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Cancer Update
A CME Issue

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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
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Cancer Organizations (NABCO)

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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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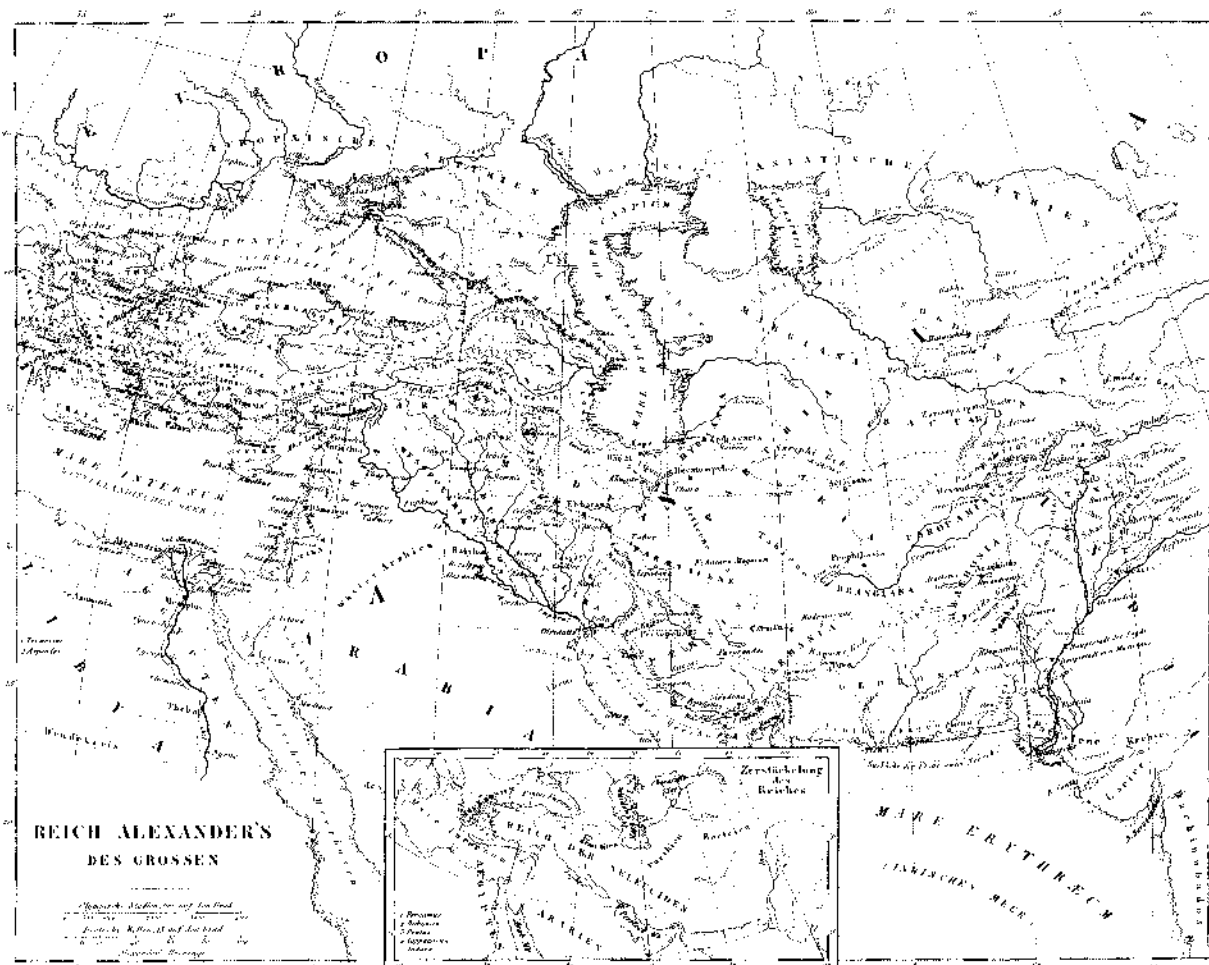
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REFERENCES



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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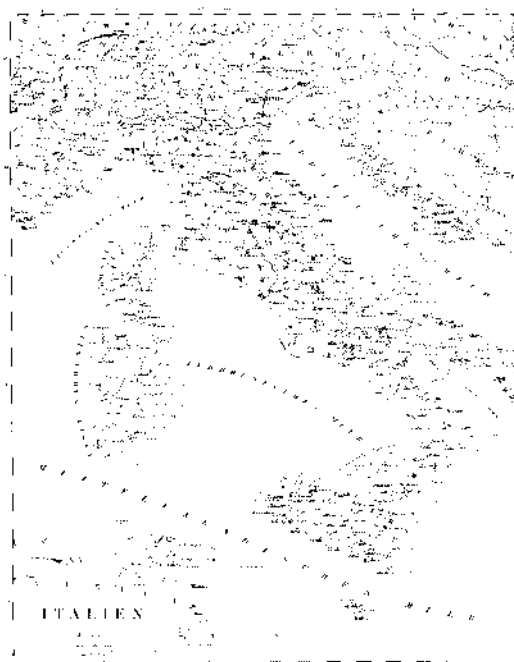
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Breast Cancer Update

Mary Anne Fenton, MD

Breast cancer is the most common non-cutaneous malignancy in women and the second leading cause of cancer mortality in the United States. Breast cancer mortality has fallen over the past four years due to early detection and gains in adjuvant therapy, yet it is projected that there will be 184,200 new cases of breast cancer this year, and 41,200 breast cancer deaths.¹ In this review I will discuss recent advances in breast cancer treatment including the multidisciplinary approach to invasive breast cancer which have resulted in a decrease in morbidity and mortality, followed by a discussion of long term health maintenance for the 2 million breast cancer survivors in the United States.

Surgical therapy of breast cancer includes resection of the primary tumor and axillary staging. Options for resection of a patient's breast tumor include **modified radical mastectomy (MRM)** and partial mastectomy followed by radiation therapy. For the appropriate patient, there is no difference in overall survival for breast conserving treatment though there is a slightly increased rate of local recurrence, with 8-year incidence of recurrence in the ipsilateral breast of 10% after partial mastectomy versus up to 8% local recurrence for MRM.² Patients who are not candidates for partial mastectomy include those who are unable to receive 6 weeks of breast radiation. Examples of such patients include those who live a great distance to a radiation facility, patients with medical or psychiatric conditions which would prevent participation in 6 weeks of daily radiation, patients with connective tissue disorders, patients who have had prior radiation to the same region, and pregnant patients. In addition, partial mastectomy is not recommended for patients who would have a poor cosmetic result from tumor resection due to a large primary tumor and patients with multicentric cancer in the breast. Most patients who undergo a MRM are candidates for immediate reconstruction, although patients requiring postoperative radiation including patients at high risk for local recurrence may be advised to delay reconstruction until after

radiation therapy has been completed to optimize cosmetic results. Neoadjuvant chemotherapy may downstage large primary tumors to allow for better cosmetic results, though this approach has yet to demonstrate an impact on overall survival.³

A standard component of surgical treatment of invasive breast cancer has included level one and two **axillary lymph node dissection (ALND)** for axillary staging and local control. Complications of ALND may include postoperative pain and numbness, lymphedema and limitation of arm movement. **Sentinel lymph node dissection (SLND)** has been studied in breast cancer patients to provide prognostic information on axillary lymph node status and avoid the morbidity of a full ALND in patients with a negative sentinel node. This technique involves identifying the draining lymph node with injection of blue dye or isotope into the tumor bed. In a multicenter validation study with preceding period of surgical training sessions, one or more sentinel lymph nodes were identified in 93% of patients. The accuracy of sentinel nodes defined as the percentage of cases in which the pathologic status of the sentinel nodes reflected the status of a ALND was 97% and the false negative rate, defined as the failure to identify metastatic disease present in the axilla was 11%.⁴ Complications of sentinel lymph node staging include a 5% incidence of local seromas. Serial sectioning and immunohistochemical evaluation of sentinel lymph nodes decrease the false negative rate but increase the detection of micrometastatic disease which would not have been noted with standard H and E staining. The clinical significance of micrometastatic disease detected by immunohistochemistry alone is unclear. The **American College of Surgeons (ACS)** and the **National Surgical Adjuvant Breast and Bowel Project (NSABP)** have initiated clinical trials to assess the impact of SLND on local control, systemic recurrence and survival. Individual surgeons participating must demonstrate their proficiency with the sentinel lymph node identification, and validate their accuracy with standard ALND. Contraindications to sen-

tinell lymph node staging include pregnancy, previous radiation to the axilla, or clinically palpable lymph nodes. In summary, SLND appears to have significant less morbidity in patients who require axillary staging but long-term follow-up data is necessary to determine incidence of axillary recurrence and impact on overall survival.

ADJUVANT THERAPY

The patient's medical oncologist will estimate the patient's risk of systemic recurrence based on established prognostic factors including histologic type, tumor size, pathologic grade, presence of lymphatic and vascular invasion, axillary lymph node status and hormone receptor status. In addition, the patient's age, menopausal status and general health will influence recommendations for systemic adjuvant therapy. The impact of HER2 receptor over expression as a prognostic factor and a predictive factor for response to chemotherapy and hormone therapy is currently under prospective evaluation following retrospective studies that suggest that HER2 overexpression is a marker of poor outcome.

The goal of adjuvant therapy is to cure micrometastatic disease. The benefits of adjuvant chemotherapy and hormone therapy in reducing the risk of systemic recurrence and death from metastatic breast cancer was validated with the 1995 overview analysis by the **Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**. This meta-analysis included all randomized clinical trials of adjuvant therapies, which began before 1990, with early breast cancer defined as surgically resectable tumors.^{5,6}

The EBCTCG findings for adjuvant tamoxifen demonstrated statistically significant benefit for disease free and overall survival for all patients with **estrogen receptor (ER)** positive tumors. Five years of tamoxifen provides a significant benefit as compared to two years of tamoxifen therapy with a proportional risk reduction of recurrence of 47% and reduction in death of 26% for patients in all age groups, regardless of lymph node status and menopausal status. Node positive patients had an absolute benefit in overall survival of 10.9% and node negative of 5.6%. In

addition, tamoxifen provides a 47% reduction in contralateral breast cancer for patients with estrogen positive tumors. Tamoxifen therapy results in a slight increase in the incidence of endometrial cancer and thromboembolic events. In the EBCCTG overview, actual excess deaths from endometrial cancer in patients receiving tamoxifen was 2 deaths per 1000 patients. An increase in pulmonary embolus was also noted, with no increase in mortality. In addition, the benefit for combination chemotherapy and tamoxifen was additive.⁶

Tamoxifen, a selective estrogen receptor modulator (SERM), is the current standard adjuvant hormone therapy for patients with estrogen receptor positive tumors. Aromatase inhibitors, which prevent the conversion of androgens to estrogens, are an effective therapy for postmenopausal women with advanced breast cancer. At the December 2001 San Antonio Breast Cancer Symposium, preliminary results of a clinical trial exploring the role of the aromatase inhibitor anastrozole (trade name Arimidex) in the adjuvant setting were presented. The trial, entitled Arimidex, Tamoxifen, Alone or in Combination (ATAC), randomized patients who were candidates for adjuvant hormone therapy to 5 years of anastrozole, tamoxifen, or the combination. At a median duration of 3 years, patients receiving anastrozole had a significant reduction in disease-free survival compared to tamoxifen alone or the combination. In addition, the incidence of contralateral breast cancer was reduced significantly in patients receiving anastrozole compared to those randomized to tamoxifen. Longer follow-up is required to determine the effect of each therapy on disease-free survival, overall survival, and to determine the risk benefit of aromatase inhibitors on bone mineral density, endometrial cancer, incidence of new breast primaries and cognitive function. The ATAC trial is the single largest adjuvant trial ever conducted in women with early breast cancer, and enrolled 9,366 postmenopausal women from 21 countries. Patient enrollment in clinical trials and completion of trials such as ATAC are crucial to answer outstanding questions in breast cancer treatment and prevention. The media portrayal of the ATAC preliminary results has raised anxiety for patients on

tamoxifen as adjuvant therapy. Patients are encouraged to discuss concerns with their physicians. In Rhode Island, postmenopausal patients completing 5 years of adjuvant tamoxifen are candidates to participate in a CALGB trial of an aromatase inhibitor vs. placebo after completion of 5 years of adjuvant tamoxifen. [Call 1-877-788-6667 for details.]

Benefits of polychemotherapy in the EBCCTG metaanalysis were statistically significant for all age groups below 70 years of age, with the proportional benefit greater for younger women. In women below the age of 50, proportional risk reduction of breast cancer relapse was 35% and death was 27%, and in women over the age of 50, the proportional risk reduction in risk of relapse was 20% and mortality 11%. In terms of actual risk reduction, polychemotherapy reduced recurrence in node positive patients by 15% and mortality by 12% and node negative recurrence by 10% and mortality by 5.7%.⁵ The EBCCTG overview also noted a statistically significant advantage in overall survival with anthracycline containing regimens, although the standard 4 cycles of **adriamycin and cytoxan (AC)** appear equivalent to 6 cycles of cytoxan, methotrexate and 5-fluorouracil.⁷ Side effects of chemotherapy include alopecia, mucositis, nausea and vomiting, and myelosuppression, and risk of cardiac toxicity from anthracycline containing regimens is less than 1%. Chemotherapy is also associated with a slight increased risk of secondary leukemia (<1.5%).

Ongoing areas of investigation include dose escalation of standard regimens and addition of newer agents such as the taxanes to standard adjuvant chemotherapy programs. Two randomized clinical trials assessed the addition of paclitaxel to standard AC chemotherapy for node positive patients. The **Cancer and Leukemia Group B (CALGB)** and NSABP have completed accrual of this regimen, data released at the NIH consensus conference in November 2000, after limited follow-up, do not show a statistical improvement in survival with the addition of a taxane. Data currently available from randomized trials of dose escalation of standard regimens or dose intense regimens with stem cell support do not demonstrate a significant survival advantage for high dose versus conventional dose chemotherapy.

In summary, the decision to recommend adjuvant treatment to a particular patient is based on overall prognosis and evaluation of predictive factors for response to hormone and chemotherapy. This is a process of shared decision making, with discussion between the medical oncologist and patient as to the benefits and toxicity of adjuvant chemotherapy and hormone treatment. Ongoing areas of investigation of adjuvant treatment include role of ovarian ablation in premenopausal women, benefit of aromatase inhibitors in ER positive patients, variations of drug dose and schedule for standard chemotherapy regimens, and the addition of novel therapies to the adjuvant setting, including the bisphosphonates and trastuzumab, a humanized monoclonal antibody directed against the HER2 protein.

MANAGEMENT OF METASTATIC DISEASE

Ever increasing options for metastatic disease include new hormone strategies, new chemotherapy agents, less toxic weekly regimens, and immune and biologic based therapies. ER positive premenopausal patients are candidates for tamoxifen or ovarian ablation with surgery, radiation, or GnRH agonists. Postmenopausal patients with estrogen positive tumors are candidates for tamoxifen or aromatase inhibitors, which reduce peripheral conversion of adrenal androgens to estrogens. Chemotherapy options now include taxanes, gemcitabine and capecitabine, an oral medication, which does not include alopecia as a side effect.

Biologic agents including angiogenesis inhibitors and signal transduction inhibitors have shown promise in the treatment of a variety of cancers in early clinical trials, and currently phase 1 and 2 trials with such agents are underway in breast cancer. Targeted immune therapy has now become standard treatment in patients with overexpression of the HER2 protein with trastuzumab (Herceptin), a humanized monoclonal antibody. HER2 is a transmembrane tyrosine kinase growth factor receptor, and overexpression is seen in 20-30% of breast cancers. Phase II trials of Herceptin as a single agent demonstrate a response rate of 26% with a median duration of 9.1 months, and in combination with chemotherapy including paclitaxel and navelbine demonstrate

an additive response rate of 38 to 75%. Issues of cardiac toxicity in combination with anthracyclines need to be clarified, but overall Herceptin has minimal side effects including chills and fever and the rare incidence of anaphylaxis.

Bisphosphonates can provide a substantial benefit in patients with bone metastasis. Pamidronate, given as a monthly IV infusion, decreases the incidence of skeletal complications and hypercalcemia.

