

Demented Politicians



A newspaper recently reported that a U.S. senator described his friend, another U.S. Senator, Strom Thurmond, almost 100 years old, as “not keen.” I am not completely confident what this means although I’m pretty sure. I’m also pretty sure that Thurmond’s press aide’s response, “That’s nonsense. He swims a full lap in the swimming pool each day,” was a troubling response. I don’t know how old the aide is, or whether he too swims a lap or two in the pool daily, but I wonder if the two of them are “not keen”.

I have wondered about Senator Thurmond for some time. William Safire, the *New York Times* columnist, recently vilified a Democratic-run committee for scheduling lengthy talks, that they knew Thurmond would not be able to stay awake for.

“Not keen.” Excessive daytime somnolence. Age 98. Are these early warnings of my own “ageism?” Although people don’t get smarter with age, many do become wiser. While mathematicians peak early, the capacity to pursue intellectual challenges requiring wisdom, knowledge and sensitivity seems to ripen with age, as is often seen in fine literature, music composition and philosophy. However, with age comes frailty and too frequently, dementia.

Is Strom Thurmond demented? Is it possible that an important political figure, who still votes in the Senate, may not know what he is voting for? Of course one might answer that it doesn’t matter, that most politicians are guided by their advisors and “handlers.” Senators have large staffs presumably full of experts on various issues, depending on the senator’s interests and the interests of his constituents and financial supporters. How much a politician is independent rather than a puppet of his financial-base var-

ies, of course, with the politician (the analogy of the physician “thought leader” who lectures for a corporate sponsor for a fee should be kept in mind here). However, regardless of who wields the power, the fact remains that the buck stops with the voter. Legislation backed by a senator, or initiated by a senator, bears that politician’s imprimatur and therefore his responsibility, regardless of who actually wrote it. To exercise this degree of responsibility, the final arbiter of a single vote, the voter must be “compos mentis.”

After Woodrow Wilson suffered a debilitating stroke, his wife took over much of the function of the president. This was a perversion of our constitution. Mrs. Wilson was never voted into an office. Even Hillary Clinton was given powers designated by the president as if she were a private citizen and did not simply assume them. It seems to me that it is a very straightforward requirement for those who serve our nation to be held to some standards of accountability and capability. While those who serve elected officials are responsible and hopefully loyal to the person they serve, there should be a higher loyalty to the office that the elected official fills. When the official is corrupt and accepts bribes, the staff is obligated to report this. They are equally obligated to report medical infirmity, which precludes adequate discharge of the office’s responsibility. The question of Ronald Reagan’s capability may be considered here as a “gray zone.” He was elderly when in office and was known to fall asleep during cabinet conferences that he chaired. He also developed Alzheimer’s disease that might have been clinically detectable while in office. Perhaps he may have exhibited **mild cognitive impairment (MCI)** only without language or personality changes. Where would

one draw the line in declaring a President unfit for office?

We all applaud Senator Thurmond’s determination and dedication, but even Cal Ripken, Jr., the new “iron man” of baseball had to retire when his skills weakened with age. I think that questions of competence that devolve into medical issues require a medical evaluation. Do we know whether our older leaders have annual medical examinations and if so, do they include neurobehavioral assessments? I, for one, would feel reassured to know that Senator Thurmond is cognitively intact and that he makes his own decisions when he votes and signs his name onto legislation.

As people live longer and work longer we need to grapple with the issues of medical competency for elected officials, just as we have them for airline pilots and some other professions. Doctors too need to consider this, rather than depending on “after the fact” reporting of incompetence, because more of us practice in our old age. Recredentialing requirements help address this issue and the Joint Commission on the Accreditation of Hospitals has recently required bylaw changes in hospitals to help weed out incompetent physicians. We need a similar procedure to deal with public officials.

– Joseph H. Friedman, MD



Some Comments On a Possible Ancestor

A Lutheran minister from Dusseldorf, Joachim Neumann by name, achieved some modest fame in the late 17th Century as an author of sacred hymns. It had been his custom to take solitary walks in a neighboring valley to help assemble the proper words and melodies for his liturgical poetry. He frequently signed his completed hymns with the name Neander, the Greek equivalent of his German name [*Neumann*, in German, meaning new man.] And years after his death, his parishioners honored his memory by naming this modest valley Neanderthal [*thal*, in German, meaning valley.]

