

Reviewing the Epidemic of Lung Cancer

a report by

Robert James Cerfolio, MD, FACS, FCCP

*Professor of Surgery, Chief of Thoracic Surgery, Division of Cardiothoracic Surgery,
University of Alabama at Birmingham*

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Although smoking rates have declined in the US, lung cancer, also called bronchogenic malignancy continues to represent a pandemic. It is the number one cause of cancer related deaths worldwide, as well as in the US. In 2003 there were 171,900 patients diagnosed with lung cancer and 157,200 people died from it in the US alone in that year. The number of deaths from lung cancer in the US is equivalent to a jumbo jet airplane filled to capacity crashing, every day, day after day with no survivors. Over 80% of bronchogenic malignancy is from non-small cell lung cancer (NSCLC) and thus is the main focus of this report.

Despite significant advances, the overall five-year survival of lung cancer remains a dismal 15% and this pales in comparison to most other solid organ tumors. It is estimated that about 172,000 Americans will die from bronchogenic malignancy in 2006 and it is not discriminatory on gender. Lung cancer takes the lives of more female Americans than the next three most common female cancers (breast, colorectal and ovarian) combined. In addition, it kills more American men than the next three most common solid organ cancers (prostate, colorectal and pancreatic) in men combined. It alone is responsible for an estimated 27% of all cancer deaths. Although the incidence of lung cancer in men has declined since 1995, it has sharply risen in women until leveling off most recently in 2004. If these current trends continue, the incidence of lung cancer is projected to be identical for women and men over the next decade.

The toll from lung cancer is highlighted when one considers just a few of the American icons whose lives were cut short from this disease. Lung cancer has claimed the lives of many famous people, including Walt Disney, John Wayne, Yul Brunner, Nat "King" Cole, Ed Sullivan, etc. All of these celebrities were smokers and it is important to note that 88% of patients who develop lung cancer are smokers. The key to survival is prevention and early detection. Lung cancer may be the most avoidable cancer since the vast majority of victims who contracted it have it from the self-inflicted habit of smoking cigarettes. Over 90% of men and 80% of women who develop lung cancer are smokers. Thus our greatest opportunity to improve

these sobering statistics is to help stop people from starting the habit of smoking cigarettes and getting those who do smoke to stop. In fact, the risk of developing lung cancer falls as the duration from one's last cigarette increases. Once one has quit for more than 15–20 years the incidence of developing this terrible cancer may almost approach that of a non-smoker. Thus smoking cessation not only improves one's overall health and pulmonary function it also reduces the risk of developing lung cancer as well as the all the other cigarette-related cancers and diseases.

The treatment of lung cancer is dependent on the stage using the TNM staging classification. The main reason the overall survival for lung cancer remains low is because the vast majority of patients present with advance, stage IIIb or IV disease. Although the overall survival remains dismal there is some reason for optimism. There has been improvement in the diagnosis and therapy especially in certain subsets of patients with non-small cell lung cancer (NSCLC). For instance, the five-year survival of those with completely resected pathologically staged Ia NSCLC, which traditionally has been reported to be only about 50–60%, has now been shown in large prospective series (that feature careful pathologic instead of just clinical staging) to be as high as 75–90%. Selected patients with stage IIIa disease now have 40% instead of 20% survival rates. New chemotherapeutic agents and strategies exist for patients in all stages and advancements are slowly being made.

Some of the most important improvements for patients with NSCLC include: screening and early detection in high-risk patients, the use of integrated fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) scans to improve clinical stage, the development of tumor markers and tumor characteristics that identify aggressive tumors, new surgical techniques that decrease pain, speed recovery and lessen operative morbidity and mortality, the use of adjuvant chemotherapy after resection, the use of neoadjuvant chemo-radiotherapy prior to resection in carefully selected patients and new types of radiotherapy. Surgery is also being applied to older patients with more



Robert James Cerfolio, MD, FACS, FCCP, is Professor of Surgery and Chief of the Section of Thoracic Surgery at the University of Alabama at Birmingham. He has given over 100 lectures at major international scientific meetings and has been selected as a Visiting Professor in a multitude of prestigious hospitals all over the world including China, Hong Kong, England, Germany, Sweden, Amsterdam and Brazil. He has written over 60 original peer-reviewed articles as well as 23 book chapters and is first author on over 95%.

co-morbidities and thus those patients who used to be denied the opportunity to have a resection are now undergoing curative surgery. Finally, careful post-operative surveillance may also help detect recurrence early and this may have favorable effects as well.

