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Lung  
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# Frontiers

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“The purpose of *Lung Cancer Frontiers* is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.”

## John A. Nakhosteen Early Lung Cancer Symposium—Part II

Readers of the *Lung Cancer Frontiers* No. 14 were treated to selected reports presented at the important celebration symposium honoring John A. Nakhosteen, one of the giants in bronchology and pulmonology in Europe on the occasion of his “retirement.” The three articles in *Lung Cancer Frontiers* No. 14 cover Nakhosteen’s relationship with the late Professor Shigeto Ikeda and two preliminary studies from his unit at the Augusta Hospital in Bochum Germany on the early identification featuring a semi-automated sputum cytology analysis system.

The two articles in this issue complete the report of this symposium. Thomas Sutedja’s “Endobronchial Treatment Options for Early Stage Cancer” may persuade North American readers that endobronchial approaches to treatment are a new frontier in our field. The detailed epidemiological study of lung cancer in Germany and Europe is probably one of the more comprehensive reviews of the multiple factors that alone or together result in lung cancer.

This issue also covers highlights of a special conference held at the Annual Meeting of the American College of Chest Physicians in San Diego in November 2002, chaired by Patricia Rivera.

Selected abstracts from the peer reviewed literature complete this issue of *Lung Cancer Frontiers*.

### Endobronchial Treatment Options for Early Stage Lung Cancer

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#### Introduction:

Current developments of new endoscopic techniques allow bronchoscopists not only to provide the proper diagnosis, but also fulfill the important tasks of screening, early detection, tumor localization, accurate staging and applying appropriate treatment whenever possible.

The key and active role of bronchoscopists in a multidisciplinary setting towards lung cancer management, especially in view of current interest in screening, is aimed to achieve a stage shift, allowing treatment at the earliest stage possible. This may improve the dismal cure rate of lung cancer patients.

#### Why early treatment?

The most important factor in the prognosis of an individual with lung cancer is the stage of the disease at diagnosis. The earlier treatment is initiated, the better the survival rate will be. High survival rate and cure can only be obtained in individuals with lung cancer without lymph node or distant metastases. Nevertheless in earlier screening trials done in the 1970s, stage shift in the study groups did not result in reduced lung cancer mortality. One of the points raised in this context refers to invasive therapeutic measures even with very early cancers with their associated

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rise and the inherent risks of smoking related diseases (COPD, cardiovascular and malignancies) translating into unacceptable morbidity and mortality in the active intervention group. Nobody can deny: “lung surgery is not the best example of tissue sparing treatment.” Surgical bronchotomy and bronchial sleeve resection as alternatives for “more wasteful” standard method of surgical resection require great technical expertise and as such is not easily executed by everybody. It is prudent to apply less morbid and less invasive diagnostic and therapeutic strategies, as many individuals may already suffer from COPD and poor cardiovascular status due to their long smoking history. Preserving lung tissue in these patients is of particular importance, more so, as they are apt to suffer from subsequent cancers due to their inherent higher risk for cancers in their upper aerodigestive tract. Minimally invasive endobronchial treatment may still offer otherwise inoperable individuals a chance for cure. The importance of preserving pulmonary function and associated quality of life is obviously important.

### When is endobronchial treatment indicated?

The definition of “early stage” lung cancer is the most important determinant for cure. The success of bronchoscopic treatment for early stage lung cancer is therefore based on the proper knowledge of carcinogenesis and the recognition of the limits of bronchoscopic modalities, rather than a choice of a particular technique per se. The different severity grades of preneoplastic changes for squamous cell carcinoma are well documented. When is the process irreversible? Our data suggest that CIS will invariably progress into invasive cancer if followed. (Chest 2000;117:1472)

Endobronchial therapy will be only curative for lesions confined to the bronchial wall and with clearly visible distal tumor margin. There is a diligent account on early cancers back in 1961 (Auerbach NEJM 1961;263:253) describing carcinoma *in situ* as: “The lesions varied in average depth from about 4 cells to a maximum of 38 cells, the majority being about 5 cells in depth.” These very early stage squamous cell cancers are located in regions accessible to the bronchoscope, of limited extent—a few millimeters thick, but relatively morbid if

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individuals have to undergo surgical resection. The correlation between endoscopic size of a lesion and the level of bronchial wall invasion, and more importantly, its relation to nodal disease, has been looked into in a series of 224 early cancers (Ono et al. Brachytherapy: NCI Tsukiji Japan). All tumors extending over more than 19 mm had crossed the cartilage border, on the other hand 51 of 67 CIS and microinvasive tumors were less than 10mm in diameter. Moreover, in early cancers having invaded extrabronchially 29% already had lymph node metastases (N1-N2).

Which diagnostic methods supply accurate information obtained about the depth of invasion and stage of the disease? The combination of HR-CT and autofluorescence bronchoscopy is helpful in this context. Of 23 occult to conventional chest radiography carcinomas 4 could be visualized by HR-CT. Of the remaining 19, 13 had borders extending beyond visibility of the autofluorescence bronchoscope (Chest 2001;120:1327). About the role of PET-scanning for early lung cancer more information is emerging. Very small lesions in the order of 2-3 mm size have been visualized (J Clin Oncol, 2001;19:4271), and more accurate exclusion of nodal involvement can be expected. Bronchial wall structures are outlined clearly by endobronchial ultrasound (EBUS). Depth of tumor invasion has been reported to be more accurately predicted in a number of patients (AJRCCM 2002;165:832), other report has been less clear about the definite role of EBUS herein (Lung Cancer 2002;35:65).

