11•].

Target population and lesions

In clinical practice, physicians manage patients with lung cancer who also suffer from smoking-related co-morbidity such as COPD or coronary vascular disease. Early intervention strategy should take into account quality of life (QOL) with optimal use of minimally invasive techniques.

High grade dysplasia and carcinoma *in situ* (CIS) are currently regarded as early stage squamous cell carcinomas that involve the central airways while atypical alveolar hyperplasia (AAH) is the forerunner of peripheral parenchymal adenocarcinoma. Much less is known about the natural history of diffuse idiopathic neuroendocrine cell hyperplasia as precursor of neuroendocrine tumours, which represent 40% of clinically overt cases [12]. Early squamous cancer measuring under 1 cm^2 and under 3 mm thick can be treated by local therapy [13]. Parenchymal lesions 7–8 mm in size seem to be clinically important. Current knowledge on molecular genetics, however, underscores the concept of clonal heterogeneity even in stage IA non-small cell lung cancer for which small size is not an absolute guarantee of a true early stage lesion in achieving cure by early detection and treatment, since more is known about its biological behaviour based on molecular studies [14•,15].

Indeterminate pulmonary nodules

Investigators have reported 43–50% detection rates of indeterminate, noncalcified pulmonary nodules with the multidectector CT [16–18]. High detection rate and nodule growth assessment lead to high number of repeat CT surveillances required, increased costs and morbidity, including the necessity for invasive procedures in 22–55% of the participants [4]. Pastorino and coworkers have used FDG-PET to simplify their diagnostic algorithm by disregarding nodules under 5 mm, whilst only FDG-PET positive lesions over 7 mm were subjected to histological work-up. Of 1035 individuals followed for 2 years, 22 lung cancers were diagnosed, of which 95% were completely resected and 77% were stage I [19].

Experts have proposed guidelines to optimize the management of indeterminate pulmonary nodules [20]. About half of all smokers over 50 years of age have at least one pulmonary nodule and 10% will develop a new nodule during the year [21]. The probability of malignancy

is correlated to lesion size [22,23]. Lethality of nodules under 4 mm is under 1%, but increased to 10–20% for nodules 8 mm or larger, which then required additional work-up, for example contrast enhanced CT, FDG-PET and biopsy [19,23,24]. Investigators should be aware, however, of technical and clinical pitfalls accompanying these tests, as well as the tremendous challenges in dealing with massive number of lesions detected [7,25–27], as 80% of nodules under 8 mm will be clinically insignificant [20].

Inconsistency of histological classifications of surgical specimens has been observed amongst the most experienced pathologists involved in screening trials [28,29]. This raises concerns about interindividual and intraindividual variability which has led to the proposal for a trained pathology panel [28,29]. Issues such as field carcinogenesis and tumour multifocality heighten uncertainty about the full clinical impact of early detected lesions, and extreme caution should be exercised in dealing with tiny biopsy specimens collected in the screening studies [30].

The Mayo Lung Project showed persistent excess of cumulative number of lung cancers in the screened arm even after 25 years of follow up [9], while a recent study [31] did not demonstrate significant stage shift when low dose computed tomography (LDCT) was compared with chest radiograph and a similar distribution of stage I and stage III–IV cancers was detected. In contrast, the Early Lung Cancer Action Program study concluded strongly that annual spiral CT screening could detect lung cancer that was curable [32]. Only 49 had pathological T_{1-2} N_0 stage among a total of 31 567 individuals screened, giving a positive predictive value of 0.15%. Of these, only 28 cancers were limited to the basement membrane and thus from interventional pulmonology perspective could be considered true occult cancers. Seventy-four cancers were detected in the annual screened group of 27 456 participants, which translated to an incidence of 269/100 000 persons at risk/year. This figure far exceeds US Centers for Disease Control and Prevention lung cancer death yearly statistics by approximately 200/100 000 persons at risk/year, if the premise that the majority of untreated early detected cancers would result in death were correct. Overdetection of these clinically irrelevant cases of such magnitude could automatically inflate the cure rate by 74% or more [33]. Other observational trials which focused on individuals with heavy asbestos exposure again demonstrated relatively low yield for early cancer and large numbers of indeterminate pulmonary nodules that required additional work-up. Only two early stage cancers were found in 633 screened individuals [34], and five out of 316 respectively [35].

