

A Publication of
**M. D. Anderson
Cancer Center**

4
Online Answers
Find clinical trials, patient referral forms, and educational resources on the Web.

6
Professional Conferences
A list of upcoming scientific and medical conferences is provided.

CME

7
Food for Thought
A few small changes at a time can improve health and reduce the risk of cancer.

REPORT TO PHYSICIANS

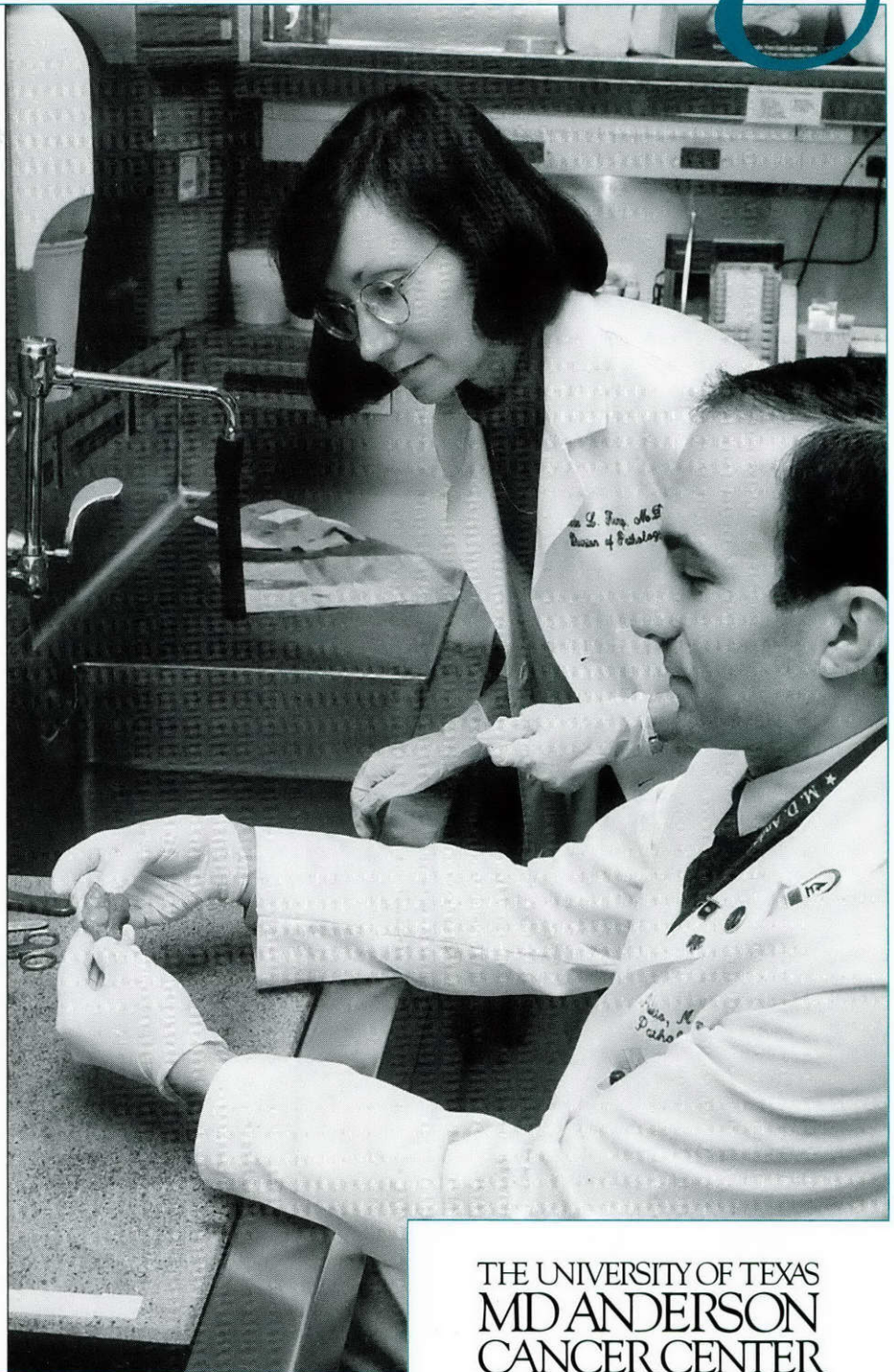
JANUARY 2001 Vol. 46, No. 1

Oncology

New Melanoma Staging System Reflects Key Prognostic Factors

by Kerry L. Wright

Since its establishment in 1959, the American Joint Committee on Cancer (AJCC) has recognized the "dynamic" nature of cancer staging and has organized regular reviews of standard staging systems. Most recently, the staging criteria for 13 common cancer disease sites have come under review in preparation for publication of the sixth edition of the AJCC Cancer Staging Manual. (Continued on next page)



Dr. Bonnie Kemp and Dr. Victor Prieto, associate professors in the Department of Pathology, examine a melanoma biopsy specimen in the laboratory. Advances in pathologic and surgical techniques contributed to the development of a new melanoma staging system.

THE UNIVERSITY OF TEXAS
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New Melanoma Staging System

(Continued from page 1)

The first group to make recommendations to the AJCC was the 18-member Melanoma Staging Committee. For the first time, the committee's recommendations were data-driven—developed after compilation and analysis of complete prognostic factor data from more than 17,000 patients with melanoma from 13 international centers—rather than derived only from a review of the literature. The results of this analysis, as well as advances in surgical and pathologic techniques, led to the development of a new melanoma staging system, which was recently approved by the executive committee of the AJCC and by the International Union Against Cancer. The revised criteria, which include changes to the T (primary tumor), N (regional lymph node), and M (distant metastasis) portions of the TNM classification as well as to the stage groupings, will be implemented worldwide and used by

more than 5,000 tumor registries in the United States when the new *AJCC Cancer Staging Manual* is published in 2002.