Subsequently the conditions, for which endobronchial therapy can be considered as an alternative treatment for surgical resection can be summarized as: a central (squamous cell) cancer <1cm in diameter and less than 3mm deep, visible distal margin using autofluorescence bronchoscopy. N0-stage should be evaluated by HR-CT, possibly also by PET-scan and EBUS. N0 stage tumors only will be potentially cured by endobronchial therapy, which is an intraluminal tumor debulking with finite depth if compared to surgical bronchoplasty or bronchotomy. Accurate staging therefore is an absolute prerogative to decision making on therapy of early lung cancers in the central airways.

Another indication for endobronchial therapy in lung cancer patients with limited pulmonary

reserve should also be considered. Prior to surgical therapy, proximal tumor extent in case of superficial mucosal infiltration can be reduced to enable a less extensive surgical resection (Kato et al. J Thorac Cardiovasc Surg 1985;90:420; Thorax 1990; 45: 493; Chest 1992; 102: 308)

Recently PDT experience for this purpose has been presented: of 26 squamous cell central cancers 4 were rendered operable only by prior application of PDT, in another 11 cases surgical procedure could be reduced to sleeve resection or lobectomy (Kato et al. IPA meeting Vancouver June 2001) Which is the best endobronchial treatment method? Several modalities of endobronchial treatment are available: photodynamic therapy (PDT), laser treatment, electrocautery, cryotherapy, argon plasma coagulation (APC) or endobronchial irradiation/brachytherapy. And last, mechanical tumor removal by extensively taking multiple biopsies may be curative in selected patients.

Experience has been accumulated with several of these methods. In a series of patients receiving PDT the rate of complete remissions was obviously dependent on the size and the growth pattern of the respective lesion and varied between 72 to 95 % (Hayata et al. Laser Med Sci 1996;11:255). With new photosensitizers, results seem even better (81-90%) with less morbidity. This is possibly due to patients' selection rather than more tumor selectivity of the sensitizers itself (Monaldi Arch Dis 2001;56:128). A comparative summary of cure rates for all different modes of endobronchial therapy shows quite variable figures (43-95%). As can be expected, the determinant factor is tumor size (T-stage) and the presence of lymph node metastases (Clinical Lung Cancer 2001;2:264).

Observing strict inclusion criteria for non-operable patients with lung cancer endobronchial therapy (PDT 5, laser 1, electrocautery 24, APC 2) was used for 32 individuals in Amsterdam. 16 patients are still alive after a follow up of 2-10 years (median 5 years), 16 have died, 7 of unrelated causes – which indicate the higher inherent risk of death for smoking related causes- 9 of lung cancer (8 with metastases of previous primaries, one because of a radiation necrosis and massive hemorrhage). There was no difference in outcome related specific to the therapeutic modality chosen.

“Of 23 occult to conventional chest radiography carcinomas 4 could be visualized by HR-CT.”

## Conclusions:

Bronchoscopic treatment is a less morbid alternative to surgical resection for early lung cancer provided accurate staging, i.e. assessment of the depth of bronchial wall involvement and nodal involvement, is possible. These factors are the most important determinants to which any treatment will have to be tailored. Treatment modalities do not seem to influence outcome (in this small series) as long as it is feasible to eradicate local clonal growth intraluminally located in the central airways.

## Epidemiology of Lung Cancer

K. Broman, K.-H. Jöckel

### Introduction, Descriptive Epidemiology

In many countries, lung cancer is the most prevalent malignancy neoplasm both in terms of incidence and mortality. In Germany, it had been the most frequent cancer in men for many years until 1998. In the same year it ranks second in men (26.3% of cancer mortality) and sixth in women (8.7% of cancer mortality) with a total number of about 38000 deaths.<sup>1</sup> In Europe with an estimated 330000 cases of death from lung cancer in 1995, the disease accounts for about one-fifth of cancer deaths.<sup>2</sup> Worldwide, more than one million persons (810400 men and 292700 women) are estimated to have died from lung cancer in 2000,<sup>3</sup> which is an increase of nearly 20% within 10 years. However, considering changes in population size and age structure by using age standardized rates, one detects that these changes are mostly due to the rise of lung cancer mortality in the developing world and among women. In Germany since the early fifties the age-standardized mortality rate has been increasing consistently and, for men, has leveled off at the end of the seventies followed by a slight decrease (Figure 1). Contrary to this, the incidence and subsequently the mortality among women has doubled compared to the early seventies due to changes in smoking behavior (Figure 1). For both sexes, the incidence of lung cancer increases sharply with increasing age. In Germany, the lifelong risk of a person born in 1940 to develop lung cancer until age 75 is about 8% in men and 1% in women.<sup>4</sup> The average age of onset in males and females is

about 66 years of age<sup>5</sup> which is comparable to cancer in general, and has increased somewhat during the past 30 to 40 years.<sup>6</sup>

Compared to the European Union in general, the mortality rates for 1997 in Germany are slightly lower with an age-standardized mortality rate of 65.6 in males and 14.3 among females (European standard population).<sup>7</sup> Men in the Benelux countries and Italy have considerably higher, men in Sweden and Portugal far lower rates. Among women these rates are highest in Denmark, Ireland, and the UK, and lowest in Spain, Portugal, and France.<sup>7</sup> In most countries there is a strong regional variation in lung cancer rates. Usually, there is a distinct difference in the rates among residents of urban versus rural areas. For the most part this difference does not originate from general air pollution but from differences in exposure to smoking and occupation.<sup>8,9</sup>