PREVENTION: RISK STRATIFICATION AND REDUCTION

Several tools are currently available to primary care physicians to assess a patient's individual risk of breast cancer. Discussion of individual risk can help reduce unwarranted fears in some patients who overestimate their risk and also identify high risk-patients who can be referred for further counseling or testing and review of strategies for risk-reduction.⁸ The most commonly used risk-prediction model is the Gail model, which predicts a woman's five year and lifetime risk of developing breast cancer based on age at menarche, age at first live birth, number of breast biopsies and the number of first degree family members with breast cancer. The Gail model is useful though it may overestimate risk for young women below the age of routine mammographic screening and underestimate risk in patients who carry a breast cancer susceptibility gene. To calculate an individual patient's risk based on the modified Gail model, access the National Cancer Institute at http://cancernet.nci.nih.gov/h_detect.html. A more appropriate model for patients who may carry a genetic susceptibility to breast cancer is the Claus model, which incorporates both first and second degree relatives including paternal relatives, although it does not incorporate other risk factors. The Claus model should be considered for patients with a family history of early onset breast cancer, breast and ovarian cancers, and women of Ashkenazi Jewish ancestry, who are at risk for carrying the two major breast-cancer-susceptibility genes which have been identified, BRCA1 and BRCA2. These patients are best served with referral to a high risk assessment clinic with facilities for assessment of cancer risk and specialized genetic counseling regarding the pros and cons of genetic testing and discussion of risk reduction strategies.

Breast cancer risk reduction strategies include chemoprevention, prophylactic surgery, and lifestyle changes. Proposed lifestyle changes currently the subject of investigation includes reduction in fat intake, increase in exercise, weight loss and reduction in alcohol intake.⁸ Surgical approaches include bilateral mastectomies and/or oophorectomy. Prophylactic mastectomies reduced the risk of breast cancer incidence and mortality by 90% in a retrospective cohort study.⁹ Prophylactic mastectomies, which can result in breast numbness and absence of nipple sensation, do not remove all breast tissue, and are irreversible, should be reserved only for very high risk women after appropriate counseling. In a study BRCA1 mutation carriers, bilateral oophorectomy was associated with a 47% reduction in the calculated risk of breast cancer and also in the incidence of ovarian cancer.¹⁰ The utility of prophylactic oophorectomy in women with increased risk of breast cancer from factors other than germ line mutations is unclear.

*Ever increasing options
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Chemoprevention has emerged as a viable alternative for risk reduction. In patients with breast cancer, adjuvant treatment with tamoxifen for five years reduced the risk of contralateral breast cancer by 47%, regardless of the receptor status of the initial tumor.⁶ This observation led the NSABP to conduct the Breast Cancer Prevention Trial, NSABP P1, a randomized placebo-controlled trial of women with a calculated 5 year risk of breast cancer based on the modified Gail model of >1.66%, which is equivalent to the 5 year risk of a 60 year old women. Tamoxifen reduced the annual odds of invasive and noninvasive breast cancer by 50%.¹¹

Tamoxifen reduced only the incidence of estrogen-receptor positive cancers, and there has been, as yet, no demonstrated effect on survival. Side effects of tamoxifen may include hot flashes, vaginal discharge, and a 1% incidence per year of vascular events including deep vein thrombosis, pulmonary embolus, and stroke. There is also an increase in the incidence of endometrial cancer. Both the vascular events and endometrial cancer are seen primarily in older patients, along with a small increase in cataracts. Women on tamoxifen should have a review of their gynecologic history, annual pelvic exams and evaluation of abnormal vaginal discharge or bleeding. Routine vaginal ultrasound or endometrial biopsies are not recommended. In contrast, two European trials failed to find any breast cancer reduction with tamoxifen, this was probably due to differences in trial design and populations.^{12,13} The impact of tamoxifen on high-risk women with risk based on family history is unknown at this time. The results of NSABP P1 led the **Food and Drug Administration (FDA)** to approve tamoxifen for the reduction of breast cancer risk in women with increased risk of the disease. No impact on survival has been shown in any prevention trial.

Tamoxifen is one of a class of compounds referred to as **selective estrogen-receptor modulators (SERM)**, with partial agonist antagonist properties on the estrogen receptor. Other SERMs may have a more favorable safety profile. Raloxifen is a SERM approved for use in prevention and treatment of osteoporosis in postmenopausal women. In the **Multiple Outcomes Raloxifen Evaluation (MORE)** trial, Raloxifen was found to reduce the annual odds of receptor positive breast cancer by 65%.¹⁴ Patients on raloxifen do experience symptoms of estrogen deficiency similar to tamoxifen including hot flashes, and is also associated with a small increase in vascular events. Raloxifen appears to have little effect on the risk of endometrial cancer based on animal models and limited clinical follow-up. Clinical data are insufficient to support the use of raloxifen for breast cancer risk reduction or treatment.

The **Study of Tamoxifen and Raloxifen (STAR)** trial is a randomized placebo control trial conducted by the **National Surgical Breast and Bowel Project (NSABP)**, in conjunction with the

National Cancer Institute. The goal of this study is to compare the effectiveness of tamoxifen and raloxifen in reducing the incidence of breast cancer in postmenopausal women age 35 or older who are at increased risk for the disease. Eligible women must be postmenopausal, at least age 35, and have a 5 year risk of developing breast cancer of >1.7%. Risks of the treatment include a slight increase in risk of deep vein thrombosis, pulmonary embolus and endometrial cancer. Ineligible women include women with a previous diagnosis of ductal carcinoma in situ or invasive breast cancer, a history of uncontrolled diabetes or hypertension, prior deep vein thrombosis, pulmonary embolus atrial fibrillation, TIA or stroke. Follow-up includes annual physical exams, mammograms, pap smears and pelvic exams. Postmenopausal women interested in participating in the STAR trial may call the Breast Cancer Prevention Group of Rhode Island Office of Clinical Research (1-877-788-6667), or the National Cancer Institute's (NCI) Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

BREAST CANCER SURVIVORS

For the more than 2 million breast cancer survivors in the United States, health concerns include risks of local and systemic recurrence, short and long term consequences of treatment, and risks of other malignancies.¹⁵ In monitoring patients for disease recurrence, there is no evidence to support intense screening with radiologic exams such as bone scans, CT scans or even chest x-ray or laboratory tests including tumor markers as compared to physical exam, mammogram and evaluation of symptoms. The **American Society of Clinical Oncology (ASCO)** guidelines for breast cancer follow-up, derived from evidence-based clinical trials, recommend review of systems and physical exam including close evaluation for evidence of local recurrence every 3-6 months for three years, then every 6-12 months for 2 years, then annually. Routine laboratory or radiologic studies may detect clinically asymptomatic disease but do not clearly alter overall survival.

A major complication from ALND is the development of lymphedema. To limit the morbidity of lymphedema preventative strategies to reduce compression or infections, include avoiding venipunc-

ture, pressure, heat or trauma to the involved limb. The incidence and extent of lymphedema will be lower in women following sentinel lymph node staging. In patients who develop significant lymphedema, symptoms may be improved with arm elevation, use of a compression stocking, or massage by a physical therapist certified in lymphedema management.

Chemotherapy frequently induces premature menopause. Menopause is accompanied by symptoms of hot flashes and urogenital atrophy and results in loss of bone density secondary to estrogen deprivation. Patients should have evaluation of bone density within 6 to 12 months of completion of adjuvant therapy, and treatment to prevent further bone loss should be considered in patients with bone mineral density well below the mean bone density for their age. Therapies for osteoporosis include bisphosphonates and calcitonin. Raloxifen, a **selective estrogen receptor modulator (SERM)** is approved for treatment of osteoporosis in postmenopausal women, but its impact on disease recurrence in breast cancer survivors is unknown.

Many therapies have been touted to reduce vasomotor symptoms such as hot flashes due to menopause or tamoxifen. Randomized clinical trials have demonstrated modest benefits from selective serotonin uptake inhibitors such as fluoxetine (Prozac®) and verlexifaxine (Effexor®) and transderm clonidine. Megestrol acetate has significant benefit but the safety in breast cancer survivors is unknown. Soy tablets have shown no improvement compared to placebo and the safety of soy phytoestrogens after breast cancer is unknown. Breast cancer survivors should discuss any herbal therapies with their physicians, as some herbal remedies provide symptomatic relief due to phytoestrogen content. The safety and benefits of hormone replacement therapy in breast cancer survivors is currently under investigation.

Postmenopausal women also may develop atrophy of urogenital epithelium from estrogen deprivation, with symptoms of urinary frequency, dyspareunia and vaginal dryness. Vaginal lubricants or moisturizers may provide some relief of mild symptoms. For patients with more significant symptoms, topical estrogens provide a more significant benefit with a

known modest systemic absorption of estrogen. Due to this systemic absorption, the safety of topical estrogens is unknown. Recently, the FDA approved a sylastic device impregnated with estrogen, which appears to have less systemic absorption than topical estrogens.

FUTURE DIRECTIONS

There has been a significant decrease in breast cancer mortality based on advances in adjuvant therapy. The current goals for patients with early stage disease are to minimize disease recurrence as well as minimize toxicity of treatment. In addition, significant advances have been made in therapeutic options for patients with metastatic disease with a particular emphasis on quality of life as well as overall survival. We should continue to encourage patients to participate in well designed clinical trials to further our goals of breast cancer prevention and cure.

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Screening for Colorectal Cancer in Rhode Island

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Colorectal cancer is the second most frequent cause of cancer deaths in Rhode Island, killing more men and women than either breast or prostate cancer. Although the incidence in Rhode Island is slightly higher than the national average, the death rate from colorectal cancer ran between 10 and 20% higher than the national average for the years 1994 to 1998.¹ Screening on a regular basis, however, can lead to the discovery - and removal - of pre-cancerous polyps.

In 1999, over 60% of the population over the age of 50 in Rhode Island never had any colorectal cancer screenings. Screening was less frequent in men than women. Over 80% of uninsured individuals have never been screened.² In response, the Rhode Island Legislature passed a Joint Resolution in the 2001 session recommending that the State Health Department in collaboration with The Rhode Island Cancer Council and other organizations raise awareness of colorectal screening and the importance of early detection.³

There is no shortage of recommendations for colorectal screening of the population - this may be part of the problem. The American Gastroenterological Association, the American Society of Clinical Oncology, The American Society of Colon and Rectal Surgery, the American Cancer Society, the Centers for Disease Control, the United States Preventive Task Force, the Rhode Island Department of Health have all addressed screening.⁴⁻¹⁰ A review of these recommendations shows considerable consistency in the recommendations for standard risk and for high risk people, but the number of available screening tests and the frequency with which they are to be performed can be confusing, not only to the specialists in endoscopy and to the primary care physicians who must recommend the procedures, but especially to the patients. Furthermore, the situation is not static. Recent pub-

lications^{11,12,13} concerning colonoscopy have forced reconsideration of the recommendations, which were written in 1996 through 2000. A recent study found that Sigmoidoscopy and **Fecal Occult Blood Test (FOBT)**, well accepted for screening of standard risk individuals and even for high-risk individuals by some^{14,15} failed to detect lesions in approximately one quarter of those tested.^{16,17} In addition no group enthusiastically supports double contrast barium enema,^{18,19} even with spiral CT.

The State Health Department asked the RI Cancer Council to review and possibly revise the recommendations in the State Cancer Plan¹⁰ for colorectal screening. We surveyed the sixty-two endoscopists who perform colonoscopy and/or sigmoidoscopy and 250 primary care physicians who may perform sigmoidoscopy but will be referring patients for colorectal screening as well. Sixty-nine percent of those endoscopists and approximately 50% of those primary care physicians responded.

This survey defined high-risk individuals as those with a family history of colorectal cancer in a first degree relative (mother, father, sister, brother). Grandparents, uncles, and aunts raise a suspicion of a somewhat higher risk. Family history of colorectal polyps and hereditary colorectal syndromes with a high incident of colorectal cancer were considered high risk. Individuals with a personal history of inflammatory bowel disease, ulcerative colitis, or Crohn's disease were also considered high risk, as well as a personal history of colorectal adenomas or colorectal cancer. Standard risk were people over the age of 50 with no known risk factors.

There was strong agreement between primary care physicians and specialists on the tests that they would recommend for standard risk population, with more primary care physicians recommending sigmoidoscopy

and more endoscopists recommending colonoscopy somewhat more frequently. (Figure 1) For high-risk populations, there was very little disagreement. Almost uniformly, both the primary care physicians and the specialists recommended colonoscopy as the procedure of choice. Almost the same uniformity of opinion was found for the frequency with which these tests should be performed. (Table 1)

We asked each group to evaluate the most important and least important barriers to colonoscopy and flexible sigmoidoscopy (Table 2). Adequate resources was the most important barrier for the primary care physicians to perform flexible sigmoidoscopy; having sufficient time was next in importance. One-third considered third-party payers an important barrier; only one-quarter ranked patient acceptance a barrier. For colonoscopy, the endoscopists ranked third-party payers as the most important barrier; resources second, followed by patient acceptance and availability of time. Primary care physicians who do not perform colonoscopy divided evenly on the four barriers to performing colonoscopy. Since the **Centers for Medicare and Medicaid Services (CMS)** (formerly the **Health Care Finance Administration, HCFA**) announced that they will pay for colonoscopy screening in July 2001, the perception of the importance of third party carrier barrier may change. Under the new guidelines, colorectal cancer screening will start at age 50. Coverage will include annual FOBT and flexible sigmoidoscopy every 4 years for standard risk individuals. For high-risk individuals colonoscopy every 2 years will be covered, but will be covered once every 10 years for standard risk. There will be co-payments required; no coinsurance or part B deductible for FOBT; 20% co-payment after part B deductible for flexible sigmoidoscopy and colonoscopy.

Based on survey responses, for

high risk individuals the endoscopists and the primary care physicians recommend the initiation of screening at least at age 50 or 10 years before a first- or second-degree relative developed colorectal cancer. The procedure of choice would be colonoscopy repeated every 3 to 5 years, or more frequently if polyps are found. For standard-risk patients, primary care physicians favored colonoscopy over flexible sigmoidoscopy but did not exclude fecal occult blood and flexible sigmoidoscopy as a reasonable screening procedure. Seventy-seven percent of the primary care physicians would recommend colonoscopy for standard-risk patients over the age of 50 every 5 to 10 years. Approximately 40% of the endoscopists considered flexible sigmoidoscopy and annual fecal occult blood an appropriate recommendation; however, 93% of these specialists favored colonoscopy as the screening test of choice with the test repeated every 7 to 10 years for standard risk patients.

In Rhode Island these recommendations could exceed our current capacity. Sixty-two specialists perform colonoscopy. Currently, they can perform between 25,000 and 30,000 colonoscopies per year. (Table 3) If colonoscopy was the recommendation for screening for standard-risk people once at the age of 50 and repeated 7 to 10 years later after a negative examination and for high-risk individuals, colonoscopy starting at least age 50 or earlier and repeated every 3 to 5 years, or more frequent depending upon findings, we would require between 55,000 and 60,000 colonoscopies per year to meet the needs of the people of Rhode Island, twice the current capacity. Actually, if only the high-risk population were to be screened as recommended starting at the age of 50, current capacity would already be exceeded.

Herein lies the problem. Increased colorectal screening is badly needed if we are to find the early cancers that can be cured and pre-cancerous lesions before they become a threat. This can change the outcome of colorectal cancer, curing most of the patients and pre-

venting cancer in the population in general. It will, in the long run, save lives and be cost effective in terms of utilization of medical resources. We must raise public awareness of the importance of colorectal screening and encourage primary care physicians to prevail upon patients to have the necessary examination. Hopefully, the number of Rhode Islanders being screened will increase over the current poor participation.

On the other hand, we must be concerned that we do not create a demand for a procedure which may not be easily available in the State. We will need to increase the number of special-

ists trained to perform colonoscopy and increase the facilities where this can be performed. Only with the cooperation of the medical community, the hospitals, and third-party payers can we accomplish our mission to lower the mortality from colorectal cancer.