The fame of the valley extended no further than its neighboring villages until 1856, when Neanderthal quarry workers encountered some human bones in a hillside cave. A local school teacher, Johan Fuhlrott, recognized them as essentially human although they exhibited some unusual anatomic features suggesting that they were derived from a different species. In the next few years bones with similar aberrant characteristics were uncovered in central and southern Europe as well as the Middle East; so many, in fact, that by 1864 they were designated as a separate hominid species [*Homo neanderthalensis*].

The Neanderthal man [now spelled Neandertal], as the representative of this newly defined species was commonly called, excited the attention of a wide audience who viewed him either as paleontological confirmation of Darwin's newly declared theory of evolution [*The Origin of the Species* was published in 1859]; or, alternatively, as a palpable threat to the accepted concept of creation which held that man was divinely created on the sixth day, as related in Genesis; and that man was biologically and theologically distinguishable from, and held dominion over, the mass of dumb creatures which had earlier been brought into being. Furthermore, declared the creationists, there was nothing in the Holy Scriptures to suggest that man, created in the perfect image of God, could have evolved from any other species, hominid or otherwise. To accept biological evolution, they declared, was therefore equivalent to accepting imperfections in God.

If indeed there had existed another human-like species in the past, it was commonly held, its members must have been little more than lumbering, cultureless beasts with anatomical features vaguely human, but who were at best brutish cave dwellers incapable of any of the social, creative or communicative attributes of humans; and therefore they were not truly "human"; nor could they be ancestors of humans.

Paleontologists gradually formed an image of this creature. He was, they speculated, quite robust, with a barrel-chest and short limbs. His head was large, its top somewhat flattened in contrast to modern man's dome-shaped skull. His nose was large, cheekbones inapparent, brows over each eye very prominent, forehead narrow and sloping, and chin small without indentation. There were very wide muscle-attachment grooves on the limb bones suggesting that Neandertal man was quite muscular. [These dramatic muscle attachment grooves had prompted Fuhlrott to surmise that the Neandertal bones were not from contemporary man.]

The composite profile of the Neandertal man was compatible with what would be expected of hominids struggling to survive in the harsh environment of the European ice age. Paleontologists concluded that this race of hominids flourished as a separate species beginning about 200,000 years ago; and then

disappeared, for unknown reasons, some 30,000 years ago, their last stand being in Spain.

Paleontologists agree on this: Modern man [Cro-Magnon man or *Homo sapiens*] and *Homo neanderthalensis* co-existed in Europe for many thousands of years. Earlier scenarios, many textbooks and certainly the film industry portrayed the primitive Neanderthals as incapable of competing with the innovative, tool-making, language-speaking, agronomically-skilled *Homo sapiens* migrating north out of Africa. And, finally, some 30,000 years ago, the last of the beleaguered Neanderthals died in some forgotten Iberian cave, leaving the European continent to the new human arrivals.

But science is never satisfied with well-rounded stories. It wasn't long before newer and more meticulous studies of Neanderthal dwellings turned up evidence that suggested a somewhat different scenario. Diggings in Spain, for example, suggested that the art of transportable fire, thought to be an exclusive skill of *Homo sapiens*, was also practiced by the Neanderthals. Furthermore, these protohumans were capable of foraging for edible plants, of creating stone tools including spearheads and of decorating pendant jewelry made of wood or bone.

And there was accumulating evidence that the two groups of hominids had co-habited for thousands of years. Then, in 1996, exploration of sites in Moravia uncovered the fossil remains of a child, dating back some 50,000 years, with the combined anatomic characteristics indisputably those of *Homo sapiens* and *Homo neanderthalensis*. Some paleontologists eagerly grasped this finding to signify that the two hominid groups, at least in certain sites, had shared certain cultural customs; and not only did they live together but they also interbred. Thus, if these inferences hinting at interbreeding are accurate, it would appear that the fate of the Neanderthals was not irreversible extinction but rather assimilation into the more adaptable, more sophisticated and numerically superior modern man.