### Survival and Prognosis

Each patient with lung cancer loses about 12-13 years in life expectancy. The total number of years of life lost is with 541300 years total (394000 in men) bigger than for any other localization.<sup>5</sup> The prognosis for lung cancer is currently better in females than in males. Based on current data, the 5-year relative survival rate is about 9% in males and 17% in females.<sup>5</sup> This rate in females is better than the European range, where for the same period the rates were 10% in males and 11% in females.<sup>10</sup> However, comparing current German data to past calculations based on data from Saarland for two time periods it becomes obvious how little has been achieved in improving the perspective of lung cancer patients, especially for men (1978-84: males: 9%, females: 11%<sup>11</sup>; 1985-89: males: 10%, females: 15%<sup>10</sup>). In addition to stage at diagnosis, age of onset is an important factor for prediction of survival and, as expected, prognosis is getting worse with increasing age of onset. This change in survival probability is particularly obvious when comparing survival rates for those below and above 70 years of age. Considering time of diagnosis, different age groups have shown a similar development of survival rates during the past 30 to 40 years.<sup>6</sup>

### Histologic Types

Nearly all lung cancers develop from epithelial

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tissue with squamous cell, small cell and adenocarcinomas being the most frequent forms. Recent studies indicate that they account for about 80% of all histologic types.<sup>12</sup> In addition, there are large cell carcinomas, other tissue types, and combination of tumors which do not allow for an unambiguous classification due to presence of several histologic forms. Relevant differences exist between the distributions of histologic types in men and women. While squamous cell carcinoma is the most frequent type in men, adenocarcinoma is most common in women. However, this difference does not relate to gender per se but rather to different exposures to risk factors, especially smoking.

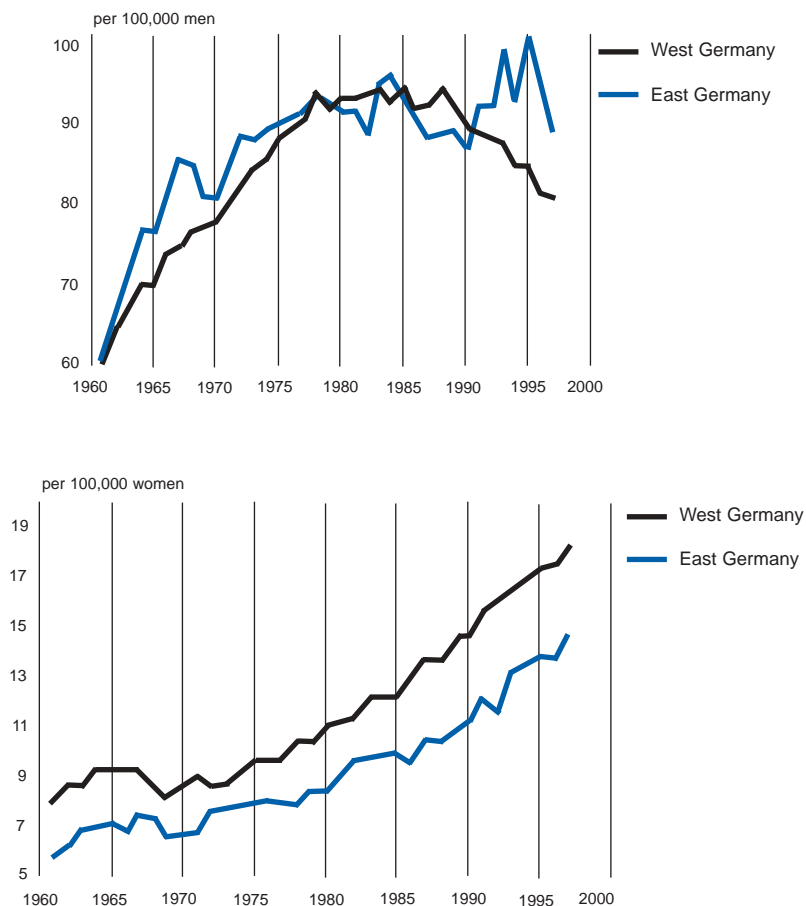
Adenocarcinomas are more frequent in nonsmokers and a large European multicenter study has shown a uniform 50% share of adenocarcinomas in male and female nonsmoking lung cancer patients.<sup>13</sup> Overall, a worldwide increase in the prevalence of adenocarcinomas has been reported. Whether this rise is real or due to changed diagnostic measures is still unclear. While there is little variation in survival by cell type, patients with non-small-cell lung cancers (NSCLC) have a prognostic advantage.<sup>14</sup>

### Risk Factors

#### Smoking

Tobacco smoking is the most important risk factor for lung cancer. Based on mortality risk estimates for current and former smokers from the report of the Surgeon General, and German data on smoking behavior and lung cancer mortality we calculated crude estimators of the attributable risk and the smoking associated lung cancer mortality for Germans above age 14 in 1998. We obtained attributable risks of 90.5% in men and 74.6% in women, resulting in 32847 cases of lung cancer attributable to smoking (25923 men, 6924 women).<sup>15</sup> The association between smoking and lung cancer was already suggested by Soemmering at the end of the nineteenth century (quoted by reference number 16) and was reported on by various investigators during the following decades based on the results from animal experiments, case reports and observational studies. One of the earliest case-control studies that confirmed this association was conducted by Mueller in the late