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Fig. 1. Colorectal Cancer Screening

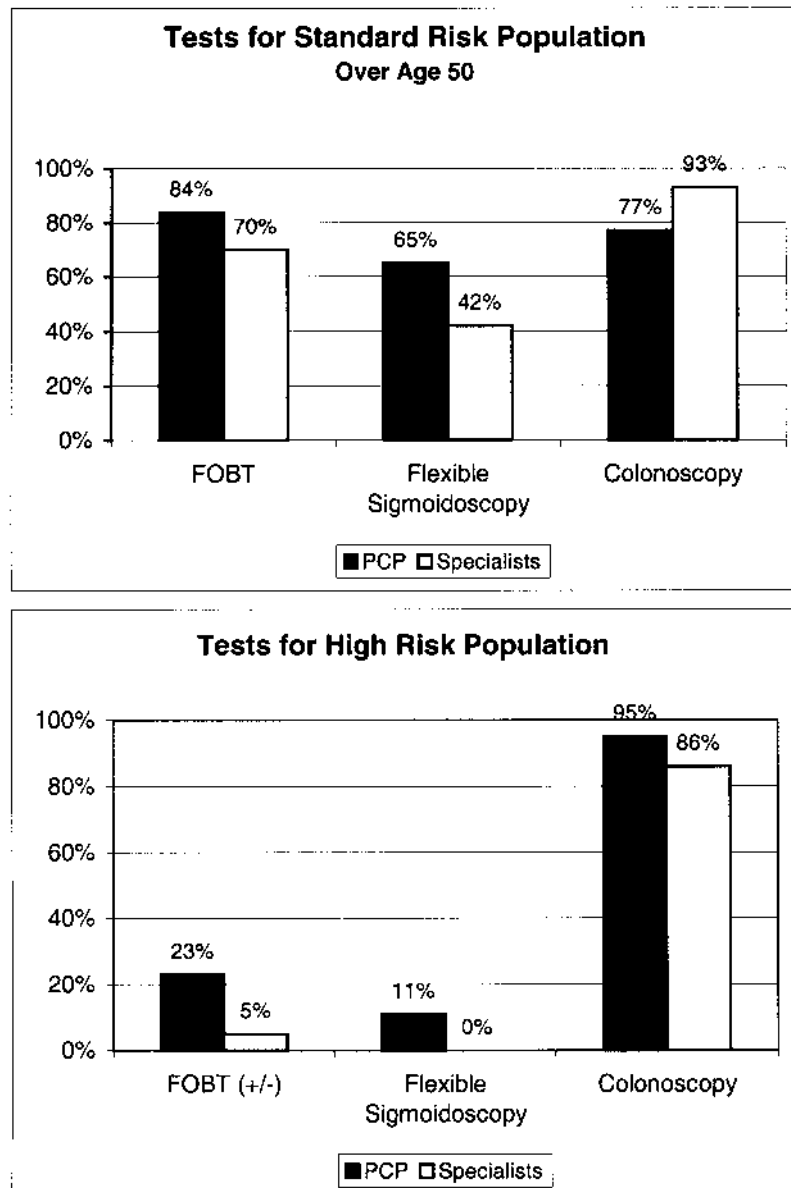


Table 1. Frequency of Tests.

Physicians	Primary Care Physicians		Specialists	
	Standard	High	Standard	High
FOBT				
Yearly	81	83	83	95
Other (or not stated)	19	17	17	5
Flexible Sigmoidoscopy				
Yearly	3	67	0	Not
3 years	43	17	11	Recommended
5 years	35	17	78	
Other (or not stated)	19		11	
Colonoscopy				
<3 years	16	12	18	19
3-5 years	43	70	23	68
7 years	5	---	5	---
10 years	7	2	40	3
Other (or not stated)	29	16	14	10

Table 2. Barriers to Colonoscopy.

BARRIERS TO COLONOSCOPY	(most important)		(least important)	
	Primary Care Physicians*	Specialists**	Primary Care Physicians	Specialists
Time	25	30	10	46
Resources	37	60	2	25
Patient Acceptance	25	51	7	18
Third Party	26	70	4	14

*None perform procedure

** All perform procedure

BARRIERS TO FLEXIBLE SIGMOIDOSCOPY	(most important)	(least important)
	Primary Care Physicians*	Primary Care Physicians
Time	44	19
Resources	54	7
Patient Acceptance	28	26
Third Party	35	14

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Childhood Cancer: Past Successes, Future Directions

William S. Ferguson, MD, and Edwin N. Forman, MD

The 20th century has had its share of horrific man-created events. One might even fantasize God looking at humanity and asking; "What reasons can be given to justify your continued existence?" One response might be the curing of children afflicted with cancer, which we believe ranks among the great achievements of the second half of the past century. Prior to this period, almost all such children died; now we expect to cure about three out of four children diagnosed with cancer (Figure 1).¹

This statistic is a remarkable testimonial to the success that can be achieved through the close cooperation of surgeons, oncologists, radiation therapists, and pathologists. Because childhood cancers typically grow rapidly and metastasize early, surgery alone - even with the addition of local radiotherapy - is typically not curative for pediatric solid tumors, and of course is ineffective against the leukemias that comprise about one-third of childhood malignancies. Therefore, it has only been since the advent of effective adjuvant chemotherapy that more than a small proportion of children could be cured of cancer.

Since cancer in children is an uncommon disease (approximately 12/100,000 children/year), even large institutions have insufficient numbers of patients to advance management rapidly. It has been through the advent of the cooperative cancer groups and the widespread use of nationally organized clinical trials that our knowledge of how best to treat cancer has progressed. In contrast to adults, the majority of children afflicted with cancer in the United States are now registered on research trials, and data strongly support the contention that these children, with access to the most state-of-art treatment, have outcomes superior to children who are not registered on national protocols.²

ACUTE LEUKEMIA

Acute leukemia is the most common malignancy in children, accounting for roughly one-third of all childhood cancers. Once universally fatal, there has been steady progress since the late 1950s both in understanding the basic biology of leukemia and in its treatment, and it is now one of the most survivable of neoplasms.

Acute lymphoblastic leukemia (ALL) comprises about 80-85% of childhood leukemia. **Acute myeloid leukemia (AML)** accounts for most of the remainder; chronic myelogenous leukemia is rare, and chronic lymphocytic leukemia unheard of in children.

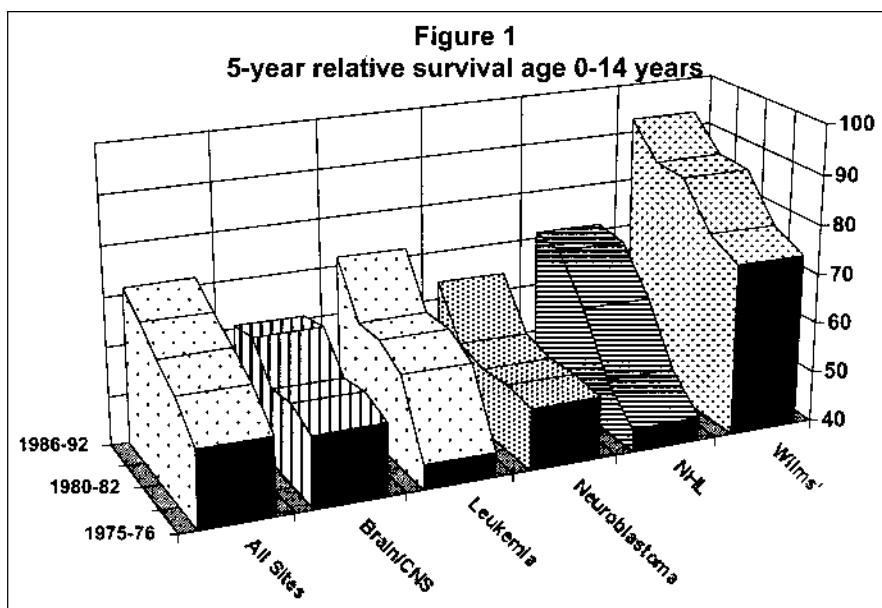
Although ALL and AML can usually be distinguished by their different histologic appearances, the identification of surface markers characteristic of different lymphocyte lineages has proved to be a powerful tool in subclassifying ALL for prognostic and therapeutic purposes. The majority (~85%) of cases of childhood ALL have markers of early B-lymphocyte differentiation, but not the surface immunoglobulins characteristic of mature B-lymphocytes; these are now generally called "B-precursor" ALL. About 15% will have markers charac-

teristic of T-lymphocytes, and 1-3% will be mature B-lymphocytes.

Additional prognostic information is provided by patient characteristics such as age, degree of wbc elevation at diagnosis, and gender; these have subsequently proven useful in modifying the intensity of treatment. More recently, a variety of cytogenetic changes have also proven of prognostic significance and may soon be the target of new modalities of treatment.

B-precursor ALL: Newly-diagnosed ALL is responsive to many chemotherapy agents. Although complete—albeit transient—remissions can be attained with single agent therapy, prolonged remissions became common only with the use of multi-agent chemotherapy. Today, induction therapy for B-precursor ALL includes glucocorticoids (prednisone or dexamethasone), vincristine, and L-Asparaginase; in high risk/poor prognosis cases, an anthracycline such as doxorubicin or daunorubicin is added. Maintenance therapy generally builds upon a backbone of antimetabolites, including mercaptopurine and methotrexate.³

In the early eras of ALL treatment, the **central nervous system (CNS)** was



a common site of recurrence, presumably because the blood-brain barrier prevents systemic therapy from consistently achieving cytotoxic levels in the CNS. Prevention of CNS relapse was first achieved with irradiation of the neuraxis. Although effective, CNS radiation is fraught with long-term complications, including learning disabilities, impaired growth, endocrine dysfunction, and secondary brain tumors. An alternative is direct instillation of chemotherapy into the CNS. Despite the need for repeated lumbar punctures, the long-term toxicity of intrathecal chemotherapy seems to be considerably less than radiation. For this reason radiation is now reserved for patients with overt CNS leukemia at diagnosis, plus selected subgroups of high-risk patients.

Survival has been further improved by the addition of a period of relatively intense chemotherapy immediately following induction therapy. For patients with favorable biologic characteristics - for example, children >1 years but <10 years of age with a relatively low **white blood count (wbc)** - intensification of antimetabolite therapy with the administration of high-dose intravenous methotrexate (rescued with citrovorum factor) can result in relatively high rates of cure (>80%).⁴ For patients with especially favorable cytogenetic changes, long-term survival may exceed 90%. The challenge for current cooperative trials is to identify whether modest additional intensification of therapy in some of these patients can improve survival without excessive additional morbidity.

For higher risk patients (e.g., high presenting wbc, unfavorable cytogenetics, or teenagers), an intensive multi-agent consolidation phase - which includes anthracyclines, cytosine arabinoside, and alkylating agents such as cyclophosphamide - clearly improves survival despite the additional drug-related toxicity.⁵ Overall survival for this group is ~65%. The optimal combination and timing of intensification therapy for high-risk patients is the object of considerable study among the cooperative groups in the United States

and Europe.

T-cell leukemia: T-lymphocyte differentiation was identified as an adverse biologic factor during the 1970s. T-cell ALL occurs more often in teenage males, who commonly present with very high peripheral wbc counts and mediastinal enlargement, which at times can be massive and rapidly life-threatening because of airway obstruction and tumor lysis syndrome. Treatments effective in B-precursor ALL have tended to be less likely to cure T-cell ALL. Aggressive multi-agent chemotherapy resulted in only modest improvement until the addition of intensive L-Asparaginase therapy, which has significantly improved survival (~75% cure). Patients with T-cell leukemia continue to be at relatively high risk of CNS relapse even with intrathecal chemotherapy, and so usually receive additional prophylactic CNS radiation.

B-cell leukemia: Defined by the presence of surface immunoglobulins, B-cell ALL is an explosive disease, often presenting with significant adenopathy and a rapidly rising wbc count. It responds poorly to conventional steroid- and antimetabolite-based regimens. However, B-cell ALL is biochemically and genetically similar to the undifferentiated non-Hodgkin's lymphomas (Burkitt's lymphoma). D.P. Burkitt first demonstrated among children in Africa that this lymphoma was quite sensitive to cyclophosphamide. Treatment now includes not only cyclophosphamide, but anthracyclines, high-dose methotrexate and cytosine arabinoside, and vincristine; although intense, treatment protocols generally last only about 6 months and have resulted in cure rates of >70%.

Relapsed leukemia: Relapsed ALL often remain chemotherapy-responsive, but traditionally second (and subsequent) remissions were of increasingly shorter duration, and long-term survival was elusive. Bone marrow transplantation and more intensive chemotherapy now offer some chance of cure for relapsed ALL, particularly in patients who relapse relatively late (e.g., >18 months after initial

diagnosis) or with relapse confined to the CNS or testicle.⁶ Perhaps 50% or more of patients with "late" relapse can attain long-term survival with either chemotherapy or bone marrow transplantation; while a fully histocompatible sibling generally confers the best chance of cure, only a minority of patients will have an appropriate donor. The relative merits of intensive chemotherapy vs. marrow transplantation from unrelated or partially-matched donors is hotly debated.

In contrast, the survival of "early" relapse patients with chemotherapy alone is dismal (<10%). Bone marrow transplantation is the preferred option in this situation, although survival remains lower than for patients who are transplanted following a late relapse.

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphomas (NHL) in children are almost always high-grade, undifferentiated malignancies. Early studies revealed that these tumors are virtually always disseminated at diagnosis, even if this is not clinically demonstrable. Thus, use of systemic chemotherapy and protocols similar conceptually to those used for leukemia have proven extremely beneficial. The rapid proliferation, which is a hallmark of these lymphomas, is also their Achilles' heel, making them relatively sensitive to chemotherapy. Indeed, the survival of patients with bulky or disseminated NHL is generally 65-75%,⁷ and for patients with clinically localized lymphomas the cure rate exceeds 90%.

The vast majority of childhood NHL fall into three categories:

Undifferentiated lymphoma, which is further subdivided into Burkitt's and non-Burkitt's lymphoma on the basis of morphology. The typical presentation in the United States is with massive intra-abdominal disease. Undifferentiated lymphomas exhibit surface makers of mature B-lymphocytes, are biologically similar to B-cell leukemia, and respond to the same short, intensive chemotherapy regimens as B-cell ALL.

Lymphoblastic lymphomas are comprised of T-lymphocytes and are

similar in behavior to T-cell leukemia, including the propensity to present with cervical adenopathy and/or an enlarged mediastinum. Treatment is similar to that for T-cell ALL, including the intensive use of L-Asparaginase.

Large cell lymphomas have variable surface markers, which may reflect an underlying biologic heterogeneity. They tend to grow somewhat more slowly than either undifferentiated or lymphoblastic lymphomas. Treatment for high-stage disease includes pulses of multi-agent chemotherapy (typically prednisone, vincristine, cyclophosphamide, doxorubicin, and methotrexate).

Although NHL most often presents with massive disseminated disease, several clinical trials in the 1980s and 1990s convincingly showed a cure rate of >90% for children with clinically localized undifferentiated and large cell lymphomas using only a 6-week course of chemotherapy alone, without the addition of radiation therapy.⁸ Children with clinically localized lymphoblastic lymphoma are treated with the same regimen followed by 6 months of therapy with mercaptopurine and methotrexate; although ~25% of lymphoblastic lymphomas treated with this regimen will recur, most patients can subsequently be salvaged with more intensive therapy.

HODGKIN'S DISEASE

Hodgkin's Disease comprises about half of all lymphomas in children. Radiation therapy has been successfully used for many years against localized or regional disease, and with the advent of effective chemotherapy regimens in the 1970s even patients with disseminated disease had a reasonable chance of cure. However, these treatments were not without significant toxicity, especially in children. Effective use of radiation mandates accurate staging (usually including staging laparotomy and splenectomy, with the resulting life-long risk of infection) and requires doses of radiation that could result in organ damage (lung, heart, thyroid), growth arrest, and second malignancies. Patients who receive prolonged chemotherapy for disseminated disease experience both severe short-

term effects as well as significant long-term toxicity, including (depending upon the drug combination) marrow suppression, damage to lung and heart, sterility, and secondary leukemia. The rate of second malignancies for adults treated with combined radiation and chemotherapy is exceptionally high.

The spectacular success in treating childhood malignancies must be weighed against the considerable short- and long-term side effects of treatment ...



The pediatric approach to Hodgkin's Disease has striven to minimize long-term toxicity by paradoxically combining moderate amounts of chemotherapy and radiotherapy.⁹ The rationale has been that modest amounts of chemotherapy can eradicate microscopic disease, thus often eliminating the need for staging laparotomy and allowing more limited fields and doses of radiation. Conversely, targeting bulk disease with radiation has allowed lower cumulative doses of chemotherapy. Several successive pediatric trials have shown that this approach can eradicate disease in the majority of patients (80-90+% depending upon stage), and the expectation of less long-term effects so far appears to be justified, although clearly longer follow-up of these patients will be necessary. For patients who relapse following combined therapy, intensive chemotherapy followed by stem cell support (also called autologous bone marrow transplantation) offers a chance of long-term survival.

