COMPARATIVE EFFECTIVENESS IN LUNG CANCER MANAGEMENT: TIME FOR CHANGE

Frederic W. Grannis Jr. M.D.

President Barack Obama recently discussed the concept of comparative effectiveness (CE) in medical care and introduced a stimulus package, allocating $1.1 billion for research in this area. CE is particularly important in the case of lung cancer.

Let's start by noting that there are two broad strategy approaches in modern cancer management. In the case of cancers of the cervix, breast, colon and prostate, there is an emphasis on early detection by screening (EDS) before patients come to their doctors with symptoms of cancer. Where lung cancer is concerned, the current strategy endorsed by the National Cancer Institute (NCI) is considerably different. At present no attempt is made to detect lung cancer in early stage. Instead, doctors are told to wait until patients come into their offices with symptoms of lung cancer before beginning efforts to diagnose, stage and treat (SD). What do we know about the comparative effectiveness of the EDS and SD approaches?

First we need to know what we mean by the term relative effectiveness.

The Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research define CE as follows.

> "Comparative effectiveness research is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions."

In simpler terms, comparative or relative effectiveness attempts to "provide better evidence about the costs, risks and benefits of two different approaches to treatment? What then is known about the relative benefits, risks and costs of lung cancer management.

Let's start first with SD. Currently in the U.S., 80% of patients with lung cancer are diagnosed in late stage (Stages III and IV) and only 7% are diagnosed in the earliest stage (Stage IA). Very few patients with advanced stage lung cancer and only 15% of all

lung cancer patients are alive five years after diagnosis despite aggressive treatment with combinations of surgery, radiation therapy and chemotherapy. Although the NCI has spent more than 30 years emphasizing research to develop treatments based upon new knowledge of the molecular biology of lung cancer, during these three decades, five-year LC survival has improved only from 12% to 15%. Recent publications from the NCI indicate that the costs of these new treatments are enormously expensive and confer relatively little benefit to patients. In other Western nations, survival is much lower. For example, in England 5-year survival is only 8%.

What about risks? The risks of treatment of advanced stage LC are considerable. In up to 30% of cases LC can only be surgically resected by pneumonectomy, i.e. removal of an entire lung, with a risk of death of 5-12%. The problems and risks associated with chemotherapy for the disease are well known to most Americans. We also know that the costs of treatment of LC are enormous, and furthermore, recent evidence from the NCI indicates that these costs are skyrocketing with the introduction of multiple new high-price drugs that provide little increase in cure or duration of survival.

What then do we know about early detection of lung cancer (EDS)?

There are currently a number of large ongoing lung cancer screening programs generating research results in the U.S., Europe and Japan. In Japan, furthermore, population lung cancer screening has been widespread for at least two decades. Early chest x-ray screening has been superseded by testing of more sensitive CT scans. It has now been established by a number or research groups that CT screening protocols can diagnose the majority of cases of lung cancer in early stage, in several large studies in as high as 80-90%. Furthermore, within early stage, LC are being diagnosed at very small sizes, as small as 1 cm. or less. It has also been demonstrated that early detection leads to striking increases in long-term survival i.e. cure. More than 80% of patients treated after screen detection of LC are alive longer than ten years in the ALCA study in Japan and the IELCAP study in the U.S.. Treatment of stage I LC is also less risky because removal of an entire lung is necessary in less than 1% of cases and radiation therapy and chemotherapy are not required after surgery in most cases. Although critics of screening warn that large numbers of screened individuals will undergo unnecessary invasive biopsies, operations for screen-detected benign lung nodules that will result in complications and deaths, results from recent prospective randomized screening studies in the U.S (PLCO Study) Denmark (DLCST) and Italy (ITALUNG) show that such biopsies or operations occur at a frequency of only 0.1% and that no screened patients died as a result of unnecessary interventions.