**Figure 1**  
Age-standardized mortality rates of lung cancer in men and women<sup>2,3</sup>



Standard population: Germany 1989 (West and East Germany)

thirties<sup>17</sup> followed by cohort studies in the US and the UK in the fifties and sixties<sup>18,19,20</sup> mostly on the effects of cigarette smoking. Here, a dose-response relationship with the cumulative dose is well established. But also, the intensity (way of inhalation) and duration of smoking have a strong effect on lung cancer risk. In addition, studies suggest that early age at onset of smoking<sup>21</sup> is a risk factor whereas the use of filters and low-tar brands reduces the risk compared to those smoking non-filter or high-tar cigarettes.<sup>14</sup> Furthermore, the type of tobacco has an impact on lung cancer risk.<sup>14,22</sup> Smoking cigars or pipe is also related to an increased lung cancer risk.<sup>23</sup>

Smoking is a risk factor for all histologic types of lung cancer but the association and the dose-dependent gradient is smaller in adenocarcinomas than in squamous-cell and small cell

carcinomas.<sup>12</sup> The frequent clinical observation that lung cancer patients had stopped smoking before obtaining their diagnosis affects the different histologic types in the same manner.<sup>24</sup>

Whether the smoking associated lung cancer risk is stronger for women than for men is still disputed. Epidemiologic evidence from large investigations exists that supports both views even after accounting for the dose of exposure. While several North-American studies have found such an effect,<sup>25,26</sup> this could not be detected in a large multicenter European study.<sup>22,27,28</sup> Potential explanations for the risk differences found by some are, e.g. estrogens, body size, body mass index<sup>29</sup>, and an increased gastrin-releasing peptide (GRP) expression.<sup>30</sup> But also artifacts could account for this apparent increased susceptibility in women such as a higher baseline risk of lung cancer for men due to their higher occupational exposure. In addition, women in the past were more likely than men to have an additional ETS exposure through a smoking spouse resulting in a higher tobacco exposure than that from active smoking.

Smoking cessation, particularly at an early age, enhances the health status<sup>31</sup> and, specifically, reduces lung cancer risk compared to smoking continuation.<sup>32</sup> This risk reduces with increasing time since smoking cessation approximates the risk of never smokers after about 20 years. However, this and the degree of risk reduction depends also on the amount and duration of the preceding exposure. At any rate, since smoking cessation is beneficial to the health status at all stages, all smokers should be encouraged to quit.<sup>33</sup>

## Environmental Tobacco Smoke

Environmental tobacco smoke (ETS), also referred to as passive smoking, is the exposure of a person to tobacco combustion products from smoking by other persons. Its public health relevance was first detected through epidemiologic studies which showed an increased lung cancer risk in non-smoking wives of smoking men.<sup>34,35</sup> Since then, many studies have examined this association.<sup>36</sup> From a toxicological point of view, the causation of lung cancer through ETS is plausible for several reasons. First, there is a higher concentration of effective carcinogens in the side stream smoke of ETS compared to the main stream smoke that an

active smoker consumes. Second, evidence from animal experiments supports the causal relationship.

However, many of the epidemiologic studies conducted on ETS focus on lung cancer risk in nonsmoking men and women.<sup>37</sup> Subsequently and repeatedly, there has been extensive criticism particularly from the tobacco industry and affiliated scientists. The arguments provided focused mainly on methodological issues such as the observation that smokers tend to be spouses of smokers. In the case of misclassifying a smoker as a nonsmoker this would necessarily lead to an artificially increased ETS associated risk. In spite of this criticism, reviews, meta-analyses and statements of official agencies such as the EPA get to the same conclusion, i.e., after accounting for all these methodological weaknesses the effect of ETS on lung cancer continues to exist. Recently, the commission of Deutsche Forschungsgemeinschaft (DFG) for the assessment of unhealthy occupational substances has classified ETS as a human carcinogen.<sup>38</sup> Part of the scientific evidence upon which this judgment is based are two German studies<sup>37,39</sup> which were part of an international study conducted by the IARC.<sup>13</sup>

## Occupation

In the early eighties, Doll and Peto have estimated that 15% of lung cancer cases among men and 5% of lung cancer cases among women can be attributed to occupational exposures.<sup>8</sup> Results from recent investigations in Germany indicate that the scenario is comparable in this country.<sup>40</sup> Joint analysis of two large German case-control studies in form of a pooled study<sup>41,42</sup> showed that occupation in very different professions and branches of industry was associated with very disparate lung cancer risks. Increased lung cancer risks were found in the branches agriculture, forestry, and fishing; energy and mining; rubber and plastics; stone, glass and pottery; metal production; engine and vehicle building; paper, wood and printing; construction and in transportation. Decreased lung cancer risks were found in wholesale and retail trade; education, health, research and sports and in administration and welfare services. For occupational positions, employment in typical blue collar jobs was associated with a relevant increase in lung cancer risk whereas this

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association was reversed for white-collar jobs. It should be noted that these results can only be partially attributed to exposure to known occupational carcinogens such as asbestos since they were obtained after adjustment for smoking and asbestos exposure. Furthermore, these results were also seen in nonsmoking participants in the IARC-study mentioned earlier.<sup>43</sup>

Among the occupational carcinogens, asbestos remains the most important one even though its production and use had been prohibited during the eighties after recognition of its adverse health effects after inhalation. Further recognized lung carcinogens are polycyclic aromatic hydrocarbons (PAH), radionuclides, dichlorodiethyl- and monochlordimethylether, arsenic-, nickel- and chrome (VI) compounds, and ionizing radiation. Evidence for the lung carcinogenic effect of the latter was provided through medical applications and through survivors of the atomic bomb in Japan.<sup>14</sup> In addition to these there are several substances with growing scientific evidence for its association to lung cancer. In particular, these are diesel engine exhaust, crystalline quartz, crystalline silica, and manmade mineral fibers,<sup>41,42,44</sup> man-made vitreous fibres<sup>45</sup> but also cadmium<sup>46</sup> and welding fumes.<sup>47</sup>