WILMS' TUMOR

Wilms' tumor is by far the most common malignant renal tumor in children. Rare in infancy, it is primarily seen in children 1-5 years of age. Like many embryonal tumors, me-

tastases occur early in the course of the disease, so historically few children were cured by surgery alone. The liver and lung are the most common sites of metastatic spread.

Wilms' tumor was the first solid tumor for which the adjuvant use of chemotherapy was shown to enhance survival. While surgery remains a mainstay of treatment, combinations of vincristine, actinomycin-D and doxorubicin - along with radiation for patients with extra-renal spread of disease—has resulted in survivals of >90% for patients with localized disease, and even patients with distant metastases have a cure rate of ~80%.¹⁰

With the development of successful treatment regimens, it became evident that the presence of anaplasia in the tumor predicted poorer outcomes. Further study has shown that a single focus of anaplastic change requires slightly more aggressive use of radiation and chemotherapy but still has an excellent cure rate. Diffuse anaplasia confers a significantly worse prognosis, although the addition of cyclophosphamide has improved survival to ~50%.¹¹ Current studies are testing new drug combinations for these patients in an effort to improve their outcome.

National studies over the last decade have focused on trying to minimize therapy (and thus long-term toxicity) while maintaining a high cure rate for the majority of children with favorable histology tumors. Indeed, patients with favorable histology tumors confined to the kidney can now be successfully treated with as little as 16 weeks of vincristine and actinomycin-D, without radiation, and even patients with more advanced tumor receive relatively moderate courses of therapy.¹⁰ For these patients, the current National Wilms' Tumor Study is focusing on identifying new biologic factors that predict relapse, thus allowing new or more intensive therapies to be targeted to high-risk patients.

Many patients who relapse after treatment for Wilms' tumor remain responsive to chemotherapy, particularly those who received relatively limited treatment initially. Initial reports

Table 1: Biological/clinical subtypes of neuroblastoma

	Type 1	Type 2	Type 3
<i>MYC-N</i>	Normal	Normal	Amplified
DNA ploidy	Hyperdiploid or near triploid	Near diploid or near tetraploid	Near diploid or near tetraploid
1p Loss of heterozygosity	<5%	25-50%	80-90%
14 q Loss of heterozygosity	<5%	25-50%	<5%
<i>TRK-A</i> expression	High	Low	Low or absent
<i>TRK-B</i> expression	Low or truncated	Low or absent	High (full length)
<i>TRK-C</i> expression	High	Low or absent	Low or absent
Age	Usually <1 year	Usually 3-4 years	Usually 3-4 years
Stage	Usually INSS 1, 2, 4S	Usually INSS 3, 4	Usually INSS 3, 4
3-year survival	95%	25-50%	<5%

(adapted from reference 12)

suggest that intensive chemotherapy followed by radiation and/or autologous bone marrow transplant may salvage many of these children.

NEUROBLASTOMA

Neuroblastoma has perhaps the most variable clinical spectrum and natural history of any childhood tumor. At one end of the spectrum are localized tumors in infants with little or no propensity to metastasize. At the other extreme are the disseminated and rapidly growing tumors of older children, which are often quite resistant to treatment.

As for other pediatric tumors, there has been parallel progress both in our understanding of the basic biology of these tumors, as well as their practical treatment. Central to both of these is the growing understanding of the biologic features that predict responsiveness to therapy and outcome. It has long been evident that localized tumors can usually (>90%) be cured with surgical resection alone. It has also been known that infants have a prognosis superior to older children, even with regional or distant spread of disease. Over the last 20 years, other biologic features have been found to be strong predictors of outcome, especially amplification of the *mycN* oncogene (which predicts a poorer outcome) and hyperdiploid DNA content (a predictor of good outcome among infants, albeit not older children).

On the basis of extended scientific study, Brodeur and colleague have suggested that there are really 3 subtypes

of neuroblastoma.¹² (Table 1) The first is comprised of localized tumors, generally arising in infants, which are hyperdiploid and lack *mycN* amplifications. These tumors have an excellent outcome with surgery alone (and perhaps without surgery - see below).

To the second group belong tumors with regional nodal spread, usually in children older than 1 year of age, with diploid DNA content but without *mycN* amplification. These tumors usually respond well to chemotherapy (typically combinations of cisplatin or carboplatin, doxorubicin, etoposide, and cyclophosphamide or ifosfamide), and in some instances may be curable with surgery alone.¹³

Finally, there are tumors that present as disseminated disease, with *mycN* amplification. The outcome for children with these tumors has been poor with conventional chemotherapy, although a recent clinical trial conducted by the Children's Cancer Group suggested that multi-agent chemotherapy (including intensified chemotherapy with stem cell support) followed by the differentiating agent *cis-retinoic acid* can result in survival of ~50% of children.¹⁴

The biologic diversity of neuroblastoma helps to explain the results of newborn screening programs for neuroblastoma conducted in Japan and Quebec. Based on the assumption that relatively unaggressive neuroblastomas in infants progress into more malignant tumors in older children, these programs screened for elevated urine cat-

echolamines in an effort to detect and treat tumors while they were still responsive to surgery and chemotherapy. In reality, screening resulted in a marked increase in the number of tumors detected at birth, but no change in the incidence of tumors diagnosed later in life.¹⁵ Based on our current understanding, the aggressive tumors developing after infancy probably were not present at

birth; indeed, many if not most neonatal neuroblastomas are probably destined to spontaneously differentiate into benign tissue - a hypothesis that is supported by recent reports from Japan showing that the majority of neonates with neuroblastoma do well with no intervention whatsoever.

RHABDOMYOSARCOMA

Arising from striated muscle, rhabdomyosarcoma is the most common soft tissue sarcoma in children. It can arise from any muscle in the body; its distribution does not parallel muscle mass, with the orbit and genitourinary tract being relatively common sites.

Unlike many other soft tissue sarcomas, rhabdomyosarcoma is quite sensitive to chemotherapy as well as radiation. Outcome is strongly influenced by how completely the primary tumor can be surgically removed, but is also dependent on the site from which the tumor arises. This site-dependent variation in prognosis is only partially due to differences in the frequency of unfavorable (alveolar) and favorable (embryonal) histologies observed at different sites, and indeed is so marked that tumors arising in certain very favorable locations (such as the orbit) are typically not subjected to attempts at complete resection that might lead to disfigurement or functional losses.

Using this data, rhabdomyosarcomas are now classified both by stage (which is based on site, size, and presence or absence of metastases) and sur-

gical group (based on degree of resection), and the intensity of treatment is adjusted accordingly. The "gold standard" treatment is a combination of vincristine, actinomycin-D, and cyclophosphamide with the addition of radiation for residual local disease. Dose intensification of chemotherapy (especially of cyclophosphamide) appears to have improved survival over the last 2 decades, especially for children with gross residual disease following initial resection.¹⁶

The outcome for children with metastatic disease remains poor (survival of <25%), although within this group younger children with embryonal histology tumors fare better. Tumors with alveolar histology in general remain more resistant to therapy than those with embryonal histology, although recent data suggest that the new drug Topotecan may be especially effective against alveolar rhabdomyosarcoma.

OSTEOSARCOMA AND EWING'S SARCOMA

Bone tumors overall comprise only a small proportion of childhood malignancies. However, since both osteosarcoma and (to a lesser extent) Ewing's sarcoma have peak incidences in adolescence, and the more common pediatric tumors peak during the preschool years, bone tumors are actually the second most common cancer seen during the second decade of life.

Although both tumors can arise from any bone, osteosarcomas preferentially develop in the metaphyses, especially of the distal femur, proximal tibia, and proximal humerus. In contrast, about half of Ewing's sarcomas will develop in the bones of the axial skeleton (especially pelvis) and even when present in long bones are often seen in the diaphysis. Both Ewing's sarcoma and the closely related **primitive neuroectodermal tumor (PNET)** can arise in soft tissue.

Visible metastases are present at diagnosis only in a small percentage of patients (<15%). However, surgery alone is rarely curative even in the absence of detectable metastatic disease; 80-90% of patients will relapse within

a year, which implies the almost-universal presence of micrometastatic disease. Lung is the most common site of spread, with bone being second most common; Ewing's sarcoma/PNET can also spread to bone marrow.

Ewing's sarcoma is moderately responsive to both chemotherapy and radiation. Current adjuvant protocols use a combination of vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide; control of the primary tumor is accomplished by surgical resection and/or radiation. Patients without metastatic disease currently have long-term survival rates of ~70%, with tumors arising in the extremities having a better survival than other sites.¹⁷ Osteosarcoma is considerably less sensitive to chemotherapy, and is also relatively resistant to radiation. Nonetheless, adjuvant regimens based on doxorubicin and cisplatin, usually accompanied by high-dose methotrexate and sometimes other drugs, has increased survival to ~65% for patients without overt metastases.^{18,19} Survival is also strongly dependent upon the ability to completely remove the primary tumor, since in most instances radiation cannot be used to control disease remaining after surgery. Impressively, improvements in surgical technique - combined with the fact that most osteosarcomas arise in the extremities - now allow the majority of patients to avoid amputation and undergo so-called "limb salvage" procedures.

Overt metastases at the time of diagnosis presage a considerably worse outcome. Despite aggressive chemotherapy and treatment of metastatic lesions with surgery and/or radiation, overall survival for patients with metastatic bone tumors is <25%. For both osteosarcoma and Ewing's sarcoma, patients with metastases confined to the lung appear to have a somewhat better prognosis than those with extrapulmonary disease.

GERM CELL TUMORS

Germ cell tumors include a bewildering array of entities. The most common germ cell tumors are teratomas, most of which are benign (= mature

teratoma). Immature teratomas are graded according to their varying content of immature neuroepithelium. The malignant germ cell tumors have varying histologic appearances, apparently representing differentiation of pluripotent germ cells along different pathways, and include yolk sac tumors (= endodermal sinus tumors), germinomas (= dysgerminoma) and seminomas, embryonal carcinomas, and choriocarcinomas. In addition to tumors with a single malignant histology, tumors may contain multiple histologic types (mixed germ cell tumors) and teratomas may also have malignant elements.

Although benign teratomas may grow to prodigious size, they are successfully treated with surgery alone. The earlier literature suggested that immature teratomas had a risk of recurrence that increased with increasing grade of immaturity. However, more recent data suggest that the presence of immature elements alone does not predict recurrence, and so the earlier results probably were skewed by the undetected presence of malignant elements, a problem ameliorated by more complete pathologic examination of resected tumors and the ability to detect low levels of tumor markers in both tissue and blood (alpha-fetoprotein, usually associated with yolk sac elements, and β -HCG, usually associated with embryonal carcinoma).

Like other childhood cancers, the malignant germ cell tumors tend to spread early in their development and so, with the exception of localized testicular tumors in young boys, are not usually curable with surgery alone. Response to chemotherapy remained mediocre until the development of platinum-based regimens. The most common combination used in the United States is bleomycin, cisplatin, and etoposide; carboplatin is also used in some regimens and for recurrent disease, although it appears to be somewhat less effective than cisplatin.

The malignant germ cell tumors are so sensitive to this combination that four cycles are curative for >90% of pediatric patients with gonadal primaries (even those with metastatic disease)

and ~75% of patients with extra-gonadal disease.²⁰ Because of this exquisite sensitivity to chemotherapy, patients who are judged to be at modest risk of recurrence (e.g., teratomas with a small percentage of malignant elements) are now often observed without adjuvant treatment, since the ability to salvage those who do relapse is excellent, and the toxicity of the chemotherapy—both acute and late—can be significant. Future research will probably focus on further decreasing the duration and intensity of treatment for low-risk patients.

CONCLUSION

The spectacular success in treating childhood malignancies must be weighed against the considerable short- and long-term side effects of treatment (growth impairment, organ damage, sterility, and second malignancies). These can be tempered, in part, by our ability to target more intensive therapies for patients at higher risk of relapse, a consequence of our burgeoning knowledge of prognostic indicators. Improved supportive care and new ways of protecting normal tissue from chemotherapy- and radiation-induced damage are also beginning to make an impact on long-term toxicity. Furthermore, our increasing knowledge of the underlying biology of cancer holds the promise that we can develop new modalities of treatment that may, at least in part, avoid some of the potential life-long consequences of traditional chemotherapy and radiation.

A recent national summit on childhood cancer, which one of us (ENF) was privileged to attend, identified goals for the 21st century. While research continues on improving the medical treatment of childhood cancer, awareness of other important issues affecting these patients must not be lost. Access to appropriate, high-quality medical care remains far from universal. Furthermore, our care must take into account not just rates of survival, but also the quality of life for our patients and their families, both during and after treatment. Beyond the medical consequences of their treatment, many children continue to ex-

perience discrimination in jobs, insurance, and education as a result of their medical history. Indeed, as more patients survive their original disease, it becomes vitally important to deal with their long-term medical, emotional, and social needs.

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Brain Tumors

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Few diseases elicit the sense of hopelessness and despair as cancer of the brain. The most common primary brain tumor, glioblastoma, is often refractory to treatment and fatal within a year of diagnosis. However, not all of the neoplasms that involve the **central nervous system (CNS)** carry such a grim prognosis. In the following, I will discuss the classification and epidemiology of primary brain tumors, the treatment and prognosis of the most common tumors and end with a discussion of CNS metastases. I hope to leave the primary care physician with a general sense of how to approach a patient with a brain tumor.

The presenting signs and symptoms of patients with brain tumors reflect the somatotopic organization of the CNS and the fact that specific regions of the brain are indispensable for specific functions. Symptoms, such as focal weakness or numbness, identify the location of the tumor as contralateral cerebral hemisphere, brainstem, or spinal cord depending on the distribution of the loss. Homonymous visual defects always reflect an intracranial process, usually in the occipital lobe. Speech and language symptoms suggest a lesion in the dominant hemisphere (the left in 90% of patients). The time course of the illness is also an important indicator of the disease process. Unlike stroke, which presents suddenly, symptoms of a brain tumor often progress over weeks or months. The exception is a seizure, which can be either focal or generalized and is the presenting symptom of a tumor in one-third of patients. Seizures represent cortical dysfunction, and focal seizures suggest involvement of the contralateral cerebral cortex. Other symptoms that are common but not localizing include headache (40% of patients), papilledema, and mental status changes, all of which can result from increased intracranial pressure.

CLASSIFICATION

The **World Health Organization (WHO)** classification of brain tumors, published in 1979, includes 9 major categories of brain tumors and nine subcat-

egories of neuroepithelial tumors that are all defined by histologic criteria.¹ A modified version of this list is presented in Table 1.

Many occur primarily in children (i.e., embryonal tumors, pineal tumors, germ cell tumors, choroid plexus tumors); most are rare. Gliomas are by far the most common in adults and can exhibit features of astrocytes, oligodendrocytes, or both (mixed glioma).² The WHO schema uses a three-tiered system where the grade of the tumor reflects the extent to which the tumor cells are morphologically abnormal (anaplasia), their apparent rate of growth, and the presence of necrosis. Low-grade tumors may appear to contain a high density of almost normal appearing cells and a growth rate of less than 2%. Anaplastic gliomas exhibit more atypical cells with pleomorphic nuclei, growth rates in the 5-10% range but no evidence of necrosis. Gliomas with high growth rates (>20%) and necrosis are classified as glioblastoma multiforme. A grading scale first described by Daumas-Duport and Szikla uses similar criteria to classify glioma patients into one of four grades where grades II, III, and IV corresponding to low-grade glioma, anaplastic glioma, and glioblastoma respectively (Grade I reserved for pilocytic astrocytoma).³ The tumor grade is the most reliable predictor of prognosis. Even if the lesion cannot be safely excised, a needle biopsy is often indicated. We are moving toward a classification system that relies more on genetics than cellular morphology, but whether it will prove a better predictor of response to therapy and prognosis remains to be proven.

Similar approaches are used to classify other neuroepithelial tumors. Anaplasia and growth rate differentiate between malignant and less aggressive tumors of the pineal, choroid plexus, and ependyma. When tumors contain neurons (gangliogliomas, gangliocytomas), this suggests a less aggressive behavior, but it is sometimes difficult to identify whether neurons are part of the tumor or just trapped by an invading glioma. The primitive neuroectodermal tumors

(medulloblastoma, neuroblastoma, retinoblastoma) are characterized by a high density of rapidly growing cells. These tumors are not graded, and prognosis depends on the extent of tumor spread.

Tumors of the nerves and nerve sheath (schwannomas, neurofibromas) are usually slow growing and carry a favorable prognosis if they can be excised. When two or more of these are found in the same patient or family, the issue of an inherited disorder, such as neurofibromatosis type 1 or 2, is raised. Unfortunately, neurofibromas can degenerate into malignant sarcomas, particularly in patients with NF1.