But then other scientists recently managed to extract some residual DNA from the bones of Neandertal fossil bones. And careful analyses of the chemical sequences within these DNA samples demonstrated no similarities with the DNA of *Homo sapiens*. Remarkd one anthropologist: "Limited interbreeding may have occurred between Neanderthals and modern humans, but that appears less likely with these new genetic data." The DNA evidence, admittedly based on only a small handful of samples, thus favored the theory that *Homo sapiens* took origin in East Africa some 100 millennia ago and then populated the world, completely replacing all other hominid species, including the Neanderthals.

Those scientists who advocate a multiregional origin of modern man still believe, however, that some Neandertal hereditary material has persisted as part of the genetic constitution of contemporary man.

It is curious that an obscure region of western Germany called Neandertal [a hybrid Greco-German word meaning new man's valley], named to honor the daily strolls of an obscure composer of hymns named Neumann, should also be the site of important fossil evidence casting some doubt upon the genetic and theological uniqueness of the new man called *Homo sapiens*.

– Stanley M. Aronson, MD, MPH

Cancer in the New Millennium

Paul Calabresi, MD, MACP

In December, 1971, our nation declared war on cancer. Thirty years later, at the beginning of a new millennium, is an appropriate time to re-evaluate our progress, assess our current status, and chart a rational course for the future. In the 1960s, approximately 30% of patients with cancer survived. Today more than 60% are cured. Of the remaining 40% of cancer cases, approximately half, or an

additional 20%, could be prevented or saved, if all the knowledge we have today were applied to all of the people. For the other 20%, we need more research.

The cancer burden, however, is increasing in America. This is due, in part, to more effective prevention and treatment of heart disease, infections, and strokes, as well as to an increase in aging of our population. Sixty percent

of new cancer patients are older than 65 years and the median age for cancer in the United States is now 70 years. It is estimated that, at current rates, the rise in cancer will be such that one in two Americans will experience the disease in their lifetime and it will surpass heart disease as the leading cause of death in just a few years.

The National Cancer Legislation Advisory Committee was created in order to address this mounting threat and to chart a strategy that would ultimately eradicate cancer as a major public health problem. A group of 21 concerned cancer scientists and survivors, patient advocates and health providers, non-profit leaders and business executives (Table I) met for 2 years to develop a comprehensive report entitled: "Conquering Cancer: A National Battle Plan to Eradicate Cancer in Our Lifetime" (Table II).¹ Building on the success of the National Cancer Act of 1971² and previous reports,^{3,4,5,6,7} the recommendations included in this document provide the President and the Congress of the United States with a roadmap for achieving this vital goal. [See Note.]

In Rhode Island, what can we do, at the local and regional level, to reduce mortality and suffering from cancer? Outlined below are 4 broad approaches that would enhance our participation in this renewed national effort to conquer cancer:

* Familiarize ourselves with the goals and recommendations provided in this report and participate in implementing those that apply to our individual activities, institutions and organizations. A summary of these actions is listed in Table II; some apply primarily at the Federal level, while others can be implemented in the State.

TABLE I

Members of the National Cancer Legislation Advisory Committee

Vincent T. DeVita, Jr., MD
NCLAC Co-Chair
Director, Yale Comprehensive Cancer Center

John R. Seffrin, PhD
NCLAC Co-Chair
Chief Executive Officer,
American Cancer Society

Anna D. Barker, PhD
President/CEO, BIO-NOVA, Inc.

Helene G. Brown
Associate Director, Community Research,
Jonsson Comprehensive Cancer Center, UCLA

Joan S. Brugge, PhD
Professor of Cell Biology,
Harvard Medical School

Paul Calabresi, MD
Professor of Medicine, Brown University

Robert W. Day, MD
President and Director Emeritus,
Fred Hutchinson Cancer Research Center

Carl F. Dixon, Esq.
President and Chief Executive Officer,
Kidney Cancer Association

Albert B. Einstein, Jr., MD
Executive Director, Swedish Cancer Institute

John H. Glick, MD
Director, University of Pennsylvania Cancer Center and the Abramson Family Cancer Research Institute