The experience in Japan is particularly striking. Although the percentage of lung cancers treatable by surgery had dropped precipitously in the U.S. during the last ten years, at the Japanese National Cancer Center in Tokyo 57% of lung cancers treated by surgery have been detected by screening and survival in this group of patients is 93% at five years.

A comparison of risks and benefits in long-term survival therefore strongly suggests to me that early detection carries a favorable comparative effectiveness for the management of lung cancer in terms of survival. What do we know about relative cost effectiveness?

The published literature on cost effectiveness of LCS yields widely varying results depending on the type of assumptions that are incorporated into the mathematical models tested. My former research student, Anthony Castleberry, now in his first year of surgical training, presented the results of his mathematical model comparing the cost of achieving a five-year lung cancer survivor with and without CT screening at the American College of Chest Physicians convention in Chicago in 2007. His model provides a broad range of results depending upon whether one inputs optimistic or pessimistic assumptions. His conclusion was that in screening of high risk individuals over age 60, the number of survivors is higher with screening in all scenarios tested, and the cost of a five-year survivor was lower with CT screening in all scenarios examined. Dr. Castleberry received the Albert Soffer Award from the ACCP for his presentation. A manuscript based upon this work is currently under editorial review.

Based upon the evidence discussed above, I believe that the weight of the evidence strongly suggests that implementation of lung cancer screening at centers of excellence using modern CT technology and managing detected lung nodules using the protocol developed by the International Early Lung Cancer Action Program has far CE than the outmoded, SD strategy now employed in the United States. Although introduction of population CT screening for LC will have high early costs, within a few years, our model suggest that relative costs will begin to decrease and the number of lung cancer survivors will increase rapidly.

How might we pay for this expensive but life-saving medical strategy? Here again, I believe that the answer is simple. When Exxon Corporation was responsible for a massive oil spill on Alaskan beaches, our society imposed upon them the obligation to pay for the clean up of the toxic disaster they had created. In similar fashion, the American tobacco industry is responsible for what amounts to the biggest toxic spill in the history of mankind by exposing one hundred million Americans and billions internationally to high dose tobacco carcinogens and the remainder of the world's population to damaging second hand smoke. Our courts and legislatures must compel the tobacco industry to pay for the cleanup of this

environmental catastrophe, including, payment for the medical monitoring of diseases caused by their products in present and former customers, including screening for lung cancer.

There are important further benefits of screening that can be reliably anticipated. In the case of breast cancer, implementation of mammographic screening has meant that radical mastectomy is now seldom used. Most of the surgical oncology fellows I have helped train have never seen this disfiguring operation! Further progress in breast cancer treatment markedly reduced the need for mastectomy. In similar fashion, ongoing research in lung cancer treatment of very small lung cancers detected by screening tests whether surgical removal of smaller amounts of lung using minimally invasive techniques can achieve equivalent results at lower morbidity and cost. Although cures of large lung cancers by radiation therapy are uncommon, preliminary results from Japan suggest that the majority of very small screen detected lung cancer might be curable, without surgery, using modern radiation therapy methods. This advantage would be particularly important for older patients and those at higher risk for surgery because of emphysema and coronary artery disease caused by tobacco products.

One final consideration. Progress in implementation of cancer screening has been driven in large part by patient advocacy. Whenever bean-counters have recommended reduced mammography use and insurance coverage, breast cancer advocacy groups have forcibly demanded public policy change to insure availability of mammographic screening for women. At present, there is much less comparable patient advocacy to empower policy change in lung cancer. In large part this is because the tobacco public relations spokespersons have been successful in falsely portraying smoking as "an adult choice" rather than an addiction caused by deliberate manipulation of nicotine delivery in cigarettes. It is callous and reprehensible for tobacco executives to "blame the victims" so that many lung cancer patients have been driven to feel a sense of personal responsibility for their disease. Advocacy groups like the Caring Ambassadors Lung Cancer Program and the Lung Cancer Alliance have a current opportunity and an obligation to work to change false perceptions of the causation and optimally management of lung cancer. They deserve our generous personal and financial support.