Meningiomas are also classified in a three-tier system: typical, atypical, and malignant. Unlike gliomas, the vast majority of meningiomas is of the lowest grade. Atypical meningiomas have a relatively increased degree of cellularity and prevalence of mitotic figures. Malignant meningiomas are defined by invasion of adjacent brain. A malignant tumor of the pituitary (pituitary carcinoma) is also, fortunately, rare. Most tumors of the pituitary are adenomas characterized by the expression and secretion of hormones.

Of the remaining tumors, most are very rare and primarily affect children. The exceptions are CNS lymphomas and metastases. Primary CNS lymphoma is a form of extranodal non-Hodgkin's lymphoma and is classified according to the International Working Formulation (National Cancer Institute 1982). Most lymphomas that involve the brain are of B-cell lineage, and diffuse large cell or immunoblastic are the most common subtypes. In CNS metastases of systemic malignancies, such as breast or lung, the lesion will have the same histologic appearance as the primary. In 15% of patients with metastases, the primary is unknown but can sometimes be discerned with immunohistochemical stains of the biopsied brain lesion

EPIDEMIOLOGY

The chance of developing a malignant brain tumor in this country is small (5.8/100,000 person years) but is high

Table 1**Tumors of Neuroepithelial Tissue***Astrocytic tumors*

Astrocytoma

Variants

Fibrillary

Protoplasmic

Gemistocytic

Anaplastic astrocytoma

Glioblastoma multiforme

Variants

Giant cell glioblastoma multiforme

Gliosarcoma

Astroblastoma

Gliomatosis cerebri

Pilocytic astrocytoma

Pleomorphic xanthoastrocytoma

Subependymal giant cell astrocytoma

Oligodendroglial tumors

Oligodendroglioma

Anaplastic oligodendroglioma

Ependymal tumors

Ependymoma

Variants

Cellular

Papillary

Clear cell

Anaplastic ependymoma

Ependymblastoma

Myxopapillary ependymoma

Subependymoma

*Mixed gliomas**Choroid plexus tumors*

Choroid plexus papilloma

Choroid plexus carcinoma

Neuronal and mixed neuronal-glial tumors

Gangliocytoma

Dysplastic gangliocytoma of cerebellum

(Lhermitte-Duclos)

Central neurocytoma

Neuroblastoma

Variant

Ganglioneuroblastoma

Olfactory neuroblastoma

Variant

Olfactory neuroepithelioma

Ganglioglioma

Dysembryoplastic neuroepithelial tumor

Desmoplastic infantile ganglioglioma

Medulloblastoma

Medulloepithelioma

Pineal tumors

Germ cell tumors

Germinoma

Embryonal carcinoma

Yolk sac tumor (Endodermal sinus tumor)

Choriocarcinoma

Teratoma

Mixed germ cell tumors

Pineocytoma

Pineoblastoma

Mixed/transitional pineal tumors

Tumors of the Meninges

Meningioma

Variants

Meningothelial

Fibrous

Transitional (mixed)

Psammomatous

Angiomatous

Microcystic

Secretory

Clear cell

Chordoid

Atypical meningioma

Papillary meningioma

Anaplastic meningioma

Hemangiopericytoma

Hemangioblastoma

Primary melanocytic lesions

Diffuse melanosis

Melanocytoma

Malignant melanoma

Variant

Meningeal melanomatosis

Lymphomas

(Esthesioneuroblastoma)

enough so that most primary care physicians will encounter a patient every few years. The majority of these patients with a single brain lesion will have a glioma, and unfortunately, the most common histologic grade is glioblastoma. Data on the incidence of brain tumors in several regions of the US have been collected by the **Central Brain Tumor Registry of the United States (CBTRUS)** and **Surveillance, Epidemiology, and End Results (SEER)** consortia. Like many cancers, the incidence of brain cancer rises with age, peaking at approximately 65-70 years (Figure 1). For glioblastoma

alone, the highest incidence occurs at 60 years of age. CBTRUS data demonstrates the incidence declines in older people (>75 years). However, several investigators, including ourselves, have reported the incidence of glioma is rising rapidly in patients over 75. The male to female ratio for all brain tumors is approximately 1.0. However, if you look at meningioma alone, the M:F is 0.5 and for malignant glioma, 1.6. In Rhode Island the M:F is 2.0 for all gliomas. The incidence of brain cancer also varies in different regions of the country. The incidence of brain tumors in Hawaii is

roughly half that of New England. In our own study of the incidence of gliomas in Rhode Island, we found relatively high rates overall (7.6/100,000 p-y compared to 5.1 from CBTRUS) and for glioblastoma alone (4.6 vs. 2.5 from CBTRUS). Specific rates for meningioma and other less common tumors have not been reported.

LOW-GRADE GLIOMA

Gliomas are grouped into three histologic categories - low grade, anaplastic, and glioblastoma. The histologic grade has important therapeutic and

prognostic implications. Table 2 lists some of the clinical and morphologic features that distinguish low-grade gliomas from the higher-grade tumors.

Although low-grade glioma carries with it a better prognosis, the majority of patients with low-grade tumors will progress to glioblastoma and will succumb to their disease. Low-grade gliomas are slow growing lesions that often do not enhance with gadolinium. Histologically they are classified as either astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. A history of symptoms can extend back many months or years, and a patient may enjoy several years of stable disease before the tumor progresses. Factors which predict a longer progression-free survival include a low mitotic index (as measured by Ki-67 or mib-1 immunostaining), younger age of patient, and a lesion that is supratentorial and amenable to resection.

How we as physicians can alter the course of this disease is the next question. Surgical resection is always the first concern. Retrospective studies suggest patients who have had a gross total resection have a longer progression-free survival than those who do not.⁴ We, therefore, recommend surgery for patients with tumors that can be safely removed. It is important to remember that the surgeon can never “get it all out”, and the tumor will progress at some point even after a gross total resection. Therefore, a disabling resection in a patient with astrocytoma or oligodendroglioma is not helpful. A subtotal resection is indicated in patients where the mass effect of the tumor is causing disability that can be addressed with decompression. In patients with pilocytic

astrocytoma, the indications for surgery are slightly different. In this disease, a complete resection may constitute a cure, and a more aggressive surgical approach may be indicated.

It is important to remember that the surgeon can never “get it all out”, and the tumor will progress at some point even after a gross total resection.



Whether to recommend external beam radiation therapy is often the next decision. Until recently, data from randomized studies has not been available. Preliminary data from a large randomized European study suggests that radiation therapy does not prolong overall survival in patients with low-grade glioma. However, there was an increase in PFS for treated patients. This benefit may be offset by a higher incidence of cognitive impairment in the treated group. Survival is not the only factor when considering RT. Patients with large tumors that are symptomatic often benefit functionally from RT. RT may also reduce seizure frequency in patients who are refractory to anticonvulsant drugs. We, therefore, recommend RT for patients with large symptomatic residual disease, but for most patients, we withhold therapy until there is radiographic or clinical evidence of tumor progression.

Focal radiation (radiosurgery or gamma knife) has been used in some patients with low-grade glioma, but there is currently no long-term follow-up data reporting a clear benefit.

Chemotherapy is in general not part of the initial management of patients with low-grade glioma. The exception to this is patients with an oligodendroglioma tumor who are either older or whose tumor has a relatively high mitotic index. These patients may benefit from PCV (procarbazine, CCNU, and vincristine) chemotherapy. The benefit of this approach is that it delays the use of RT, which can result in long-term cognitive impairment, particularly in the elderly patient. Chemotherapy, however, is not without risk, and chemo-induced leukemia occurs in approximately 1-2% of patients treated with PCV who survive 5 years.

Although the prognosis for patients with low-grade tumors is much better than anaplastic glioma and GBM, it is still a fatal disease for most patients. The median survival for patients with astrocytoma is 5-7 years and for oligodendroglioma, 7-10 years.

ANAPLASTIC GLIOMA

Anaplastic glioma is an intermediate grade tumor which has a higher mitotic index than low-grade gliomas but lacks the necrosis seen in glioblastoma. It commonly affects patients in the 35-50 age range, and patients often present with a history of symptoms that goes back several weeks. A complete surgical resection of the lesion is again the best first step, but a heroic disabling procedure is not beneficial. The majority of patients with anaplastic tumors will receive both radiation therapy and chemotherapy at some point. In anaplastic astrocytomas, patients should receive RT soon after surgery. In a large randomized study published 15 years ago, adjuvant PCV chemotherapy was shown to be of some benefit.⁷ Subsequent studies have not confirmed a survival advantage to adjuvant PCV. Temozolomide is an oral chemotherapeutic drug that is approved for the treatment of recurrent anaplastic gliomas. The chance of a response (ei-

Table 2
Grades of Gliomas

	Low-Grade Glioma	Anaplastic Glioma	Glioblastoma
Symptoms Duration	years	months	weeks
Age at Diagnosis	5-30	30-50	> 50
MRI Enhancement	-	+/-	++
Pathology	Hypercellular	Anaplastic	Necrosis Endothelial Cell Proliferation
Mitotic index (Ki-67)	< 2%	5-10%	> 10%
Treatment	observe	RT	RT and chemotherapy
Survival	5-10 years	3-4 years	12 months

ther complete, partial, or stable disease) is high (40-50%), and it is very well tolerated. It is currently being evaluated as adjuvant to radiation and concomitant with radiation therapy in patients with anaplastic astrocytoma. The postsurgical approach is somewhat different in patients with anaplastic oligodendrogliomas and mixed anaplastic gliomas. There is an approximately 70% chance these patients will respond to PCV chemotherapy. We, therefore, recommend PCV (6 cycles if tolerated) prior to RT in most patients. There is now a chromosomal marker (loss of heterozygosity at 1p and 19q) that can predict with 95% sensitivity whether a patient will respond to PCV chemotherapy. Patients that lack this marker have only a 30% chance of responding, and their prognosis is much worse. This and other genetic markers may soon play an important role in how we decide which therapies to use.

The prognosis for patients with anaplastic astrocytoma is approximately 3 years (median survival), and again anaplastic oligodendrogliomas do better, particularly if the tumor has the chromosomal abnormalities described above. Aggressive chemotherapy (with bone marrow transplant) has not significantly prolonged survival.

GLIOBLASTOMA MULTIFORME

This is both the most common and most aggressive of the gliomas and unfortunately the least likely to respond to therapy. The average age at presentation is 62 years, and males are at higher risk than females (M:F 1.5-2). The term multiforme refers to the gross appearance of the tumor. There are often areas of necrosis, areas of hemorrhage, and areas of fleshy tumor, all in the same lesion. At a clinical and a molecular level, there is a dichotomy in how a GBM develops. In younger patients with GBM, a long history of seizures can sometimes be elicited suggesting their tumor developed from a lower grade precursor. In older patients with GBM, symptoms often develop quite suddenly suggesting the tumor did not evolve through less aggressive precursors. Genetic studies confirm this dichotomy. Tumors from older patients with GBM frequently have amplification of the gene encoding the EGF receptor, whereas GBM in younger patients often exhibit mutation of p53 and loss of portions of chromosome 19,

changes which are also seen in low-grade and anaplastic tumors.

The first step in treatment is best surgical resection. Patients who are younger, have a normal examination and have had a gross total resection have the best prognosis. Postoperative RT clearly benefits these patients and is the standard of care.⁵ In a large randomized study conducted in the 1970s, patients with GBM who received RT had a median survival, roughly twice that of those who did not.⁶ In patients with a small volume of residual disease (less than 3 cm in diameter), a focal radiation boost has also been shown to prolong survival. The benefit of chemotherapy is more controversial. BCNU is an intravenous chemotherapy that penetrates the brain, but most studies suggest that only 20-25% of patients will benefit. BCNU can also be delivered directly to the brain in a biodegradable wafer (Gliadel) at the time of surgery. This approach has resulted in a modest improvement in survival when used at either tumor recurrence or at the initial surgery. Temozolomide is now the most commonly used FDA approved drug for patients with recurrent GBM. Response rates are higher than BCNU (30-40%), and it is better tolerated. There are currently a wide variety of clinical trials of new agents for patients with recurrent or recently diagnosed GBM. I strongly encourage clinicians to get these patients involved in at least one of them.

The median survival for patients with GBM who have received RT is slightly less than a year. The chance of survival at 2 years is 5-10%, and the chance of survival at 5 years is less than 2%. Long-term survivors are often younger patients who have had complete resection and received both radiation therapy and some form of chemotherapy. The fact that survival rates for patients with GBM have not changed in 30 years is discouraging but emphasizes the need for more basic science and clinical research.

MENINGIOMA

Meningioma is a tumor of the fibrous connective tissue that forms the dura. They are classified into three grades, typical, atypical, and malignant, based on their mitotic index and whether they invade normal brain. Fortunately, the vast majority of these tumors is typical meningioma and is slow growing. Autopsy studies have shown that most

meningiomas are asymptomatic. On MRI they appear as a dural-based, homogeneously enhancing mass. The incidence of the disease increases with age, and meningiomas are more common in women. Meningiomas frequently express estrogen and progesterone receptors, and the risk of tumor progression may increase with pregnancy or estrogen replacement. Because they grow slowly, these tumors can achieve a remarkable size before they are discovered. A common scenario is that an elderly patient is noted to have behavioral changes and cognitive decline, potentially attributable to dementia, and imaging reveals a 4-5 cm subfrontal mass.

In patients with typical meningioma, surgical resection alone can be curative, and the chance of recurrence at 10 years following gross total resection is less than 20%. In patients with subtotal resection, the chance of recurrence is much higher (60% at 5 years), and RT or preferably focal radiation (gamma knife or radiosurgery) is indicated. Patients with atypical meningioma or malignant meningioma should be treated with radiation even if a gross total resection is achieved. Chemotherapy for recurrent tumors has been attempted but with little success. Interferon alpha and hydroxyurea have been used in slowly growing tumors; response rates are less than 20%. For tamoxifen (anti-estrogen) and mifepristone (anti-progestin), the data are more promising (PR + SD 30%), but larger studies in progress are likely to show lower response rates. Aggressive chemotherapy with ifosfamide and adriamycin in rapidly growing tumors has been tried but again with little success.

PNET AND OTHER TUMORS

Medulloblastoma, pinealoblastoma, and other primitive neuroectodermal tumors are rare and primarily affect children. These tumors often appear as a homogeneously enhancing mass adjacent to the third or fourth ventricle, and patients typically present with nausea, headache, and double vision. Histologically they appear as hypercellular lesions with a high nuclear to cytoplasmic ratio. Surgical resection is again the best first step in management. Unlike gliomas, these tumors frequently seed the CSF, and patients can develop drop metastases in the spinal cord. In medulloblastoma, patients are classified as low risk if they have had a complete sur-

gical resection and have no evidence of CSF dissemination. Patients in this group who are treated with craniospinal RT have a 60% chance of 5-year progression-free survival. The addition of chemotherapy may raise this chance to as high as 80% in children.⁸ High-risk patients with CSF involvement or metastases usually receive both RT and chemotherapy but are at much higher risk of recurrence. Pinealoblastomas and other PNETs are treated in a similar fashion.

Tumors that contain neuronal elements are referred to as gangliogliomas or gangliocytomas. These lesions develop from cells that are precursors for both neurons and glia. Radiographically they appear as a nonenhancing cystic mass adjacent to the lateral ventricle. In general, they are more indolent than glial tumors. When symptomatic, they should be removed. However, asymptomatic tumors can be observed and addressed with surgery or RT only if they progress.

PRIMARY CNS LYMPHOMA (PCNSL)

Primary CNS Lymphoma (PCNSL) is a form of extranodal non-Hodgkin's lymphoma that involves the brain, eyes, and CSF.¹⁰ Immunocompetent patients usually present in the 5th or 6th decade with a homogeneously enhancing lesion located adjacent to the lateral or third ventricle. Multiple lesions occur, and the differential diagnosis often includes glioma and metastases. The vitreous and the CSF are frequently involved (20% and 33% respectively), but tumors are rarely seen outside the neuraxis. Patients are treated with high-dose intravenous methotrexate or a combination of chemotherapy and RT. Unlike malignant glioma, the chance of responding to therapy is high (70%), but patients frequently relapse within 3 years. The risk of PCNSL in the general population historically has been 1-2 per million person years, but several lines of evidence indicate it is rising. In Rhode Island we see 3-5 patients a year. Patients with acquired or congenital immunodeficiency have a much higher risk of PCNSL (2-6% of AIDS patients, 1-5% of transplant patients). Unless the immune deficiency can be rectified, these patients may have a more malignant course.