M. Alfred Haynes, MD
Chair, Institute of Medicine Study on
Unequal Burden of Cancer

Ronald B. Herberman, MD
Director, University of Pittsburgh
Cancer Institute and President,
American Association of Cancer
Institutes

Paula Kim
Chairman of the Board & Co-Founder,
Pancreatic Cancer Action Network (PANCAN)

Amy S. Langer
Executive Director, National Alliance of Breast
Cancer Organizations (NABCO)

Deborah Mayer, RN, MSN
Chief Medical Officer, Cancer Source.Com

Susan Kenyon Parsons, MD
Assistant Professor in Pediatrics,
Dana-Farber Cancer Institute

Janet Rowley, MD
Blum-Riese Professor, Department of
Medicine, University of Chicago

Ellen V. Sigal, PhD
Chair, Friends of Cancer Research

George Vande Woude, PhD
Director, Van Andel Institute

Armin D. Weinberg, PhD
Co-Founder, Intercultural Cancer Council and
Director, Chronic Disease Prevention &
Control Research Center, Baylor College of
Medicine

Fran C. Wheeler, PhD
Director, Office of Public Health Practice,
University of South Carolina School of
Public Health

- * Unite the many resources in our community to re-establish a Cancer Center with translational research capabilities that would move new drugs and technologies forward into clinical trials, and ultimately develop new methods and products to prevent and cure cancer (Table II, Goal 4).
- * Provide an organization for coordinating and implementing State-

based cancer action plans, in collaboration with all relevant experts in the region (Table II, Goals 9, 10, 11, 12). The Rhode Island Cancer Council, established in May 1999 and described in more detail in this issue of the Journal,⁸ already provides the basic mechanisms and initial resources for implementing these programs. In this respect, we are ahead of most other states in

the country.

- * Improve access to and delivery of quality cancer care to all of our patients. Although these goals are addressed in public health terms in the Conquering Cancer report (Table II, Chapters 3 and 4), specific recommendations (Table II; Goals 8, 11 and 12) can only be implemented if every physician and health care professional assumes a personal obligation to become more informed, knowledgeable, and qualified to provide quality cancer care.

Accordingly, it is important for all physicians to be fully aware of the new advances in this field and state of the art approaches to prevention, early detection, diagnosis, and treatment. For this special issue of the Journal, review articles dealing with 3 of the most common neoplasms were selected: carcinoma of the lung, carcinoma of the breast and colorectal tumors. Dr. Todd Moore and Dr. Neal Ready have presented a thorough update of the status of non-small cell carcinomas of the lung, which comprise 80 to 85% of lung cancers in the United States and are responsible for the largest number of cancer deaths in both men and women. Dr. Mary Anne Fenton has provided a detailed review of our recent advances in the treatment of carcinoma of the breast, stressing the benefits of a multidisciplinary approach to therapy and including a discussion of long-term management for the many survivors of this most common neoplasm of women in America. Reflecting the fact that chemotherapy and radiation therapy have contributed little to the treatment of colorectal cancers, Dr. Arvin Glicksman has incisively outlined a strategy that could prevent most of the deaths from the second most frequent cause of cancer lethality in Rhode Island, for both men and women.

In addition, papers in 2 important and contrasting oncologic specialty areas have been included: Pediatric Oncology and Neuro-Oncology. Dr. William Ferguson and Dr. Edwin Forman have offered us a rewarding

TABLE II
Conquering Cancer:
A National Plan to Eradicate Cancer in Our Lifetime

Chapter One: Discovery Research and Training

- Goal 1 Fund the National Cancer Institute (NCI) Bypass Budget in this and future years and provide additional supplemental funding for critical research that is not adequately covered in the Bypass Budget.
- Goal 2 Increase the pool of talented and well-trained biomedical researchers.
- Goal 3 Increase National Institute for Environmental Health Science and NCI funding for cancer research that examines the interaction of genes and the environment.

Chapter Two: Translating Scientific Discoveries into New Cancer Medicines and Technologies

- Goal 4 Enhance our cancer research centers (and other cancer-focused efforts) to build a multidisciplinary network of translational centers to move new drugs and technologies forward into clinical trials, and ultimately develop new methods and products to prevent and cure cancer.
- Goal 5 Streamline and accelerate the Food and Drug Administration's approval system for cancer drugs, biologics, devices and technologies.
- Goal 6 Empower federal agencies to build public-private partnerships across the entire continuum of cancer research to ultimately develop new cancer treatments, preventives and technologies.