## Radon

Radon is an inert gas that develops from radium during the natural decay of uranium. An increased lung cancer risk has been observed in uranium miners with a high exposure to radon and radon-decay products. Therefore, a risk elevation from indoor radon exposure seems likely. Based on extrapolation from measurement of household exposure levels it was estimated that about 7% of lung cancer cases in former West Germany were caused by environmental radon.<sup>48</sup> Whether this estimation can be extrapolated to areas of low dose exposure levels remains controversial due to disparate findings from epidemiological studies on indoor exposure. A study conducted in a West German region with increased radon concentrations showed a borderline significant risk elevation associated with indoor radon exposure<sup>49</sup> and these findings are in line with the results of a meta-analysis conducted by Lubin and Boice.<sup>50</sup>

## Air Pollution

Based on the observation of clearly increased lung cancer mortality rates in urban areas and due to the prevalence of various known or suspected carcinogens in the air (caused by traffic, particularly from diesel exhausts, industrial processes, and oil combustion) general air pollution was suspected to contribute to the development of lung neoplasms. However, the ecological studies conducted to examine this hypothesis could not adequately account for smoking and occupational exposures. According to current state of knowledge the associated relative risk is below 1.5. Not more than 5 to 10% of lung cancer cases in high exposure areas and about 2% in Germany should be attributable to air pollution.<sup>9</sup> Recently however, a large study has linked long-term exposure to fine particulate air pollution to an increased lung cancer mortality.<sup>51</sup> Furthermore, cooking fumes have been mentioned as an additional type of (indoor) air pollution that may contribute to lung cancer which has been shown in non-smoking Chinese women.<sup>52</sup>

## Nutrition

In many epidemiologic studies, frequent consumption of fresh fruits and vegetables was associated with a reduction in lung cancer risk,<sup>53,54</sup> and there is consistent evidence that such a diet has a protective effect on cancer in general. An effort has been made to identify the specific components that are responsible for this risk reduction. Based on biochemical data it seems plausible that this protection is an effect of beta-carotene. Another micronutrient potentially involved in lung cancer prevention is vitamin E. However, previous endeavors of using beta-carotene or vitamin E for chemoprevention were not successful.<sup>55,56</sup> Vitamin C as well as selenium are assumed to have a protective effect whereas a diet high in cholesterol and fat seems to be associated with an increased risk.<sup>14</sup>

## Genetic Factors

While up to 90% of lung cancers can be attributed to cigarette smoking, little more than 10% of smokers develop the disease and a considerable share of lung cancer patients are nonsmokers. Therefore, it is believed that susceptibility genes contribute to an individual's risk to develop the disease, and this is supported

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by different types of investigations. First, molecular epidemiologic studies have indicated that certain gene polymorphisms may be more prevalent in lung cancer patients. In the past, these studies have primarily focused on genes which are involved in both phases of the metabolism of environmental carcinogens, e.g., the cytochrome P450 system, *GSTMT1* and *NAT2*. More recent studies have also investigated genes such as the Dopamine receptor gene *DRD2* which may contribute to nicotine addiction and, subsequently, to lung cancer. Second, classical epidemiologic studies with information about relatives have shown an aggregation of lung cancer in certain families, especially in those of patients with an early onset of disease. Finally, segregation analyses have indicated a certain compatibility of inheritance patterns with Mendelian models. For an overview see, e.g.,<sup>57</sup> However, interpretation of these results is particularly difficult since family members share not only genes but other risk factors such as smoking and other lifestyle factors etc. as well.<sup>57,58</sup> Current evidence for the role of genetic susceptibility markers remains ambiguous especially since different polymorphisms exist in different populations. However, it seems likely that an interaction of genetic and environmental factors contributes to disease occurrence. More specifically, it is expected that multiple genes of low penetrance interact in disease development<sup>59</sup> and this believe is supported by the results from animal experiments.<sup>60</sup>

### Other risk factors

It has been repeatedly observed that patients with asbestosis and silicosis have an increased lung cancer risk. Also, based on what has been described above, such an association is plausible. At the same time, the role of other lung diseases such as tuberculosis is less clear.

The existing evidence for the role of pet bird keeping is inconsistent.<sup>61</sup> Further potential risk factors discussed relate to psychosocial factors,<sup>62</sup> the immune system, and hormones.<sup>14</sup>

### Prevention and Early Detection

The prognosis for lung cancer remains poor despite all progress in research and efforts made to improve diagnosis and treatment. As has been mentioned earlier already, patients with a diagnosis at an early stage (0 or 1) have the

highest chance for an extended survival. Therefore, it is desirable to detect lung tumors as early as possible, i.e. at an asymptomatic state. High-risk individuals such as those with high levels of environmental and smoking exposure and high susceptibility should benefit most from screening efforts and the positive and negative predictive value of any test at a given sensitivity and/or specificity improves with increasing prevalence of disease in the population tested. However, randomized clinical trials so far could not demonstrate a relevant advantage in terms of lower mortality as a result of those early detection efforts.