METASTASES

For the medical oncologist and in-

ternist, this is perhaps the most common neuro-oncology issue that comes up. Twenty-five percent of all patients with cancer will develop CNS metastases at some point. This can take the form of solid tumors compressing the brain and spinal cord or cancer cells infiltrating CSF and peripheral nerve. CNS metastases from lung cancer are the most common primary tumor that metastasizes to the CNS (50%) followed by breast (33%), GI tumors (9%), and melanoma (7%). The time interval between the primary diagnosis and CNS metastasis is dependent on the tumor type. For lung cancer, the median interval is 4 months and for breast, 3 years. CNS metastasis is an indicator of poor prognosis and portends a survival of less than 6 months for most patients.

Although treatment is clearly palliative, most patients do benefit from CNS directed therapy. Whole brain radiation therapy is indicated for most patients with parenchymal brain lesions. If only a single lesion is present and the systemic disease is stable, surgical resection of the lesion should be considered. Similarly, focal radiation is helpful only in patients with one or two lesions and are otherwise stable.¹¹ Both of these local approaches do not address the significant chance of new lesions occurring elsewhere in the brain, and patients should also receive RT.¹² Symptoms consistent with a spinal cord metastasis include back pain, incontinence, sensory loss in a dermatomal pattern, or bilateral motor deficits in the absence of mental status changes. These patients need to be evaluated urgently. The chance for neurologic recovery is dependent on the functional status at the time of diagnosis. Therefore, evaluation with MRI or myelogram and treatment with surgery, RT, or both should proceed without delay. Carcinomatous meningitis commonly presents with headache, nausea, and cranial neuropathies. The diagnosis is made by CSF cytology and meningeal enhancement on gadolinium MRI of the brain or spine. The treatment involves direct infusion of chemotherapy (methotrexate or cytarabine) into the spinal fluid via a lumbar puncture or preferably an Ommaya reservoir.

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CME Background Information

This CME activity is sponsored by Brown Medical School.

TARGET AUDIENCE

This enduring material is designed for physicians licensed in Rhode Island.

CME OBJECTIVES

At the conclusion of this course, participants should be able to:

- * describe diagnosis, staging and treatment of non-small cell lung carcinoma
- * describe multidisciplinary approach to breast cancer, including the long-term maintenance of breast cancer survivors
- * describe recommendations for colorectal screening
- * describe the childhood cancers and their treatments
- * describe treatment and prognosis of common brain tumors

NEEDS ASSESSMENT

Diagnosis and treatment of cancer have made dramatic advances in the past decade. This issue will inform Rhode Island physicians of those advances.

ACCREDITATION STATEMENT

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This issue was published January 2002. This activity is eligible for CME credit through December 2002.

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Please evaluate the effectiveness of the CME activity on a scale of 1 to 5 (1 being poor; 5 being excellent) by circling your choice.

- | | | | | | |
|--|---|---|---|---|---|
| 1. Overall quality of this CME activity | 1 | 2 | 3 | 4 | 5 |
| 2. Content | 1 | 2 | 3 | 4 | 5 |
| 3. Format | 1 | 2 | 3 | 4 | 5 |
| 4. Faculty | 1 | 2 | 3 | 4 | 5 |
| 5. Achievement of educational objectives | | | | | |
| * Describe diagnosis, staging and treatment of non-small cell lung carcinoma | 1 | 2 | 3 | 4 | 5 |
| * Describe multidisciplinary approach to breast cancer, including the long-term maintenance of breast cancer survivors | 1 | 2 | 3 | 4 | 5 |
| * Describe recommendations for colorectal screening | 1 | 2 | 3 | 4 | 5 |
| * Describe the childhood cancers and their treatments | 1 | 2 | 3 | 4 | 5 |
| * Describe treatment and prognosis of common brain tumors | 1 | 2 | 3 | 4 | 5 |

Please comment on the impact that this CME activity might have on your practice of medicine.

Additional comments and/or suggested topics for future CME activities.

Cancer in the New Millenium Questions

- 1) The percentage of patients with cancer that can be cured in 2001 is approximately:
 - A) 20%
 - B) 40%
 - C) 60%
 - D) 80%
 - E) None of the above
- 2) The median age for patients with cancer in the United States is:
 - A) 50 years
 - B) 55 years
 - C) 60 years
 - D) 65 years
 - E) 70 years
- 3) The largest number of cancer deaths in the United States occurs from:
 - A) Brain tumors
 - B) Prostate cancer
 - C) Lung cancer
 - D) Colorectal cancer
 - E) Breast cancer
- 4) During the past 40 years we have made the most progress in the treatment of:
 - A) Tumors in the elderly
 - B) Tumors of childhood
 - C) Colorectal tumors
 - D) Brain tumors
 - E) Breast tumors
- 5) The intervention that would have the most impact on decreasing mortality from non-small cell lung cancer would be:
 - A) Public health programs that decreased the number of teenagers who start smoking.
 - B) Screening programs using high resolution CT scan of the chest.
 - C) Aggressive surgery for stage I and II lung cancer.
 - D) More extensive use of multi-agent chemotherapy.
 - E) Use of positron emission scanning to identify surgically curable sub-clinical disease.
- 6) Standard therapy for stage I or II non-small cell lung cancer would be:
 - A) Surgery followed by post-operative chemotherapy.
 - B) Surgery followed by post-operative radiation.
 - C) Surgery alone.
 - D) Pre-operative chemotherapy followed by surgery.
 - E) Surgery followed by post-operative chemotherapy and radiation.
- 7) The current standard treatment for unresectable stage III non-small cell lung cancer in patients with good performance status is:
 - A) Chemotherapy alone.
 - B) Radiation alone.
 - C) Sequential chemoradiotherapy (chemotherapy followed by radiation).
 - D) Concurrent chemoradiotherapy (chemotherapy and radiation given at the same time).
 - E) Twice per day radiation therapy.
- 8) Which women are not candidates for partial mastectomy?
 - A) Patients who live too far from a radiation facility to receive 6 weeks of breast radiation
 - B) Pregnant patients
 - C) Patients with connective tissue disorder
 - D) Patients with multicentric cancer in the breast
 - E) All of the above
- 9) Which statement is true?
 - A) There is no significant difference in outcome between 5 years of tamoxifen therapy and two years.
 - B) Chemotherapy is associated with a large increased risk of secondary leukemia.
 - C) Capecitabine does not include alopecia as a side effect.
 - D) Bisphosphonates provide no benefit in patients with bone metasis.
 - E) No statement is true.
- 10) Which statement is true?
 - A) For patients with a genetic susceptibility to breast cancer, the Claus model is more appropriate than the Gail model.
 - B) Clinical data support the use of raloxifen for breast cancer risk reduction.
 - C) To monitor patients for disease recurrence, physicians should screen with bone scans and CT scans.
 - D) A and C are true.
 - E) No statement is true.
- 11) Screening for colorectal cancer was performed on less than _____ % of the Rhode Island population.
 - A) 40%
 - B) 50%
 - C) 60%
 - D) 80%
 - E) Not known
- 12) Both primary care physicians and endoscopists preferred which study for high-risk individuals?
 - A) FOBT and sigmoidoscopy
 - B) Flexible sigmoidoscopy
 - C) Colonoscopy
 - D) Double-contrast barium enema
 - E) None of the above
- 13) If the recommendation for standard risk individuals to be screened using colonoscopy once at age 50 and every 10 years thereafter unless some pathology is found for high-risk individuals every two years were to be implemented, current resources could handle the load.
 - A) True
 - B) False
- 14) An individual's risk of developing cancer between birth and 20 years of age is approximately
 - A) 1 in 500
 - B) 1 in 1000
 - C) 1 in 5,000
 - D) 1 in 10,000
 - E) 1 in 25,000
- 15) In a child with newly diagnosed acute lymphoblastic leukemia, all of the following are required/important for therapeutic decisions except
 - A) Lumbar puncture
 - B) Chest x-ray
 - C) Testicular biopsy
 - D) Cytogenetics of leukemic cells
 - E) None of the above
- 16) The number of Rhode Island children newly diagnosed with cancer each year is approximately
 - A) 20
 - B) 40
 - C) 80
 - D) 160
 - E) 250
- 17) The most common primary brain tumor is:
 - A) Glioma
 - B) Pituitary adenoma
 - C) Meningioma
 - D) CNS lymphoma
 - E) Medulloblastoma
- 18) The chance a meningioma recurs within 10 years of complete surgical resection is:
 - A) Less than 5%
 - B) Less than 20%
 - C) 50%
 - D) Greater than 60%
 - E) 80%
- 19) The most common source of brain metastases is:
 - A) Melanoma
 - B) Breast cancer
 - C) Lung cancer
 - D) Lymphoma
 - E) Prostate cancer

Prevention and Treatment Recommendations for Community Acquired Pneumonia

Deidre Spellisey Gifford, MD, MPH

Each year in the United States there are an estimated two to three million cases of **community acquired pneumonia (CAP)**, resulting in approximately ten million physician visits, 500,000 hospitalizations, and 45,000 deaths.¹ Pneumonia is the sixth most common cause of death in the US, and the overall rate of death due to pneumonia (together with influenza) is rising. Appropriate and timely antibiotic therapy for CAP has been shown to decrease mortality rates. Three recently published guidelines have evaluated the available evidence on the appropriate treatment of CAP.²⁻⁴ Below is a summary of some of their treat-

PREVENTION OF PNEUMOCOCCAL PNEUMONIA

All patients 65 years and older who are not allergic to the pneumococcal vaccine and who have not received the vaccine (or received it more than five years ago, if prior to age 65), should be offered the pneumococcal vaccine. If a hospitalized vulnerable elderly patient is eligible and not up-to-date with the pneumococcal and influenza vaccines, then the patient should receive the vaccines while hospitalized.

PROMPT INITIATION OF THERAPY

For patients requiring hospitalization, the importance of prompt initiation of empirical antibiotic therapy cannot be over-emphasized. In an analysis of 14,000 patients hospitalized for pneumonia, initiation of antibiotic therapy within eight hours of hospital admission was associated with a 15% reduction in 30 day mortality.⁵ However, in this national study, nearly one quarter of patients received their first dose of antibiotics more than eight hours after hospital arrival,

emphasizing the opportunity for improvement in this area. Empirical antibiotic therapy based on the most likely causative organism should begin as soon as the diagnosis of CAP is made, and should not be delayed pending results of blood culture, sputum gram stain, or any other microbiological studies. For most patients, this will require that the initial antibiotic dose be given in the emergency department rather than waiting until the patient is transferred to a medical ward or intensive care unit.

TABLE 1
Causative Agents and Initial Therapy for Community Acquired Pneumonia

Patient Characteristics	Most likely causative agents	Recommended initial antibiotic therapy
Outpatients	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , <i>Legionella</i> , <i>H. influenzae</i> , viruses, <i>M. tuberculosis</i> , endemic fungi	Advanced generation macrolides (azithromycin or clarithromycin); OR, doxycycline
Outpatients with cardiopulmonary disease or other modifying factors* +	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , mixed infection <i>C. influenzae</i> , enteric gram-negatives, viruses, <i>Moraxella catarrhalis</i> , <i>Legionella</i> , anaerobes, <i>M. tuberculosis</i> , endemic fungi	Beta-lactam PLUS macrolide or doxycycline; OR, antipneumococcal fluoroquinolone (alone)
Hospitalized: General medical ward, no cardiopulmonary disease or other modifying factors* +	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , mixed infection, viruses, <i>Legionella</i> , <i>M. tuberculosis</i> , endemic fungi, <i>P. carinii</i> .	IV azithromycin alone; OR, antipneumococcal fluoroquinolone (alone)
Hospitalized: General medical ward, with cardiopulmonary disease or modifying factors* +	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , mixed infection, enteric gram-negatives, aspiration, viruses, <i>Legionella</i> , <i>M. tuberculosis</i> , endemic fungi, <i>P. carinii</i> .	IV beta-lactam PLUS IV or oral macrolide or doxycycline; OR, IV antipneumococcal fluoroquinolone alone
Hospitalized: ICU	<i>S. pneumoniae</i> , <i>Legionella</i> , <i>H. influenzae</i> , enteric gram negatives, <i>S. aureus</i> , <i>M. pneumoniae</i> , viruses, <i>C. pneumoniae</i> , <i>M. tuberculosis</i> , endemic fungi	IV beta-lactam, PLUS either IV macrolide or IV fluoroquinolone (modify for patients at risk for <i>P. aeruginosa</i> +))

*Age >65, beta lactam therapy within past 3 mo., alcoholism, immune-suppressive illness, multiple medical comorbidities, exposure to a child in a day care center, nursing home resident, underlying cardiopulmonary disease.
+ structural lung disease, corticosteroid therapy, broad-spectrum antibiotic therapy for >7d in past month, malnutrition.

ETIOLOGY AND ANTIBIOTIC SELECTION

In nearly half of cases, the etiologic agent of CAP is never identified. Epidemiological studies have shown that the causative agents of CAP differ depending on the site of acquisition, the severity of the infection and the comorbidities and immune status of the patient.²⁻⁴ Table 1 summarizes the recommended initial antibiotic therapy for various patient characteristics, based on the guidelines of the American Thoracic Society.⁴ Advanced generation macrolides are recommended for uncomplicated outpatient CAP, because of *H. Influenzae* resistance to erythromycin and the improved side-effect profile of the advanced generation drugs. Initial recommended therapies for inpatients and outpatients, with and without additional risk factors are described Table 1.

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The author assumes full responsibility for the accuracy and completeness of the ideas presented. This article is a direct result of the Health Care Quality Improvement Program initiated by the Health Care Financing Administration, which has encouraged identification of quality improvement projects derived from analysis of patterns of care, and therefore required no special funding on the part of this Contractor. Ideas and contributions to the author concerning experience in engaging with issues presented are welcomed.

Information for Contributors, *Medicine & Health/Rhode Island*

Medicine & Health/Rhode Island is a peer-reviewed publication, listed in the [Index Medicus](#). We welcome submissions in the following categories.

CONTRIBUTIONS

Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be camera-ready. Photographs should be black and white. Slides are not accepted.

CREATIVE CLINICIAN

Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

POINT OF VIEW

Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

ADVANCES IN PHARMACOLOGY

Authors discuss new treatments. Maximum length: 1200 words.

ADVANCES IN LABORATORY MEDICINE

Authors discuss a new laboratory technique. Maximum length: 1200 words.

MEDICAL MYTHS

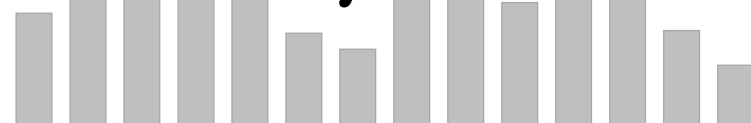
Authors present an iconoclastic, research-based analysis of long-held tenets. Maximum length: 1200 words.

For the above articles: Please submit 4 hard copies and an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, Joan Retsinas, PhD, 344 Taber Avenue, Providence, RI 02906. phone: 272-0422; fax: 272-4946; e-mail: JRetsinas@aol.com

IMAGES IN MEDICINE

We encourage submissions from all medical disciplines. Image(s) should capture the essence of how a diagnosis is established, and include a brief discussion of the disease process. Maximum length: 250 words. The submission should include one reference. Please submit the manuscript and one or two cropped 5 by 7 inch prints with the author's name, degree, institution and e-mail address to: John Pezzullo, MD, Department of Radiology, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903. Please send an electronic version of the text to: JPezullo@lifespan.org.

Health by Numbers



Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Jay S. Buechner, PhD

☞ Rhode Island Hispanics Have Mainstream Cancer Rates ☞

John P. Fulton, PhD, and Jay S. Buechner, PhD

The 2000 US Census enumerated more than 85,000 persons in Rhode Island who self-identified as Hispanic, representing about 8.5% of the state's total population and comprising the state's largest racial or ethnic minority group. Producing regular health statistics for Hispanics is challenging because ethnicity is difficult to measure in health surveillance systems of even the best design. Here we have evaluated the ability of two major surveillance systems, the Rhode Island Cancer Registry and the Vital Records death certificate file, to measure cancer morbidity and mortality among resident Hispanics.

Methods

Because Census Bureau inter-censal estimates of the number of resident Rhode Island Hispanics were inconsistent with counts from the 2000 Census, new inter-censal estimates were constructed for resident Rhode Island Hispanics by year, sex, and age group for the years 1989-1998, using linear interpolation and extrapolation from 1990 and 2000 Census counts.