Chapter Three: Improving access to Quality Cancer Care

- Goal 7 Provide adequate health insurance coverage for all Americans concerned about or diagnosed with cancer.
- Goal 8 Significantly increase the pool of health care professionals trained to conquer cancer.
- Goal 9 Launch a National Cancer Screening Initiative to increase substantially the early detection of cancer.

Chapter Four: Delivering Quality Cancer Prevention and Care through a Coordinated Health Care System

- Goal 10 Implement comprehensive state-based cancer action plans, in collaboration with all relevant experts in the region.
- Goal 11 Develop, communicate and use universal guidelines and practice standards to provide quality cancer care to all cancer patients, and monitor progress through improved quality care surveillance systems.
- Goal 12 Implement a National Cancer Prevention Initiative that focuses on eliminating tobacco use, increasing physical activity, and improving nutrition.

description of an important field, tumors of childhood, which illustrates and characterizes the best progress we have made against cancer during the past 30 years. Dr. Lloyd Alderson, on the other hand, has had the unenviable task of analyzing objectively one of the most difficult and challenging areas of oncology: tumors of the central nervous system.

I am deeply grateful to these outstanding Rhode Island oncologists for their comprehensive and informative contributions to this special issue of the Journal, dedicated to a most important and timely topic.

Note: It should be noted that, notwithstanding the current international problems with terrorism, the White House has already expressed great interest in this report and Senators Dianne Feinstein (D-CA) and Sam Brownback (R-KS) have held hearings on the subject with a plan to introduce appropriate legislation in 2002.

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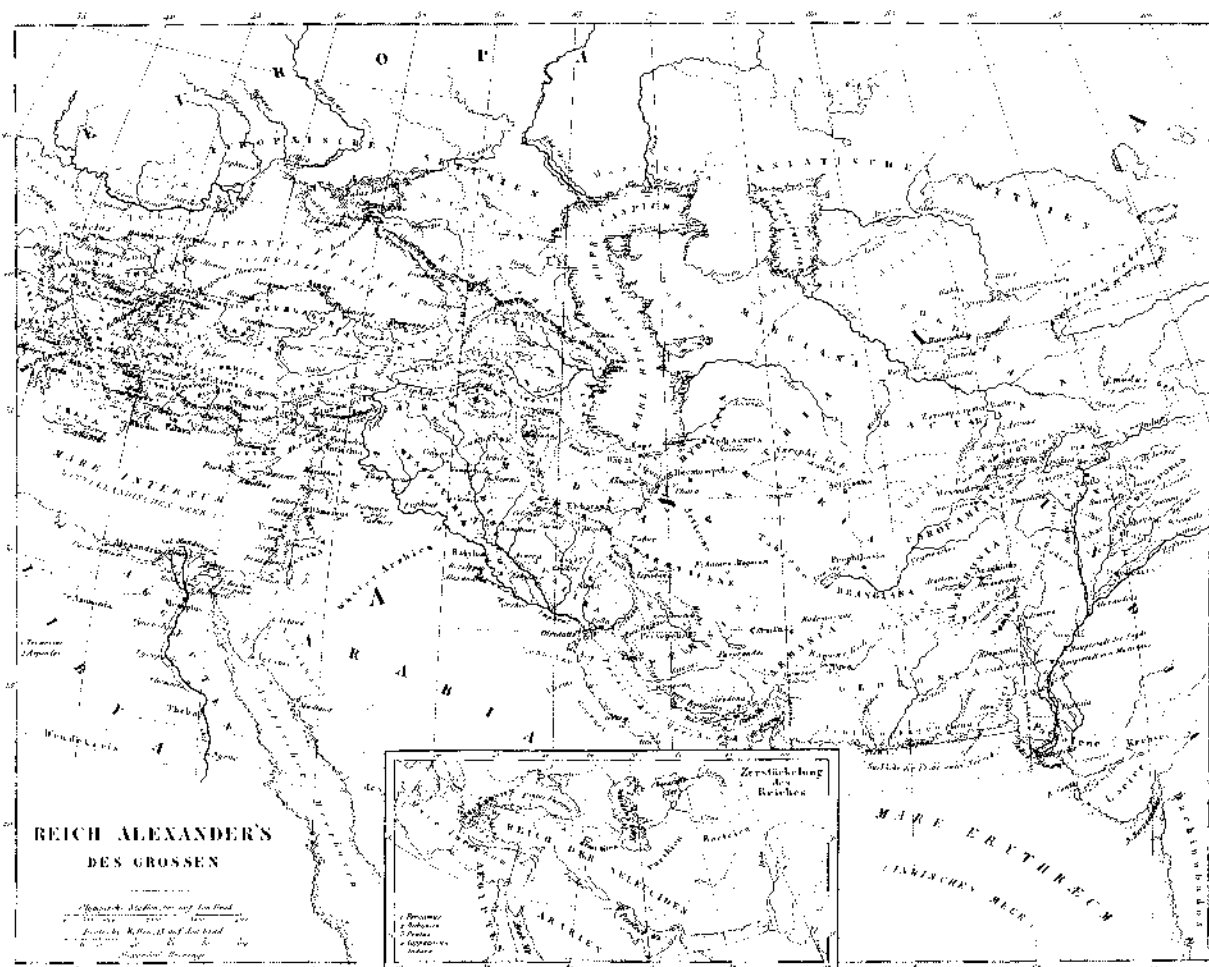
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Update in Non-Small Cell Lung Cancer