The following methods are worth mentioning when discussing early detection and screening for lung cancer: Chest radiography, low-dose computer tomography (low-dose CT, spiral CT), and studying molecular markers in specimens obtained by sputum, peripheral blood, or by even more invasive methods such as bronchoalveolar lavage (BAL), bronchoscopic examination, fine-needle aspiration of peripheral nodules, transbronchial, open lung or mediastinal biopsies.<sup>63</sup> Routine screening with chest radiography had been given up based on results from earlier clinical trials which failed to demonstrate a benefit in terms of mortality reduction. Also, its application combined with sputum cytological analysis has failed to show a reduction in lung cancer mortality rates in several trials such as the Mayo Clinic Study, the Johns Hopkins Study, the Memorial Sloan-Kettering Study, and the Czechoslovakian Lung Cancer Screening Study.<sup>64</sup>

Another method based on radiation is the low-dose spiral CT. Its potential application in lung cancer screening has received a lot of attention since it allows to capture more data with less radiation and a higher sensitivity than chest radiography.<sup>64</sup> However, it is still unclear whether its use is only limited to detecting the disease earlier and at smaller sizes or if it actually helps to reduce mortality.<sup>65,66</sup> One should keep in mind that the assumptions of an association between tumor size and biologic behavior and of equivalence between small lesions and early-stage disease have not been confirmed for lung cancer.<sup>66</sup> Also, the cost-effectiveness and the risks related to radiation which may increase the risk of mortality from other causes need to be considered.

Sputum analysis has been used in lung cancer diagnosis since the 1930s. The sole use of conventional sputum analysis for screening is not useful due to its low sensitivity (20-30%) in early lung cancers. The addition of sputum analysis to annual chest radiography in the Johns Hopkins and the Memorial Sloan-Kettering Studies did not show any advantage. However, several approaches to improve sensitivity are currently under development such as immunostaining, PCR, computer-assisted image analysis, and high throughput technology.<sup>64</sup> Also, its combination in screening with low-dose spiral CT has been favored by some.<sup>67</sup>

The more invasive methods BAL and bronchoscopy all have important drawbacks. While BAL and white light bronchoscopy (WBL) turned out to be low in sensitivity, the improvement light-induced fluorescence endoscopy, also called LIFE bronchoscopy, which is supposedly an improvement of WBL suffers from low specificity. The value of newer bronchoscopy techniques such as endobronchial ultrasound (EBUS) and optical coherence tomography in screening for early stage lung cancer cannot be judged at this point in time.

On a general note, while potential markers of early disease such as the heterogeneous nuclear ribonucleoprotein (hnRNP) have been identified, genetic aberrations and other molecular markers of preclinical disease obtained from multiple sites need further evaluation in clinical studies before they can be applied in screening. The same holds true for all types of screening methods available so far and it is too early to recommend any of these methods for mass screening. Also, one should not focus on the reduction of disease specific mortality exclusively when evaluating these methods. Instead, one should consider the broader term all-cause mortality.<sup>5</sup> Not only is all-cause mortality unaffected by bias due to misclassifying the cause of death as the authors point out correctly, but also do screening efforts such as chest radiography and spiral CT have side effects which may eventually cause death for reasons other than lung cancer. Exclusive consideration of disease-specific mortality conveys a rather limited and potentially biased perspective of the benefit gained by screening and examples of randomized trials exist where benefits were gained in terms of disease-specific but not in all-cause mortality and vice versa.<sup>68,69</sup>

At the current stage, primary prevention is clearly the most effective method in lung cancer prevention. In essence, anti-smoking programs pursue the following three objectives: First, to prevent people, particularly adolescents, from taking up smoking. Second, to support people to quit smoking or, at least, to reduce their exposure levels. Third, to protect the general population from passive smoke exposure. In addition to smoking prevention measures, it is desirable to lower or remove relevant occupational exposures.

### Outlook

Lung cancer is a widespread malignant neoplasm and the archetype of a multifactorially caused cancer disease. Therefore, the burden on the population and the economic consequences are accordingly big while at the same time the search for risk factors is difficult aside from the main factor smoking. On the other hand, many factors especially those relating to occupation have already been identified calling for primary preventive action.

Further research is needed for better understanding of molecular-biological principles, gene environment interaction as well as the potential of early detection and therapy of this tumor. It should be the ultimate goal to identify and quantify potential risks, to take the appropriate steps where relevant exposures have already been identified and to improve the possibilities of early detection and therapy.

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*M. Patricia Rivera*

## Targeted Therapy in the Multi-modality Treatment of Lung Cancer

Nearly 200 pulmonologists, oncologists, thoracic surgeons and other specialists attended an exciting morning symposium on new developments in the management of lung cancer at the annual meeting of the American College of Chest Physicians in November. The conference was opened by Chairperson M. Patricia Rivera, Assistant Professor of Medicine and Co-Director of the Multi-Modality Cancer Program at the University of North Carolina in Chapel Hill. Joan H. Schiller, M.D., Section of medical Oncology, University of Wisconsin; Ronald B. Natale, M.D., Acting Medical Director, Cedar Sinai Comprehensive Cancer Center and Alan B. Schandler, M.D., Medical Director Thoracic Oncology, Director, Vanderbilt-Ingram Cancer Center, Vanderbilt, all gave presentations on new therapeutic approaches and targets in the management of non-small cell lung cancer. The common theme of these discussions was that modern management is multi-modality and includes cytotoxic-chemotherapy employing two or three agents, which has reached a plateau in terms of efficacy. Though small advances in

improved survival and quality of life have been achieved, the bottom line is that the stage at which most lung cancers are diagnosed today remains advanced and overall prognosis is quite dismal.

