2.1 Introduction

Lung cancer continues to be a disease of epidemic proportion. This year alone, it is estimated that 172,570 people will be newly diagnosed with the disease and 163,510 will die in the USA (ACS, Cancer Facts & Figures 2005; http://www.cancer.org/docroot/STT/stt_0.asp). Thus, more people will die from lung cancer than from breast cancer (40,870), colorectal cancer (56,290), and prostate cancer (30,250) combined. Lung cancer alone is responsible for 28.7% of cancer death in the USA. The magnitude of the problem is similar in Europe. Because of an increasing prevalence of cigarette smoking in most parts of the world, it is anticipated that the annual lung cancer mortality may exceed 10 million by 2030. It is estimated that one-third of all deaths in people between the ages of 35 and 69 years are attributable to cigarette smoking in the USA. The relative risk for lung cancer in current smokers is between 10- and 80-fold greater than for those who have never smoked, increasing with the amount smoked and with earlier age of smoking initiation. Almost half of lung cancers currently diagnosed in the USA occur in people with a prior history of cigarette use who successfully quit years before. In addition, lung cancer in those who have never smoked in their life, defined as having smoked less than 100 cigarettes, is on the rise, and estimated to contribute to approximately 16,000 cases per year.

The World Health Organization’s international histopathologic classification of lung cancer was last revised in 1999 [1]. The term “lung cancer” comprises all malignant neoplasms of the lung. The current terminology has evolved over the last century and is based on distinct light-microscopy criteria. Squamous and glandular differentiation were the first recognized patterns, followed by the description of “oat-celled sarcoma of the mediastinum” as a lung cancer by Barnard in 1926, and the “bronchogenic large-cell carcinoma” as a lung cancer without squamous or glandular features by Patton in 1951. These four major histologic lung cancer types account for approximately 31% (squamous cell carcinoma), 21% (small cell carcinoma), 35% (adenocarcinoma), and 11% (large cell carcinoma) of cases respectively (SEER data 1983–1992; http://seer.cancer.gov). The remaining cases are other histopathologic lung cancer entities that include adenosqua- mous carcinomas, adenoid cystic carcinomas, mucopidermoid carcinomas, carcinoïd tumors, malignant mesotheliomas, and others. From a cell biological perspective, carcinoids and mesotheliomas are clearly distinct from adenocarcinomas, squamous carcinomas, and large-cell carcinomas. Adenocarcinomas, squamous carcinomas, and large-cell carcinomas, hereafter referred to as non-small-cell lung cancers (NSCLC), are closely interrelated, share common risk factors and epidemiology, are frequently found simultaneously in tumor specimens, and are uniformly approached with common therapeutic interventions.

The 5-year survival from lung cancer has kept pace with the improvement in 5-year survival from all cancers over the last 40 years. Yet, it remains disappointingly low at approximately 15%. This improvement in 5-year survival is a result of heightened awareness, better technology for detection, better selection of patients for various therapeutic options, and the selective use of palliative interventions. However, lung cancer mortality remains extraordinarily high, and it is the benchmark by which future generations will judge our success in effectively combatting this disease.

Survival of patients with lung cancer is predominantly a function of disease stage, and it declines with increasing
stage [2]. For patients with stages I and II NSCLC, long-term survival (≥5 years) can be achieved by surgery with or without systemic therapy. For patients with stage III disease, long-term survival is less likely (15–25% 5-year survival), and the mainstay for treatment is radiation in combination with systemic therapy if possible. Patients with stage IV disease rarely live beyond 5 years, and treatment predominantly consists of systemic therapy given with the goal of palliation.

For lung cancer patients, achieving 5-year survival most often (approximately 95% of cases) means that the disease will not recur and thus not cause mortality. It is exactly this observation that forms the basis for the lung cancer screening hypothesis, that implementation of a methodology that allows for detection of the disease at a point in time when it is surgically resectable rather than when it is unresectable will result in cure and consequently a decrease in mortality.

This hypothesis sets the stage for the primary outcome parameters by which studies that test lung cancer screening modalities must be judged. These are a stage shift: a reduction in the number of people with unresectable disease in the screened group compared to an unscreened group and mortality (i.e., a reduction in the number of people who die in the screened group compared to an unscreened group). In successful screening, demonstration of a stage shift precedes demonstration of a mortality reduction.

Other parameters are often considered as measures of screening efficacy. The two most frequently used are an increase in 5-year survival and an increase in the number of resectable cases. Both of these outcome parameters are necessary, but insufficient antecedents of a mortality reduction. They are insufficient indicators of a screening benefit because an increase in the number of resectable cases and improved 5-year survival may also result for lead-time and length-time bias. These biases, inherent to screening of asymptomatic subjects, prevent consideration of either the number of resectable cases or an improved survival as surrogate indicators of mortality, and cannot ultimately serve to assess the success of a screening program. Both biases are well explained in recent reviews [3–5].

Among the methodologies available for lung cancer screening, radiography has been most extensively studied. Other methods include cytomorphology, and more recently, molecular assays.

### 2.2 Standard Chest Radiography

Three large randomized trials were coordinated by the United States National Cancer Institute (the NCI Collaborative Lung Cancer Trials) during the 1960s and 1970s [6–8]. These trials differed from earlier screening trials conducted in Europe [9] by testing whether sputum cytology plus chest radiography (CXR) would lead to a greater reduction in lung cancer mortality than CXR alone. A similar trial was conducted in Czechoslovakia in the 1970s [10]. People without symptoms for lung cancer had CXR two to three times per year for up to 6 years. The results are summarized in Table 2.1. In all trials, more cancers were surgically resectable, and 5-year survival rates were better in the screened groups compared to the control groups. However, mortality rates from lung cancer, overall mortality, and the number of unresectable cases were not significantly reduced on final evaluation. As a result, professional organizations currently do not recommend using CXR for lung cancer screening. Interestingly, in all these trials, the more intensely screened arms had more lung cancer cases. Had these excess cases appeared early during screening followed by equalization of case numbers later on, the excess might be explained by lead- or length-time bias. Because the excess cases persisted after several years of screening, they are more likely the result of overdiagnosis. Overdiagnosis is an extreme form of length-time bias, where asymptomatic persons are diagnosed with the disease as a result of screening; however, the disease would have not impacted on their lives. In addition, contamination of the control groups may have contributed to these disappointing results, since many persons in the control groups actually had CXR more frequently (approximately every 24 months in the Mayo study) than would be expected in a healthy population.

### 2.3 Computed Tomography of the Chest

Computed tomography (CT) of the chest has several distinct advantages over standard CXR as a tool for lung cancer screening. First, CT sensitivity is superior to CXR in the detection of pulmonary lesions that may represent lung cancer [11], a finding that was confirmed in two screening trials that compared low-dose CT with CXR in the same people (27 lung cancers detected by CT vs 7 by CXR in one study; 13 by CT vs 5 by CXR in the other study) [12, 13]. Second, images on CT are acquired digitally, which facilitates automated image analysis. CT technology has advanced to a level whereby high-resolution imaging studies of the chest can be performed in seconds, thus reducing the inconvenience to the subjects. However, CT screening also has disadvantages. These include high cost, high radiation exposure, and the high rate of detection of lung abnormalities that may not be neoplastic.

The actual economic cost for lung cancer screening is unknown, but it has been suggested that it is between US$ 116,000 and US$ 2,300,000 per quality-adjusted life-year gained if screening by CT is done on a population of current and former smokers over the age of 60 years.