Todd Moore, MD, and Neal Ready, MD, PhD

Lung cancer is a common and virulent disease with an estimated 164,000 new cases and 156,900 deaths annually in the US.¹ The magnitude of the burden of lung cancer is exemplified by the fact that the number of deaths annually from lung cancer approximates the total number of deaths from the second through fifth leading causes of cancer mortality combined (colorectal, breast, prostate and pancreatic cancers). Non-small cell carcinomas (adenocarcinoma, squamous cell and large cell carcinomas) account for 80-85% of lung cancers and have been traditionally considered collectively for purposes of treatment. As our experience with molecular-targeted therapy grows, future therapy may be directed at specific molecular abnormalities associated with the different subtypes of non-small cell lung carcinoma. This review will cover screening, staging and treatment of non-small cell lung carcinoma.

Smoking is the cause of most lung cancers and has been estimated to account for 80% of lung cancer deaths.² The accepted link with smoking coupled with educational activity and recent legislative efforts (smoke-free areas and restrictions on tobacco advertisements) have been temporally associated with an overall decrease in the incidence of lung cancer since the late 1980s.¹ The potential for secondary prevention strategies is obvious given that smoking is a largely preventable behavior. Counseling and pharmacotherapy have been shown to be effective treatments for tobacco dependence and a recently published clinical practice guideline summarizes these interventions.³

Several salient factors in non-small cell lung cancer suggest a potentially important role for screening programs. Clinical symptoms occur late in the natural history of lung cancer and, at present, over half of patients present with metastatic (40%) or unresectable locally advanced disease (15%). Patients with pathologic stage I disease, currently

only 15% of patients, have 5-year survival which approaches 70% with surgical resection. Detection of early stage cancers in the asymptomatic at-risk population would thus be expected to improve survival. However, randomized controlled trials conducted in the 1980s showed no improvement in lung cancer mortality with chest x-ray and sputum cytology screening in male smokers⁴⁻⁶ and no national advisory group currently recommends screening for lung cancer. Recent results with the use of low-dose **computed tomography (CT)** screening have called this pessimistic view into question and spurred renewed interest in screening efforts. The initial report of the **Early Lung Cancer Action Project (ELCAP)**, which is investigating annual low-dose CT screening, found 27 cancers (23 of which were stage I) in 1000 volunteers. Chest radiography detected only 7 of the 27 cancers found by low-dose CT.⁷ The NCI has recently launched a 3000 person randomized trial of screening low-dose CT and chest radiography which will address the feasibility of doing a larger study.

Five-year survival is approximately 60-70% for stage I and 40-50% for stage II cancers following complete surgical resection.