The improvement of survival of patients with lung cancer, like most malignancies is centered on early detection. Recently patients who are at high-risk of developing NSCLC, such as those who have a 20-pack-year history of cigarette smoking, are undergoing routine surveillance screening CT, even though they are asymptomatic. Although the cost effectiveness of this strategy and its true impact on survival are pending the completion of a large multi-institutional on-going study, the early results are promising.

Integrated positron emission tomography using fluorodeoxyglucose that is blended with concomitant computed tomography (FDG-PET/CT) is the best non-invasive imaging test for staging patients with non-small cell lung cancer. It provides targets to biopsy such as lymph nodes or potential metastatic sites. It has improved clinically staging when compared to CT scan alone but biopsies of suspicious sites are still mandatory. A positive PET in a certain location is only an indication that a biopsy of that lesion is needed. Integrated FDG-PET/CT has been shown in multiple randomized prospective trials and in other peer reviewed multi-intuitionally studies to help predict the pathology of an indeterminate pulmonary nodule, to stage the mediastinal for the presence of metastatic disease in regional mediastinal (N2) and hilar (N1) lymph nodes, to determine the presence of metastatic M1 distant disease between the eyes and the thighs, specifically in the adrenals, liver, bones, and lungs. It is better and more accurate than CT scan or any other non-invasive tests. Integrated FDG-PET/CT has become the standard of care in patients with an indeterminate, suspicious or biopsy-proven-cancerous pulmonary nodule in order to help clinically stage patients. In addition, integrated FDG-PET/CT provides the maximum standardized uptake value (maxSUV) of the primary tumor, of lymph nodes and of potential metastatic sites. The maxSUV, which is calculated by the software contained in the PET scanner, quantifies the biological aggressiveness of a cancer and it has been shown to be a better predictor of survival than the current TNM staging system. The change in the maxSUV is also the best technique to objectively gauge the response of chemotherapy and radiotherapy. Finally, integrated FDG-PET/CT scan may be the best test to help detect recurrence after chemo-radiotherapy or surgery.

Once the stage of the NSCLC has been clinically suggested by integrated FDG-PET/CT PET, it should be definitive determined by the liberal use of

mediastinoscopy, endoscopic ultrasound with fine needle aspirate and video-assisted techniques to rule out N2 or N3 nodal disease. MRI of the brain, bone scans or other appropriate tests should be implemented as needed to rule out PET suspicious metastatic disease as well. Once the stage is definitively determined, therapy is stage dependent. A quick review of the current standard of care for each stage of NSCLC is as follows. Stage Ia NSCLC is best treated by resection alone followed by careful follow-up every six months for two years and then yearly thereafter. The best treatment for Stage Ib disease is controversial at present. Resection (which should always include a complete, margin negative, R0 resection with aggressive thoracic lymphadenectomy) followed by adjuvant chemotherapy became the standard of care for patients with resected pathological stage Ib NSCLC in 2005. However, new data are emerging, but not yet published, that suggest that patients with Ib disease do not benefit from adjuvant chemotherapy. Careful review of recently completed multi-institutional studies is needed to help answer this question. Patients with stage IIa and IIb disease should be considered for adjuvant chemotherapy after complete surgical resection and the role of neoadjuvant chemotherapy for biopsy-proven N1 disease remains controversial. Patients with stage IIIa NSCLC from biopsy-proven (not clinically suggested) N2 disease represent a heterogeneous group of patients. Those with bulky N2 disease that remain node positive after neoadjuvant therapy probably do not benefit from resection. However other types of patients with N2 disease do. The role of adjuvant therapy after resection for these patients is also controversial. The treatment for patients with stage IIIB and stage IV cancer remains medical. However, recent advances in novel therapies that are target specific as well as new chemotherapeutics regimens using concurrent high-dose irradiation have increased the median survival and improved the quality of life in these unfortunate patients.

In conclusion, lung cancer and specifically NSCLC, remain an epidemic of staggering proportions in the US. The prevention of smoking and the cessation of smoking in those who continue to light up cigarettes daily remains the best way to reduce some of the morbid statistics presented above. The importance of educational programs that discourage our youth from starting smoking cannot be over-stressed or over funded. New advances aimed at early detection and the development of new treatment strategies that combine surgery, radiation and chemotherapy have improved survival for some patients. However, prevention via the eradication of cigarette smoking remains our best hope for cure. ■

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