The future, of course, depends on upon early identification and intervention in Stage I or even non-invasive stages of disease. When Stage I cancer is diagnosed by modern techniques, including sputum cytology and CT imaging, augmented by fluorescent bronchoscopy when appropriate, five-year survival in Stage I lung cancer is 65-85%. Previous issues of Lung Cancer Frontiers have continued to emphasize the importance of early identification and intervention and the abandonment of historical dogma that lung cancer screening does not work. The standard of care for early stage lung cancer remains surgical resection. Whether or not adjuvant chemotherapy or other tumor modifying agents improve survival in early stage lung cancer remains unanswered.

The exciting thrust of the symposium was the study of novel therapies based upon new understandings of the molecular biology of the NSLC. Emphasis on epidermal growth factor receptor inhibitors, angiogenesis inhibitors and matrix metalaprotinease inhibitors was covered in detail.

Modest progress has been made in studying several epidermal growth factor receptor (EGFR) inhibitors, most notably Iressa® and Tarceva®. Dramatic anecdotal clinical responses occasionally occur and case examples were presented. Issues regarding the biological predictors of response and what tumor marker or surrogate marker is predictive of tumor response were discussed. The big question is “is over expression of EGFR necessary for clinical responses to occur?” The answer is that nobody knows. Mutant EGFR receptors may explain differences in response. Thus far, no clearcut molecular markers have been identified that predict clinical responses.

Approximately one-third of patients with advanced stage disease, previously treated with chemotherapy have shown symptomatic, roentgenographic or combined responses to Iressa®. Two hundred and fifty milligrams per day of Iressa® seems to be the minimum effective dose. Five hundred milligrams per day is more toxic and not much more effective. The oral drug

taken once daily is reasonably well tolerated with transient diarrhea and acne, but serious side effects are rare. Measurable improvements in quality of life with statistically significant improvement in symptoms usually occur within four weeks and are sustained for many months in some patients. Thus, the fact of clinical response is not in doubt, but the factors associated with improvement and tumor regression are not yet well delineated. Both Iressa® and Tarceva® appear to be modest advances in managing advanced stage lung cancer in randomized, placebo-controlled prospective clinical trials.

In my opinion, the excitement of the symposium is not so much in the outcomes, but in the development of new therapeutic strategies designed to do better than standard chemotherapy in advanced stage disease. Using EGFR receptor blockade, early stage strategies as an adjuvant to resectional surgery to inhibit or abort micrometastasis seems to be an attractive new strategy. Such controlled clinical trials are currently underway, using these drugs in the chemoprevention of emergence from dysplastic sputum epithelial changes, i.e., pre-cancerous lesions, is also currently under study in specialized programs of research excellence in the United States today.

I continue to believe that lung cancer is the new frontier for pulmonary medicine. It is conferences such as this one that convince me that this notion may be correct. (TLP, ed)

## Citations from the Literature

### ‘Early’ Peripheral Lung Cancer: Prognostic Significance of Ground Glass Opacity on Thin-section Computed Tomographic Scan.

Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R.

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**B**ackground: The number of peripherally located lung cancers with an excellent prognosis has been increasing, possibly due to the introduction of computed tomography for lung cancer screening in Japan. The concept

of peripherally located “early lung cancer” remains controversial.

**Methods:** A retrospective study was conducted on 1,540 lung cancers resected at our institute between May 1992 and December 2000. The sizes of solid attenuation and ground glass opacity were evaluated radiologically and the relationships between radiologic findings and clinicopathologic features were investigated to define peripheral early lung cancer.

**Results:** Sixty-nine (4.4%) lung cancers showed a large ground glass opacity component on thin-section computed tomographic scan. The maximum tumor dimension ranged from 6 to 41 mm, and all tumors were clinical stage I. Forty-seven patients were diagnosed as having bronchioloalveolar carcinoma pathologically. None of the tumors showed lymph node involvement or lymphatic invasion. Only two showed vascular invasion, but all were pathologic stage I disease. Most of the lung cancers that showed pure ground glass opacity were bronchioloalveolar carcinoma.

**Conclusions:** Peripheral lung nodules with a large ground glass opacity component on thin-section computed tomographic scan, which do not disappear during follow-up, tend to be bronchioloalveolar carcinomas or minimally invasive adenocarcinomas of the lung. These findings warrant a feasibility study of limited surgical resection for such lung tumors.

#### **Editorial Comment (TLP):**

As CT scans are more widely applied, hopefully mostly to high-risk patients, more and more peripheral nodules with ground glass opacity will be found. Those that remain or grow should be the subject of future investigations for definitive diagnosis. How long watchful waiting should prevail could be debated and may require more studies.

## **Surgical Resection of Multifocal Non-small Cell Lung Cancer is Associated with Prolonged Survival.**

**Battafarano RJ, Meyers BF, Guthrie TJ, Cooper JD, Patterson GA.**

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**Background:** Revisions in the international system for the staging of lung cancer, adopted in 1997, assigned the T4 descriptor to separate tumor nodules in the same lobe and the M1 descriptor to tumor nodules in a different lobe. Consequently, these changes shifted the stage of patients with these lesions to stage IIIB or stage IV. The goal of this review was to determine the impact of multifocal non-small cell lung cancer on survival.

**Methods:** A database analysis of our cardiothoracic surgery tumor registry was performed to identify all patients who underwent surgical resection of non-small cell lung cancer (NSCLC), who were ultimately determined to have pathologically node-negative disease from 1994 to 1999. All pathology reports were individually reviewed. Survival data were collected on each patient from the date of surgery with a mean duration of follow-up of 46.3 months. Kaplan Meier actuarial survival was determined for all patients.