Following a diagnosis of non-small cell lung cancer, staging is undertaken to assess the extent of disease prior to definitive therapy. CT scanning of the chest and upper abdomen is routinely performed to exclude metastases to the lung, liver or adrenal glands and to assess invasion of the chest wall, vertebrae or mediastinal structures. CT scanning can also identify enlarged (> 1 cm) me-

diastinal lymph nodes, but the sensitivity and specificity of CT for detecting metastatic carcinoma is low (50-60%). Mediastinoscopy is therefore a critical investigation in patients with enlarged mediastinal lymph nodes by CT to avoid denying patients a potentially curative resection. While the precise definition of "inoperable" disease is debated, mediastinoscopy is also useful for identifying patients with contralateral or extensive ipsilateral lymph node spread who do not benefit from surgical resection.

Recent studies using PET (**positron emission tomography**) scanning suggest that PET is more accurate than CT in the detection of involved mediastinal nodes. PET scanning utilizes tracers such as F-18 **FDG (fluorodeoxyglucose)** which allow tumor identification by its increased anaerobic metabolism of glucose relative to normal tissues. Sensitivity and specificity of PET scanning for mediastinal node involvement by carcinoma have been approximately 80% and 80-90%, respectively, in reported series. The negative predictive value of PET (86-93%) may be sufficient to forego mediastinoscopy prior to attempted resection, but given the reported positive predictive value of PET for mediastinal disease of between 80-90%, mediastinoscopy remains a crucial procedure to avoid denying patients a potentially curative resection.⁸ Staging by mediastinoscopy for potentially resectable lung cancer remains the standard of care unless large clinical trials validate the use of PET scan staging alone. PET scanning may also have utility in assessing disease status after definitive chemoradiation, a situation where residual fibrosis often makes interpretation of response or detection of recurrence by CT difficult.⁹

The primary prognostic factors for patients with early stage disease are the presence of lymph node spread and the size of the primary tumor. Stage I cancers have no lymph node involvement

and stage II cancers have involvement of intrapulmonary or ipsilateral hilar lymph nodes. Surgical resection is the treatment of choice for these patients. Five-year survival is approximately 60-70% for stage I and 40-50% for stage II cancers following complete surgical resection. Despite the fact that many patients will relapse following surgery, there is no proven role for adjuvant radiotherapy or chemotherapy. Postoperative radiotherapy does not improve survival in this group of patients, and in fact a published meta-analysis has suggested a detrimental effect on survival in patients with resected early stage cancers.¹⁰ Adjuvant chemotherapy trials have similarly failed to show significant survival improvements in this setting. Despite these disappointing results, the poor survival rates and the understanding that survival is determined by systemic recurrence justify ongoing attempts at improving systemic adjuvant therapy. Administration of chemotherapy prior to surgical resection (neoadjuvant chemotherapy) is an attractive approach in this setting where delivery of adequate systemic therapy postoperatively is often difficult. A recent study of neoadjuvant chemotherapy in early stage disease reported a response rate of 56% with 86% of patients able to undergo complete resection without excessive toxicity.¹¹ Randomized trials of neoadjuvant chemotherapy in this setting are planned to determine whether survival can be improved for these patients.

Stage IIIA non-small cell lung cancer is composed primarily of patients with involvement of ipsilateral mediastinal or subcarinal (N2) lymph nodes. The optimal management of these patients is controversial and the large amount of clinical data is often difficult to interpret. Patients with N2 disease are recognized to be a heterogeneous group with a wide variation in prognosis based upon the extent of mediastinal node involvement. A recent French study reported 5-year survival rates with surgery of 34% for patients with involvement at only one node level, but only 11% and 3% for those with multiple levels of involvement or preoperatively determined N2

node involvement, respectively.¹² Postoperative adjuvant therapies have not shown benefit for resected stage IIIA cancers. Postoperative radiotherapy has been reported to decrease local recurrence in some studies but does not improve survival. Similarly, postoperative adjuvant chemotherapy has not produced meaningful improvements in survival. A meta-analysis of eight cisplatin-based chemotherapy trials reported a 13% reduction in the risk of death with chemotherapy, which suggests an absolute benefit of 5% at five years.¹³ The most recent Intergroup trial of postoperative adjuvant chemoradiotherapy has also been reported to show no survival advantage following complete surgical resection.¹⁴ Given these data, the routine use of postoperative adjuvant therapy is not justified. Phase II trials of preoperative chemotherapy and radiation followed by surgical resection in selected, good performance status patients have produced promising results. Two phase III trials of neoadjuvant chemotherapy have reported survival benefits in potentially resectable IIIA disease, but both trials were small and, although promising, have not become accepted as standard treatments. Progress in this difficult area will only be made through enrollment of patients into prospective randomized trials.