Data on resident cancer cases and deaths identified as Hispanic were extracted from Cancer Registry case reports and from Vital Records death certificates for the ten years 1989-1998 and aggregated by age group, sex, and year of event.

Alternative counts of cases and deaths for resident Rhode Island Hispanics were estimated using a validated US Census technique for identifying Hispanics by surname.¹ For resident males, data on surname from cancer case reports and from death certificates with cancer as the cause of death for the years 1989-1998 were searched for any of "639 most frequently occurring heavily Hispanic surnames" identified by the Bureau of the Census. ("Heavily Hispanic" means that 75% or more of the people with a particular surname self-identified as Hispanic on the survey.) For resident females, data on

father's surname from death certificates with cancer as the cause of death for the years 1989-1998 were searched for any of the 639 names. (Data on father's surname are not available on Rhode Island Cancer Registry case reports.)

Synthetic aggregates of Hispanic cancer cases and cancer deaths were created by adding the additional cases and deaths classified as Hispanic on the basis of the surname analysis to those deaths identified as Hispanic in case reports and on death certificates. These

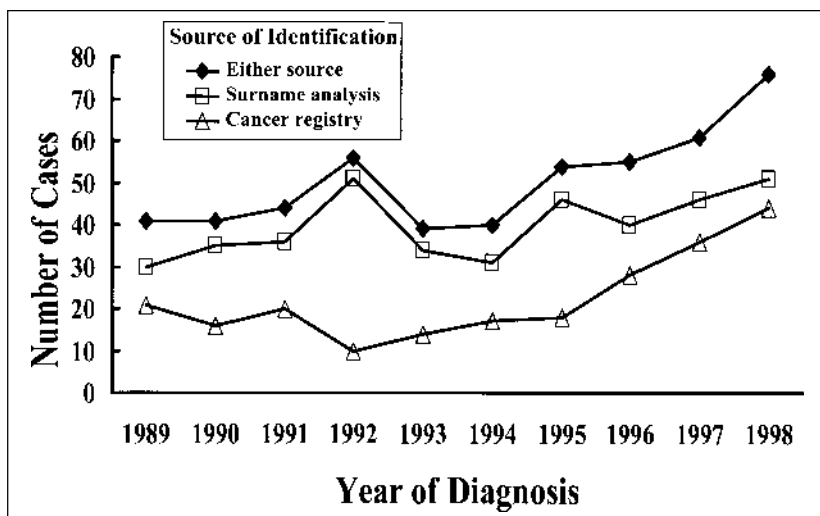


Figure 1. Number of Diagnosed Cases of Cancer among Hispanic Males, by Year and Source of Hispanic Identification, Rhode Island, 1989-1998.

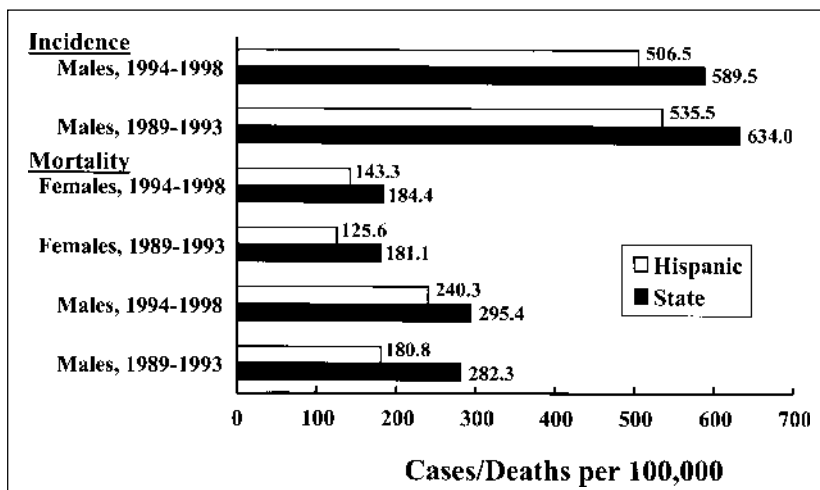


Figure 2. Age-adjusted Cancer Incidence and Mortality Rates per 100,000 Population, Hispanics and All Residents, by Sex and Year (Grouped), Rhode Island, 1989-1993 and 1994-1999.

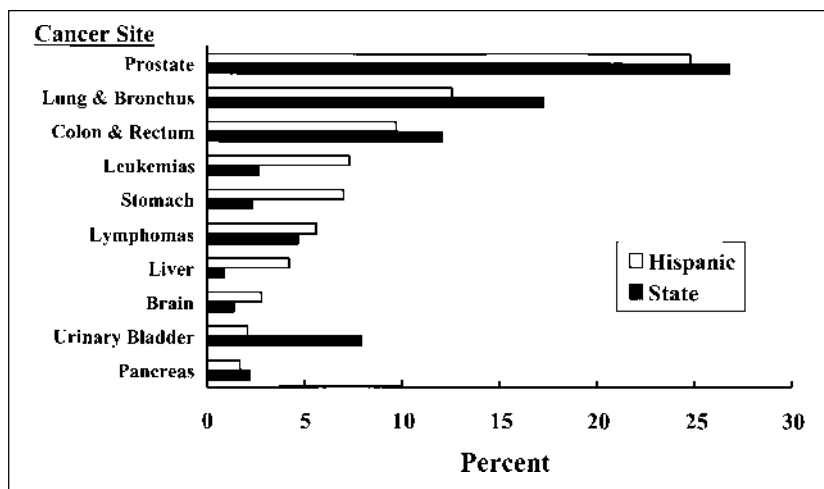


Figure 3. Anatomic Site of Diagnosed Cases of Cancer among Hispanic Males and among All Males, Rhode Island, 1994-1998.

estimates were combined with the estimates of the Hispanic population of Rhode Island for 1989-1998 to construct age-adjusted cancer incidence rates (males only) and age-adjusted cancer mortality rates (males and females). The year 2000 standard U.S. population was used for age-adjustment.

The synthetic aggregates of Hispanic cancer cases were also used to examine the proportion of cancer cases by anatomic site, comparing them with similar data for the Rhode Island population as a whole.

Results

Over the ten-year period examined, a total of 507 diagnosed cases of cancer were identified among Hispanic males, identified either from case reports or from the surname analysis. Of these, 224 (44.2%) were identified from case reports, and an additional 283 (55.8%) were identified only by Hispanic surname. By year, aggregation of cases from the two methods more than doubled the number of cases originally reported to the Cancer Registry as Hispanic in each of the first eight years of observation, and enhanced case counts substantially in 1997 and 1998 as well. (Figure 1) The number of cancer deaths among Hispanic males and females during this period showed similar enhancements from the surname analysis.

Figure 2 presents age-adjusted cancer incidence and mortality rates for resident Rhode Island Hispanic males and age-adjusted cancer mortality rates for resident Rhode Island Hispanic females in 1989-1993 and in 1994-1998, along with comparable rates for the state as a whole. In all comparisons, Hispanics have age-adjusted cancer rates that fall near but below age-adjusted cancer rates for the state as a whole.

The three most frequently occurring cancers by anatomical site during 1994-1998 were the same for Hispanic males in Rhode Island as for all males: prostate; lung and bronchus; colon and rectum. (Figure 3) Among other major sites, resident Hispanic males were more likely than resident males overall to develop cancers of the stomach and liver and leukemias, and less likely than resident males overall to develop cancer of lung and bronchus and of the urinary bladder. Patterns for the period 1989-1993 were similar.

Discussion

This analysis of data on cancer incidence and mortality among Hispanic Rhode Island residents supports conclusions concerning both patterns of disease and the reliability of the underlying data.

The use of an authoritative list of Hispanic surnames to augment Hispanic origin information on cancer registry case reports and death certificates approximately doubles the number of cancer cases that are presumably Hispanic in each of the two databases. Thus, these reporting systems are substantially understating the extent of cancer in this population.

Based on the rates produced from the synthetic aggregates, Hispanic cancer rates are generally similar to statewide cancer rates for all sites.

The site distribution for cancer incidence among male Hispanics follows the statewide distribution with two divergences worth noting. The observed higher proportions of stomach and liver cancers may be linked to the dietary patterns and infectious disease patterns (e.g., Hepatitis B) in developing countries and in immigrants from those countries. The high proportion of leukemias is consistent with a population whose age distribution is heavily weighted towards the very young.

Healthy People 2010 set a national goal of eliminating health disparities, in particular among disadvantaged racial and ethnic populations.² To support the accomplishment of this sweeping goal, public health surveillance data must have accurate and consistent reporting of race and ethnicity. The Rhode Island Department of Health has recently revised its policy on the collection of data on race and ethnicity and intends to improve the quality of the collected data as the changes in policy are implemented.³ The findings of this analysis show the clear need for such quality improvement efforts.

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The Rhode Island Cancer Council

Arvin S. Glicksman, MD, and Paul Calabresi, MD

Although Rhode Island's cancer incidence rate is not above the national average for an aging population in an urban industrial state in the Northeast, the number of deaths from cancer in Rhode Island exceeds the national average. Even with the state's excellent hospitals and educational facilities, coupled with a large corps of dedicated physicians, Rhode Island has a significant cancer problem. Based on the rule that "all politics is local," programs to improve the well being of Rhode Islanders must be local.

The Rhode Island Cancer Council was established to encourage cooperative, comprehensive and complementary planning among the public, private and volunteer sectors of the State by maintaining an integrated information network of resources for all to use. The Council became operational in May 1999; the Governor, the Senate Majority Leader, and the Speaker of the House of Representatives appointed the nine members to the Board, chosen for their leadership in oncology and in the community (Table I). [The national plan, "Conquering Cancer," calls for the establishment of comprehensive State-based cancer action plans in collaboration with all experts in the region - See "Cancer in the New Millenium," this issue).

In conjunction with the Department of Health, the Rhode Island Cancer Council has the responsibility to keep the Cancer Plan for the State of Rhode Island current and broadly applicable for all residents.

As one of our first tasks we re-examined the treatment algorithm for breast cancer. A panel of experts addressed the issue of screening and diagnosis. Another panel developed treatment guidelines. A third panel is addressing supportive care and quality of life. [This responds to the

recommendation of the NCLAC (Table II, Goal 10).] The cooperation and collegiality of the participants in developing the algorithm for breast care is encouraging and bodes well for its incorporation into medical practice in the State. Although mammography utilization in Rhode Island is above the national average, our death rate is 10% above the national average.

Colorectal cancer is the second leading cause of cancer deaths after lung cancer. Our death rate is 34% higher than the national average for men and 21% higher for women. Although early detection by regular screening can reduce our death rate, fewer than 50% of the population over the age of 50 have ever been screened for colorectal cancer. We recently surveyed two groups: the sixty-two gastroenterologists and surgeons who perform colonoscopy, and over 120 primary care physicians. The data point to a good deal of uniformity on screening guidelines across the specialists and the primary care physicians. [See "Colorectal Screening," this issue.]

The Council has embarked upon a broad public and professional education program. To reduce cancer deaths in Rhode Island, we must remove barriers to Rhode Island's state-of-the-art cancer programs. The Council maintains an integrated information network of resources. Our website, www.ricancercouncil.org, provides cancer-related information for Rhode Island, much of which is not available anywhere else (Table II).

Each month the Rhode Island Cancer Council provides a health column for an e-magazine, www.findri.com. Shortened versions of these columns are distributed to the churches, synagogues and mosques in Rhode Island for inclusion in their monthly bulletins.

The Rhode Island Cancer Council maintains a Cancer Forum (message board) on the Internet. In addition, the Council receives inquiries by telephone. Frequently people ask for assistance with the cost of medications. We relay information on the Drug Assistance Program at the University of Rhode Island and state programs. When appropriate we recommend clinical trials, referring callers back to their oncologists to discuss the appro-

TABLE I
Members of The Rhode Island Cancer Council
(for biosketches, see www.ricancercouncil.org)

- Paul Calabresi, MD, MACP** - Medical Oncologist, Chairman
- The Honorable J. Joseph Garrahy** - Former Governor of Rhode Island
- Arvin S. Glicksman, MD, FACP** - Radiation Oncologist, Executive Director
- Laura Hilderley, RN, MS** - Nurse Oncologist
- Louis Luzzi, PhD** - Dean, School of Pharmacy, University of Rhode Island
- Marlene McCarthy** - Breast Cancer Activist
- Charles McDonald, MD** - Dermatologist
- Patricia M. Nolan, MD, MPH** - Director, Department of Health
- The Honorable George Panichas** - Former Member of the State Legislature, Treasurer

TABLE II
Cancer Resources in Rhode Island
 (available on www.riancercouncil.org)

- Oncologists:**
 - Subspecialties
 - Geographic Area
- Mammography Centers:**
 - Geographic Area
 - Handicap Accessibility
 - Hours of Operation
 - Languages Spoken
- Support Groups:**
 - Disease Specific
 - Geographic Area
- Clinical Trials:**
 - Disease Site
 - Stage of Disease
 - Principal Investigator
 - Contact Information
- Smoking Cessation Programs:**
 - Geographic Area

priateness of their participation. Health insurers in Rhode Island cover the costs associated with Phase II, III, and IV clinical trials, as well as the costs of drugs used off-label.

The Rhode Island Cancer Council has developed free printed "Fact Sheets" on the most prevalent cancers and brochures on screening guidelines. (Table III)

Following up on Resolution 2000-H-6942 of the House of Representatives, the Rhode Island Cancer Council has contacted every city and town in Rhode Island, making our services available to develop cancer awareness programs. To date, Pawtucket, Foster, Warren, Warwick, Cranston, Tiverton, and Cumberland have responded; program development is in progress.

The Council has produced thirty-second information spots, shown on cable television, as well as on the wide screen in the Food Court at the Warwick Mall. The Council broadcasts radio spots on most of the popular stations. Frequently, the Council places cancer-related announcements in local newspapers.

Initially the Legislature asked the Council to catalogue all laws and resolutions in Rhode Island relating to the detection and/or treatment of cancer. We have completed this task. The Secretary of State now has a new category "cancer."

Last fall the Council sponsored a public information forum, "Successful Survivorship After Cancer." Dr. Julia Rowland, Director of the Office of Survivorship at the National Cancer Institute, was the keynote speaker. Over 150 individuals attended. Another public forum in conjunction with the Oncology Nurses Society on Quality of Life issues associated with end-of-life was held in spring of 2001, again drawing an audience of over 150. In the fall, a public forum on complementary care was held, a joint effort with the Rhode Island Chapter of the Leukemia and

Lymphoma Society and The Rhode Island Breast Cancer Coalition. The Council will repeat this program in different parts of the State.

Last year the Council renewed the Waterman Dialogue lectureships in conjunction with the American Cancer Society. Dr. Judah Folkman and Dr. James F. Holland spoke on "Cancer Treatment for the 21st Century." The Council will continue the Waterman Dialogue, bringing experts to Rhode Island. The Council has also sponsored lectures by visiting professors on bladder cancer, prostate and other urological cancers, and breast cancer.

The Rhode Island Cancer Council encourages new research programs. Last year the newly-formed Transition Support Grant Program, awarded four grants (each approximately \$15,000) to individuals who were in the process of applying for funds from national agencies but required support to enhance their competitiveness in the national pool. Three of the four were successful for a total of approximately \$6,000,000 in research funds coming into Rhode Island. The fourth grant is under review. This year the Council hopes again to fund four or five promising projects.

Last year the Council held a roundtable on "Women's Issues in Cancer," bringing together twelve community leaders in this field. Copies of this report are available from the Council office.

The NCLAC report stresses the importance of implementing a National Cancer Prevention Initiative that eliminates tobacco use, increases physical activity, and improves nutrition (Table II, Goal 12). The Rhode Island Cancer Council has been an active participant in the tobacco wars as a member of the Rhode Island Tobacco Leadership Coa-

TABLE III
Cancer Fact Sheets and Resource Brochures
 (available on www.riancercouncil.org and in printed form)

- Cancer Fact Sheets:**
 - Bladder Cancer
 - Breast Cancer
 - Cervical Cancer
 - Chemotherapy
 - Colorectal Cancer
 - Head & Neck Cancer
 - Hodgkin's Disease
 - Lung Cancer
 - Ovarian Cancer
 - Melanoma
 - Prostate Cancer
 - Stomach (Gastric) Cancer
 - Testicular Cancer
- Resource Brochures:**
 - Breast Prostheses
 - Cancer Screening Guidelines
 - Smoking Cessation Programs
 - Support Groups
 - Wigs

lition, a group representing essentially all of the organizations and programs working to reduce tobacco use in the State. The Coalition will launch a major advertising campaign to reduce tobacco use in Rhode Island.