**Results:** Forty-four patients were identified who underwent complete resection of multiple NSCLC tumors. During this same period, 504 patients underwent complete resection of stage I NSCLC tumors. The 3-year actuarial survival for patients with T1/N0/M0 tumors was 79.6%. In comparison with patients with T1/N0/M0 tumors, the 3-year actuarial survival rates of patients with T2/N0/M0 tumors (72.3%,  $p=0.056$ ), T4/N0/M0 tumors (66.5%,  $p=0.058$ ), and T1 to T2/N0/M1 tumors (63.6%,  $p=0.201$ ) were lower. However, these differences did not achieve statistical significance.

**Conclusions:** Although there was a trend toward decreased survival in patients with multifocal NSCLC compared with patients with stage I NSCLC, this did not achieve statistical significance. Importantly, survival in these

subgroups of patients with stage IIIB or stage IV disease (stage determined solely on the basis of multifocal NSCLC) is better than the survival reported in the series that formed the foundation for these staging changes. These data support complete surgical resection of multifocal lung tumors in patients with node-negative NSCLC.

**Editorial Comment (TLP):**

It is not surprising that non-NSCLC can be multifocal. Nonetheless surgical resection may be curative in selected patients.

**Pathologic Review of the Mayo Lung Project.**

Colby TV, Tazelaar HD, Travis WD, Bergstralh EJ, Jett JR.

Department of Laboratory Medicine and Pathology, Mayo Clinic Scottsdale, Scottsdale, Arizona.

**B**ackground: In the Mayo Lung Project Screening Trial, there were more carcinomas identified in the screened group compared with the control group. The screened group had better survival, but there was no difference in lung carcinoma mortality between the screened group and the control group. The purpose of this study was to review all available original pathology from the trial to determine whether overdiagnosis (carcinomas that do not result in the death of the patient) or misdiagnosis of lung carcinoma may explain this discrepancy.

**Methods:** All available lung pathology slides from patients who underwent surgery at the Mayo Clinic were reviewed independently by three blinded lung pathologists. Tumors were classified according to the 1999 World Health Organization criteria. In addition, agreement among the pathologists was assessed.

**Results:** Among 106 patients who underwent surgery at the Mayo Clinic, slides were available for review from 105 patients, including 77 slides from the screened group and 28 slides from the control group. The original diagnosis of carcinoma was confirmed in all patients. In 7 patients (6.7%), there was unanimous agreement that the lesion was preinvasive (carcinoma *in situ*), and these lesions all were from the screened group. In 90 patients (85.5%), there was

unanimous agreement that the tumors were invasive. In 8 patients (7.8%), there was some disagreement between the observers about whether lesions were invasive or preinvasive; 7 of these 8 lesions were from the screened group. The level of agreement among pathologists for invasive carcinomas was >94% for all comparisons, and the kappa statistic ranged from 0.67 (substantial agreement) to 0.84 (almost perfect agreement). There was good agreement among the pathologists about tumor cell type with the kappa statistic  $\geq 0.65$ .

**Conclusions:** The histologic diagnosis of carcinoma was confirmed for all 105 slides that were reviewed. The results of this study indicate that misdiagnosis does not explain the increased numbers of carcinomas identified in the screened group. The increased numbers of *in situ* carcinomas in the screened group resulted in increased numbers of squamous carcinomas in the screened group compared with the control group and may have contributed to the better survival. It is possible that carcinoma *in situ* accounted for some instances of overdiagnosis. Cancer 2002;95:2361-5. Copyright 2002 American Cancer Society. DOI 10.1002/cncr.10930

**Editorial Comment (TLP):**

At last we get solid data that more carcinomas were found in screened compared with the control group. And the screened group had better survival. Many of the carcinomas in the screened group were *in situ* and this probably contributed to a better outcome. Isn't that what early identification is all about?

**Asbestos Bodies in the Sputum of Asbestos Workers: Correlation with Occupational Exposure.**

Paris C, Galateau-Salle F, Creveuil C, Morello R, Raffaelli C, Gillon JC, Billon-Galland MA, Pairon JC, Chevreaux L, Letourneux M. Occupational Disease Dept, Rouen University Hospital, Rouen, France. christophe.paris@chu-rouen.fr

**A** cross-sectional medical survey including collection of three consecutive sputum samples was carried out among 270 retired workers of a textile and friction materials

factory, in order to investigate the relationship between asbestos body identification and asbestos exposure. The individual cumulative asbestos exposure, determined by means of a plant-specific job-exposure matrix based on asbestos air measurements in the workshops, proved to be heavy with a mean cumulative exposure of 217 fibres x mL(-1) x yr.

Macrophages and asbestos bodies were identified in sputum samples by light microscopy. The lung origin of the sputum, suggested by the presence of macrophages and/or asbestos bodies, was confirmed in 82.6% of subjects, and 53% of these samples were positive for asbestos bodies. The prevalence of asbestos bodies was not related to sex, smoking status or latency. Conversely, multivariate analysis showed a positive relationship with cumulative exposure, duration and intensity of exposure to asbestos, as well as

age and time since retirement. These findings suggest that sputum analysis for asbestos bodies may remain a relevant and noninvasive marker of heavy occupational exposure to asbestos, even years after retirement. Owing to the new perspectives in lung cancer screening, it might contribute to the identification of high-risk subjects.

#### Editorial Comment (TLP):

Sputum analysis may be used, not only for identification of progressive stages of dysplasia, carcinoma *in situ* and invasive carcinoma, but also as a practical non-invasive marker for heavy occupational exposure to asbestos. Thus, as sputum cytology becomes more widespread, the finding of asbestos bodies, even those with remote asbestos exposure history, should lead to more aggressive surveillance.

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