Postoperative adjuvant therapies have not shown benefit for resected stage IIIA cancers.



A combination of chemotherapy and radiation therapy is the standard treatment for most patients with unresectable locally advanced (unresectable stage IIIA and stage IIIB) non-small cell lung cancer. Stage IIIB includes patients with N3 disease (contralateral mediastinal node involvement) or T4 lesions. Historically the prognosis for these patients has been dismal with 5-year survival of less than 5% with surgical resection and less than 10% with primary radiotherapy. Recent tri-

als of combined modality therapy in this setting have produced promising results. A phase II trial of weekly paclitaxel, carboplatin and concurrent radiation reported a 75% response rate with 38% survival at 2 years.¹⁵ An ongoing randomized trial is looking at the addition of induction chemotherapy to this chemoradiotherapy regimen.

Progress in the treatment of metastatic non-small cell lung cancer has been incremental and modest. Trials from the 1980s showed that cisplatin-based chemotherapy improved survival by a matter of weeks when compared to best supportive care.¹³ More recent trials using doublets of cisplatin, carboplatin, paclitaxel (Taxol), docetaxel (Taxotere), navelbine, and gemcitabine (Gemzar) have produced average survival improvements of several months. One-year survival rates of up to 50% have been reported in some aggressive phase II cooperative group trials of combination chemotherapy. These encouraging response rates have not always been confirmed in randomized trials, however. A recent Intergroup trial of over 1000 patients comparing four current generation chemotherapy regimens showed disappointing response rates of 15-20% and median survivals of about 8 months for patients with good performance status.¹⁶ No chemotherapy regimen has been shown to be clearly superior in the initial treatment of metastatic disease. Interestingly, however, single agent docetaxel has shown improved one-year survival and enhanced quality of life as second line therapy when compared to supportive care.¹⁷ There is no demonstrated survival benefit for chemotherapy in patients with poor performance status and the decision to recommend therapy for these patients is often difficult. Novel therapeutic agents will be needed to make significant progress in the treatment of metastatic non-small cell lung cancer.

Hope for improved outcomes for patients with advanced non-small cell lung cancer comes from advances in molecular biology, immunology and pharmacology. Anti-cancer therapies kill tumor cells by initiating an intracellular process of programmed self-destruction called apoptosis.

Chemotherapeutic agents and radiation initiate apoptosis by damaging DNA or directly interfering with basic cellular components such as microtubules. Recent preclinical research has demonstrated that small biologic molecules or monoclonal antibodies that interfere with growth factor receptor signaling pathways can also initiate apoptosis. Typically a growth factor binds to a receptor on the cell surface which activates a signaling cascade that ultimately leads to gene expression for proteins that stimulate tumor cell growth and inhibit apoptosis. By designing monoclonal antibodies against the growth factor receptors or small molecules that inhibit components of the signaling cascade, cell proliferation can be inhibited and programmed cell death initiated. An example of effective antibody therapy is the clinical activity of Herceptin in breast cancer that over-expresses the HER-2 growth factor receptor. Small molecules such as zidovudine that interfere with the function of the epidermal growth factor receptor have shown great promise and are currently being tested in numerous trials in lung cancer and other solid tumors. It is of particular importance that cytotoxic chemotherapeutic agents and these new imolecular-targeted therapies are often synergistic in causing tumor cell apoptosis. Many oncologists believe that our best chance to improve therapy for cancer patients will be by combining traditional chemotherapy with one or more novel therapeutic agents directed at new molecular targets. Clinical investigators at the **Brown University Oncology Group (BrUOG)** and the Rhode Island teaching hospitals have been active in both participating in and designing these important clinical trials.

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