The NELSON trial involving current and former smokers randomizes individuals at risk to LDCT versus expectant management and is powered to detect 25% decrease in lung cancer mortality over a period of 10 years [36]. The complex issue of screening may be elucidated in 2013, provided contamination in the control group remains negligible in current and future practice as advanced imaging technologies will become more readily available in the near future and make it tempting for everyone involved to apply CT or PET/CT as the initial diagnostic tool in chest diseases when there is any suspicion of malignancy.

Other obstacles to lung cancer screening

The lack of consensus despite available guidelines among physicians and the different attitudes adopted may reduce the efficacy for a large scale implementation of lung cancer screening [37]. A recent telephone survey of current, former and nonsmokers revealed that the group at risk tended to be of lower socioeconomic status, and were more reluctant to participate and to comply if cancer was diagnosed [38•].

Practical implementation may not result in an optimal screening programme but can potentially reduce its cost-effectiveness. Analysis based on a computer simulated model aimed at achieving 50% stage shift and incorporating lead, length and overdiagnosis biases has shown that cost-effectiveness can vary widely for the different cohorts screened. For example, screening current smokers was estimated at US$42 500 per quality-adjusted life-year (QALY) if favourable estimates were used; however, for quitting and former smokers, the incremental cost-effectiveness was US$558 600 and US$2 332 700 per QALY gained respectively [39].

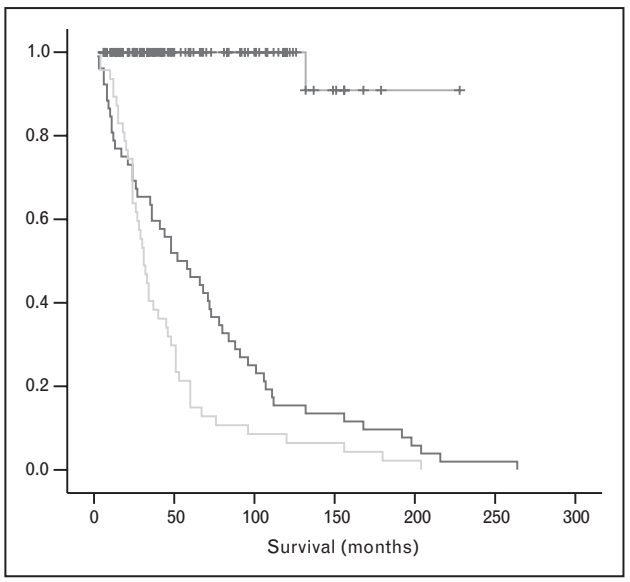
Early central airway cancer detected by autofluorescence bronchoscopy

Similar conceptual problems apply for observational studies in central airway lesions as autofluorescence bronchoscopy is more sensitive for the detection of early central airway cancer than conventional white light or video-bronchoscopy. The potential of sputum cytology for screening seems elusive as early tumours detected by autofluorescence bronchoscopy were completely missed by sputum cytology alone [40]. High grade dysplasia has the highest potential of progression to lung cancer: 33 and 54% at 1 and 2 years respectively [41]. Although squamous metaplasia is regarded as benign and may spontaneously regress, our published report cautions about the stepwise concept of carcinogenesis as some might be clonally malignant and could mimic biologically aggressive interval cancers that occur despite CT surveillance [30]. Notably a large majority of preneoplastic lesions detected by autofluorescence bronchoscopy do not progress to lung cancer and this observation in our opinion could be attributed to the performance of biopsy as they are often small and several millimetres thick.

Autofluorescence bronchoscopy combined with conventional bronchoscopy is more specific in excluding individuals who do not harbour central airway cancer and is better at identifying those with low risk for cancer [42]. Apparent 'false positive' lesions defined as suspicious autofluorescence bronchoscopy and normal histology seem to contain malignant molecular signatures [43]. Thus, application of autofluorescence bronchoscopy to routine bronchoscopy for individuals at risk may assist in reducing downstream testing by selecting out the low risk group for whom follow up can be discontinued. Moreover, we have demonstrated that early intervention of autofluorescence bronchoscopy-detected occult airway cancers with endobronchial electrosurgery or cryotherapy is also cost-effective [44].