The Rhode Island Cancer Council has undertaken a study of tobacco use on the campuses of the eleven colleges and universities in the State. We developed a questionnaire based, in large part, on the published Centers for Disease Control and Prevention (CDC) questionnaire, modified with questions concerning readiness to quit for current smokers. In the first year, this was administered to approximately 100 freshmen at each campus. Students have also been offered the opportunity to participate in focus groups concerning tobacco use. Referrals to smoking cessation programs are available. Of particular importance has been information from Focus Groups held on three campuses last year, giving us unusual insights to students' attitudes and influences. The questionnaire to the second group of freshmen have been distributed on the various campuses throughout the State and some of this year's data have already come in for collation.

This population is the fastest growing tobacco users. It had been generally accepted that children who did not start smoking by the age of 18 would probably never be addicted to tobacco; however, since the tobacco settlement, tobacco companies have targeted their media campaigns on 18 year-olds. Accordingly, we are seeing a rise in smoking among college students. Our program is designed to understand how students balance the pressures from the tobacco industry and from the various public health anti-tobacco campaigns. This program will yield information concerning attitude, about pressures coming from multiple sources. Importantly, the Behavioral Study Group of The Miriam Hospital/Brown University provides an intervention component.

"Conquering Cancer" urges a National Cancer Screening Initiative to increase substantially the early detection of cancer (Goal 9). The State of Rhode Island has been involved in screening programs for some time and has published a "Guide to Cancer Screening." In addition the Council has initiated a mammography program for early detection of breast cancer.

Annual screening mammograms are provided to all insured women in Rhode Island and are covered by Medicare for women over 65. For women without health insurance, the Department of Health has received funds from the Centers for Disease Control and Prevention to support mammograms for underinsured and uninsured women between the ages of 50 and 64. The program, working through the Community Health Centers, provides for outreach to the at-risk population. In addition, the program provides medical attention for

women with positive mammograms. This includes a biopsy of the suspicious area of the breast and a pathological analysis leading to a diagnosis. If cancer is detected, a network of providers is prevailed upon so that necessary surgery, medical oncology, radiation oncology, and psychosocial support are available. This program is not available to women below the age of 50 under the CDC grant. However, the State Legislature enacted legislation last year that established a comparable program for women between the ages 40 to 49. The State Health Department uses the existing network by extending the age eligibility. The Rhode Island Cancer Council funds this program under the legislation as passed. In the first six months of the fiscal year, 154 women have been screened. Since this program is now established by law, it will continue to provide services for women between the ages of 40 and 49 in future years.

Since its inception the Council has emphasized providing information in a timely and usable way to the public. It has developed programs with the assistance of a broad array of recognized leaders of oncology, and it has found strong support from many civic-minded public leaders without whom we could not have moved so rapidly to establish our programs. We believe that in this environment we can achieve our goal to diminish the burden of cancer in Rhode Island and improve cancer literacy throughout the State. The Council can also serve as a model for other community cancer programs as envisioned by the National Cancer Legislation Advisory Committee.

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Judicial Diagnosis

What Now?! The OIG Worries About Physician Billing, Reflected In the 2002 Work Plan

Lawrence W. Vernaglia, JD, MPH

The Bush administration has wavered in its reaction to the health care enforcement efforts and bureaucracies of the Clinton era. Former Wisconsin Republican Governor Tommy Thompson, the new Secretary of the **Department of Health and Human Services (HHS)**, appears torn between two desires: to loosen-up health care red tape, and to guard against those who abuse or neglect the elderly beneficiaries of government health programs. For example, in March 2001, Thompson pledged, "I am fairly certain, without saying for sure, there will be some modifications to simplify and to lessen the financial burden" of compliance with the mammoth Clintonian health information privacy regulations. However, two weeks later he allowed the regulations to roll out (in Thompson's words, "begin the process of implementing") on schedule, and without a single edit. Observers await promised interpretive guidelines that will mitigate some of the more onerous requirements.

On October 1, 2001, the HHS **Office of the Inspector General (OIG)**, under its new boss, Janet Rehnquist, daughter of Chief Justice William Rehnquist, released its Work Plan for 2002.¹ The Work Plan provides insights into the OIG's planned research and investigations for the coming year. This Work Plan does not depart from past policing policies of the physician community, as some had hoped. This essay will outline some of the OIG's plans for review of physician billing, patient care, and business practices, as reflected in the 2002 Work Plan, and will offer predictions for the government's enforcement interests.

The OIG's large-scale physician investigations of the 1990s related to billing by teaching physicians, interns and residents, and all doctors providing evaluation and management services. These investigations generated fear and confusion in the industry, particularly because the underlying requirements were vague, inconsistently applied, and difficult to translate into clinical practice. The OIG now promises new investigations into these same issues.

***Physicians at Teaching Hospitals**

The OIG plans an initiative "to verify compliance with Medicare rules governing payment for physician services provided in the teaching hospital setting and to ensure that claims accurately reflect the level of service provided to patients." Fortunately, the requirements for teaching physician billing have been made clearer since 1995.

*** Billing for Residents' Services.**

A related investigation will focus on whether hospitals are properly using their interns' and residents' **physician identification numbers (PIN)** when billing Medicare. Residents may bill Medicare only when they are "moonlighting." The OIG's Work Plan defines "moonlighting" as "providing medical treatment, other than in the resident's field of study, in an outpatient clinic or an emergency room." It is curious that the OIG omitted resident services in a physician's office as "moonlighting" for reimbursement purposes.

*** Physician Evaluation and Management Codes.**

The proper selection of **evaluation and management (E&M)** codes for patient encounters continues to be a bug-bear for a great many physicians. The **American Medical Association (AMA)** and the **Centers for Medicare and Medicaid Services (CMS, formerly HCFA)** have sparred over revisions to the E&M coding guidelines for a decade. Currently, physicians may use either the 1995 or 1997 coding guidelines in selecting codes. Consequently, it is extremely difficult for a physician to choose a particular E&M code level with any certainty - unless the physician is able to bill based on the amount of time spent with the patient. Despite this chaotic coding environment, the OIG plans to "determine whether physicians correctly coded evaluation and management services in physician offices and effectively used documentation guidelines." They will also evaluate whether the carriers are doing enough to hunt down improper E&M coding, a clear signal to the carriers to step-up their E&M enforcement efforts.

*** Services and Supplies Incident to Physicians' Services.**

A similarly confusing billing area relates to physician "incident-to" billing. Under these rules, physicians may bill for the services provided by other professionals, such as nurses, technicians, and therapists, as incident-to their professional services. Incident-to services must generally be provided by an employee of the physician and under the physician's "direct supervision." There remains a level of uncertainty as to what "direct supervision" means, and how and when to submit a bill for incident-to services. Moreover, there is a proposal to do away with the "employee" requirement that should be in effect by January 1, 2002. Nevertheless, the OIG plans to investigate physician com-

pliance in this area.

The OIG plans to investigate two customary relationships between physicians: consults and emergency room staffing arrangements.

*** Consultations.**

This study promises to review whether physician consultations are properly billed. Under Medicare policy, consultations are generally reimbursable if made at the request of the patient's attending physician, the consulting physician reviews and examines the patient's condition, and the report of the consult is made part of the patient's permanent medical record. [Medicare Carriers Manual § 2020.C.] The OIG did not indicate in the Work Plan what vulnerabilities exist in the consulting relationship. However, in the past several years, the government has loosened restrictions on billing for consultations. It will be informative if the OIG believes that these policy changes have produced undesirable results.

*** Reassignment of Benefits.**

The OIG is interested in investigating how physician staffing or practice management companies manage hospital emergency rooms. A potential vulnerability is in the reassignment of Medicare payment from the physician to the staffing company. If the company does not employ the physician - and state law may prohibit the employment of

doctors by such an entity - then the physician should not reassign payment rights to the company.

*** Advance Beneficiary Notices.**

The government continues its quest to be sure that Medicare providers and suppliers offer patients **advance written notice (ABNs)** prior to a service that may not be medically necessary, and agree to submit a "demand bill" to Medicare if the patient so desires, or else be unable to bill the patient privately. The OIG will look into whether physicians are following the ABN rules, "especially with respect to noncovered laboratory service."

Finally, three other procedure-specific investigations are planned regarding inpatient dialysis services, bone density screening, and preventative services such as annual screening mammography for all women aged 40 and over; screening pap smear and pelvic exams every 3 years; colorectal screening; and bone mass measurements to identify bone mass, detect bone loss, or determine bone quality, all of which were made reimbursable by the Balanced Budget Act of 1997.

These proposed investigations are varied, but one feature is clear: the OIG plans to continue reviewing some of the billing rules that are the most complex and confusing to physicians. Whether these studies result in recommendations to clarify the rules, or prosecutions of more doctors



Vital Statistics

Rhode Island Department of Health

Patricia A. Nolan, MD, MPH, Director of Health

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	January 2001	12 Months Ending with January 2001		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	291	3,063	309.9	4,109.0**
Malignant Neoplasms	214	2,401	242.9	6,495.0
Cerebrovascular Diseases	58	503	50.9	770.0
Injuries (Accident/Suicide/Homicide)	24	364	36.8	6,792.5
COPD	53	481	48.7	372.5

Vital Events	Reporting Period		
	July 2001	12 Months Ending with July 2001	
	Number	Number	Rates
Live Births	1142	13,428	13.6*
Deaths	775	10,199	10.3*
Infant Deaths	(4)	(98)	7.3#
Neonatal deaths	(4)	(84)	6.3#
Marriages	929	8,557	8.7*
Divorces	246	3,266	3.3*
Induced Terminations	451	5,488	408.7#
Spontaneous Fetal Deaths	90	995	74.1#
Under 20 weeks gestation	(81)	(919)	68.4#
20+ weeks gestation	(9)	(76)	5.7#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 988,480

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population
** Excludes two deaths of unknown age.

Rates per 1,000 live births

for their inability to navigate these regulatory mazes, remains to be seen.

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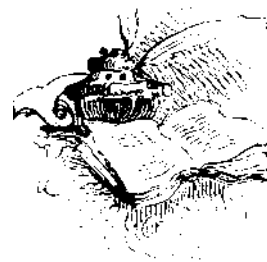
1. http://www.hhs.gov/oig/wrkpln/2002/Work_Plan_2002.htm.

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– A Physician’s Lexicon –



Medical Lexicon: Nausea and Vomiting

“Everything is gratuitous, the garden, this city and myself. When you suddenly realize it, it makes you feel sick and everything begins to drift. . . that’s nausea.”

Jean Paul Sartre wrote this fragment of autobiographic self-appraisal in 1938, a part of his larger commentary called “Nausea.”

Nausea - and its intimate companion, vomiting - harkens back to an earlier Greek word, *nautio*, meaning seasickness, and is etymologically related to the Latin, *nauticus*, meaning from the sea, and its many English language derivatives, including nautical, nautilus [a genus of mullusk], navy, navigate, as well as argonaut, aeronaut, cosmonaut and astronaut [all of whom, in principle at least, are subject to seasickness]. There also was a prominent character in ancient Greek legend called Nausicaa. She was the daughter of Alcinous, king of the Pheacians. Her name, literally, means burner of ships.

Dictionaries and high school English instructors insist that nausea, nauseous and nauseated are not interchangeable. Nausea defines the clinical state of queeziness and vertigo; nauseous defines those chemical or physical states which cause nausea; and to be nauseated is to be a victim of nausea.

Vomiting, the inseparable partner of nausea, comes from the Latin, *vomere*, meaning to throw up or, in an earlier meaning, to ulcerate or poison. A vomitory is any agent which causes vomiting and vomit is the term to describe that which is vomited. The Latin word, *vomer*, defines a plowshare, namely, an agricultural tool which throws up the soil. And the bone in the nasal septum is called vomer because of its resemblance to a plow. [Sudden blows, incidentally, to the facial vomer are known to cause acute nausea and vomiting.]

The Latin, *vomere*, is related to and originally derived from an earlier Greek word, *emetos*, also defining the act of vomiting. This Greek word has produced a number of direct English language offspring of its own, including emesis [the act of vomiting], hematemesis [blood-tinged vomitus], melanemesis [black-colored vomitus], copremesis [fecal vomiting] and emetine, the principal alkaloid of ipecac, a strong emetic.

And then there is Nux Vomica, a prominent member of the 19th Century physician’s pharmacopeia. Nux Vomica [from the Latin, literally meaning the nut that poisons] is extracted from the seed of an East Indian tree containing strychnine. [The vomica, in this case, refers back to the poisonous quality of the seed extract since *nux vomica* generally does not cause vomiting. It was typically prescribed in the form of a weak tincture which allegedly stimulated the cardiac and respiratory systems.]

The agent, strychnine, was first isolated from the plant *Strychnos ignatii* in 1818 by the French chemist, Pelletier. *Strychnos*, in Greek, meant deadly nightshade and may have been derived from an earlier Greek word, *trychno*, meaning a destroying agent.

– Stanley M. Aronson, MD, MPH



NINETY YEARS AGO

[JANUARY, 1912]

Among the obituaries was one for Oliver Henry Arnold, born in Coventry, Rhode Island. Dr. Arnold had received his AB from Brown ('65), his MD from Harvard ('67), his AM from Brown ('68). A member of the American Institute of Homeopathy, he practiced in Providence and Pawtucket. "He was interested in the biological and comparative anatomy departments at Brown University and left a large part of his property for their support." [The Arnold Laboratory at Brown was named in his memory.]

D.L. Richardson, MD, the Superintendent of the City Hospital at Providence, contributed "Laryngeal Stenosis following Diphtheria." The condition developed in 1-3% of cases. "The common impression that intubation, particularly if roughly performed, is responsible for the condition is erroneous. It occurred as frequently before O'Dwyer made intubation practicable, and as frequently now in countries where tracheotomy is more general than intubation." At the Providence City Hospital, Dr. Richardson opted to give the larynx a rest by tracheotomy and removal of laryngeal tube. He described the cases of 3 young children.

Dr. Charles V. Chapin, in "Health of Providence," reported 255 deaths for October 1911, or 12.95 per 100,000 (based on an estimated population of 231,848). This was "the lowest death rate ever recorded for October." November's rate was higher [276 deaths, a rate of 14.46], the same as for November 1908, but lower than average. Diphtheria was more prevalent; scarlet fever, less.

FIFTY YEARS AGO

[JANUARY, 1952]

Lawrence A. Senseman, MD, contributed, "Who Sees the Psychiatrist?" He found encouraging "this new acceptance of the psychiatrist by his fellow practitioners and their acceptance of the advice and opinion regarding the emotional aspects of the patient's illness." To answer the question of the title, he surveyed 250 of his consecutive new patients. Roughly half (52%) were women, 60% were between 21 years and 50 years of age; 66% had functional problems; 27% had neurological problems. Dr. Senseman routinely gave complete physical exams ("as much a part of the psychiatrist's armamentarium as it is for the internist...")

An editorial, "Progressive Health Education," praised the City of Providence for issuing 16-page Health Record booklets to parents of each newborn child.

TWENTY FIVE YEARS AGO

[JANUARY, 1977]

Paul B. Metcalf, MD, FACS, in "Perspectives on Hospitalization," called for "an objective, reproducible, widely applicable means of measuring quality of care." In particular he cited the shortfall of ALOS (average length of stay) as the overall barometer. The ALOS didn't include transfers, hospital size, or patient's status. The ALOS, though, was over-emphasized as one solution to reducing costs.

W.E. Lockhart, Jr. MD, FACA, who practiced in Alpine, Texas, near Big Bend National Park, contributed "Treatment of snakebite." An accompanying editorial urged physicians to recognize the symptoms.

Gerald E. Meyer, PharmD, Louis P. Jeffrey, MS, George K. Boyd, MD, Charles D. Mahoney, MD, and Philip N. Johnson, PhD, contributed "Theophylline derivatives: A Current review." They explained, "With improved understanding, theophylline preparations can be more judiciously utilized."

An editorial, "Lifestyle and Health," highlighted the shifting role of the patient. "For centuries it has been the patient who has been the supplicant, asking the physician to heal wounds, restore energies, or even fend off death. Now conversely, in the face of escalating health care costs, it may well be the time for the physician to enlist the help of his patients in order to balance our books." The editorial cited the "self-induced ailments," like emphysema, cirrhosis of the liver, peptic ulcer, and hypertension.



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