We recently analysed our data of secondary screening in 228 very high risk individuals with previous lung or ENT cancers for field cancerization. After a median follow-up of 40 months (range, 17–73), 217 new primary lung cancers developed of which 181 cancers were detected with autofluorescence bronchoscopy and 36 by CT. Thirty-six patients had multiple roentgenographically occult central airway cancers with distinct margins that were successfully treated with bronchoscopic therapy. To date, 123 (54%) individuals with at least one previous aero-digestive tract cancer are still alive (Fig. 1, unpublished data). Possible interplay of factors such as lead, length and overdiagnosis biases as well as significant co-morbidity makes outcome interpretation difficult. Disease-specific mortality is 21% (47/228; 7%/year), which seems acceptable for this cohort made up of elderly (median age 70 years) current and former smokers with COPD and coronary heart disease. Moreover, recent data on stereotactic body radiation therapy as an alternative therapy for medically inoperable patients with early stage lung cancers cautioned about its nonselective use as treatment-related toxicity led to four deaths out of six patients with centrally located lung cancers [45].

Figure 1 Lung cancer related mortality in 228 individuals at risk over 10 years



There is no significant difference between disease specific mortality, i.e. lung cancer related deaths (dark grey curve, 47/228), and non-lung cancer related deaths (light grey curve, 58/228) After a median follow-up of 40 months (range 17–73), 54% are still alive. The lung cancer deaths' cohort was significantly older and suffered from more severe COPD (American Thoracic Society criteria).

Ideally a randomized study of early versus no treatment would address overdiagnosis and overtreatment. Unfortunately, it is highly unlikely that these individuals having been diagnosed with subsequent early lung cancers, while almost half have experienced previous ENT or lung cancer primaries, would comply to such a protocol, particularly since no morbidity or mortality associated with autofluorescence bronchoscopy or bronchoscopic treatments has ever been encountered in our extensive experience [44,46–48]. Despite potential biases, one could counterpropose that it is perhaps successful early intervention that allows more individuals with lung cancer to live longer and to eventually suffer and die from their competing comorbidities, an analogy that mirrors highly active antiretroviral therapy in AIDS [49]. Certainly, these concepts are interesting fodder for academic discussions but may prove completely irrelevant in clinical practice and the individual management of our patients [50].

Conclusion

In summary, although a sensitive imaging method such as multidetector CT can detect cancer in the asymptomatic phase, overwhelming numbers of additional diagnostic and therapeutic procedures may be required due to its low specificity and poor predictive value under 1% and great difficulty to differentiate malignant from benign pulmonary nodules. In fact, observational studies show incidence of early detected lung cancer in the order of 0.1–1% of the population screened, and even fewer pathological N_0 lesions amongst the so-called early detected lung cancers. These issues together with cost-effectiveness limit its widespread implementation.

Sputum cytology remains problematic as a screening test. Although autofluorescence bronchoscopy appears more promising for early central airway lesions due to its high specificity, it is after all still an invasive procedure. One could, however, argue in favour of autofluorescence bronchoscopy as it facilitates early detection in a cost-effective manner if combined with concurrent treatment of occult cancers with endobronchial electrosurgery or cryotherapy.

It remains difficult to prove that screening is effective based on available data from observational studies, as these screen-detected lesions may not become a threat for imminent suffering or death, regardless of whether a treatment has been successful or failed. Moreover, the heterogeneous time clock of clonal carcinogenesis, low specificity of CT as a screening tool, and competing co-morbidity underscore our inability to precisely identify that 10% individuals who have the highest chance of suffering and will ultimately die from lung cancer. Until the results of randomized trials are available, one should anticipate that a significant reduction in lung cancer death statistics over subsequent years following successful implementation of screening and early intervention is the only proof of principle, as significant overdiagnosis and treatment of pseudo-disease may mask the reduction of mortality rate. This is and will be in stark contrast to the anxiety experienced by the individual diagnosed with lung cancer and the desperate measures he or she is willing to take at any cost.

New information derived from calculations based on data from CT screened lung cancer observational studies cast doubt on the premise that all early detected lung cancers are fatal. It would appear that a view that seems startlingly obvious from the clinical perspective must not be assumed as the absolute truth especially in the dynamic process of carcinogenesis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 348).

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