"There are dramatic changes in the staging system that will better reflect prognosis and more accurately represent the nature of the disease," said Jeffrey E. Gershenwald, M.D., an assistant professor in the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center and a member of the Melanoma Staging Committee. M. D. Anderson Professor of Surgical Oncology Merrick I. Ross, M.D., is also a member.

Owing to the histologic nature of several newly incorporated prognostic factors, pathologic analysis will play a larger role than ever in the new system, said Victor G. Prieto, M.D., an associate professor in the Department of Pathology. Cox multivariate regression analysis of the data identified several prognostic

factors that were being used in clinical trials but had not been reflected in the previous staging system, including ulceration of the primary tumor, number of lymph nodes with metastases, site of distant metastases, and elevation in levels of serum lactate dehydrogenase (LDH).

"Because of these features, pathology will definitely be key in staging," said Dr. Prieto. "Most of the staging criteria—I would say in more than 90% of tumors—will be based upon the pathology report," he said.

For the T classification, tumor thickness (Breslow thickness) is now considered a more important prognostic variable than level of invasion (Clark level). The current breakpoints for Breslow thickness and for subdividing the T classification—0.75 mm, 1.5 mm, and 4 mm—will be replaced with whole-integer breakpoints of 1 mm, 2 mm, and 4 mm, which are as reliable as the old ones and more clinically convenient, said Dr. Gershenwald. The new system also inaugurates the use of ulceration as a prominent staging criterion. For a given T subclass, the presence of ulceration will place the disease in the next highest subclass.

With respect to the N classification, most studies showed that the number of lymph nodes with disease present was more prognostically significant than the size of the largest metastasis, said Dr. Gershenwald.

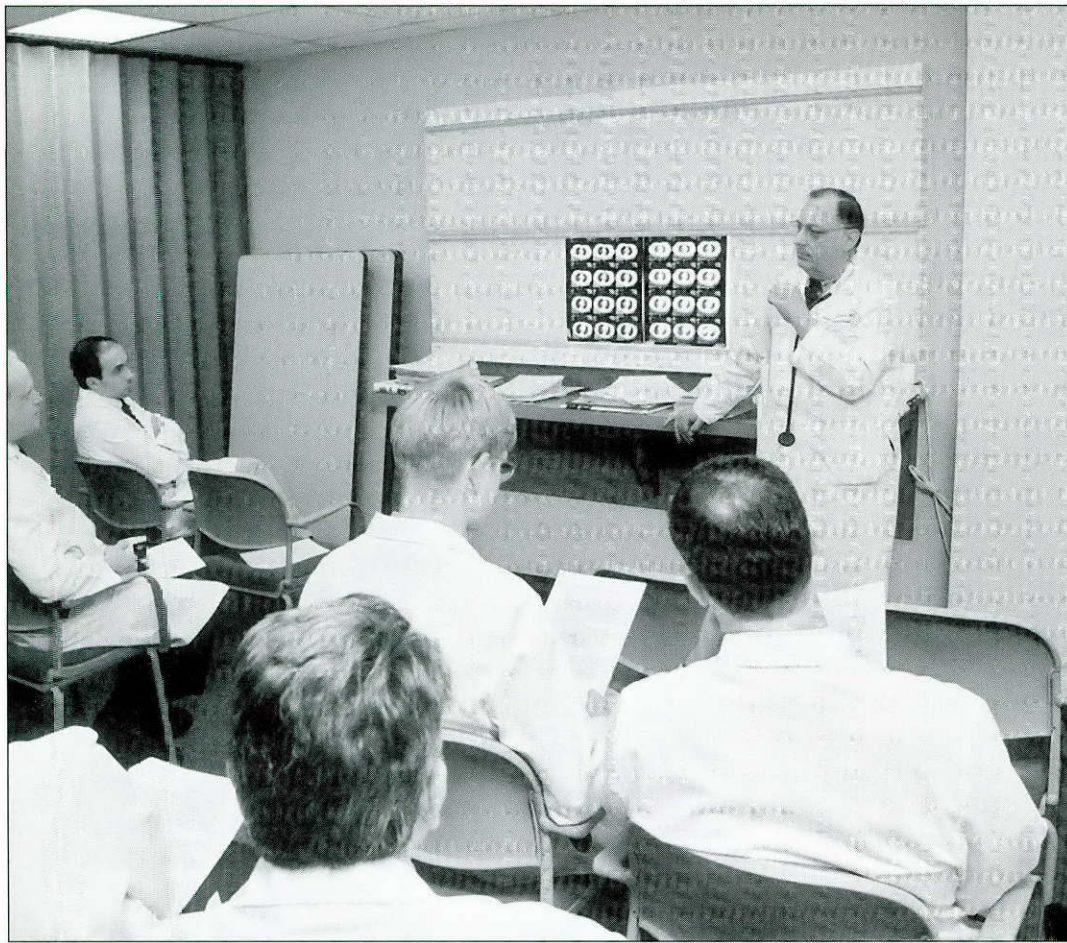
"So now, rather than the size of the lymph node metastasis, the number of lymph nodes will be the stratification scheme," he said. Moreover, the data showed that ulceration, traditionally a prognostic factor for primary tumors, was an independent adverse factor even among patients with node-positive disease. Therefore, the presence of ulceration will place the disease in the next N subclass. The nodes will be classified according to whether they have micro- or macrometastases, as patients with clinically occult metastases fared better than those with clinically evident disease.

Disease-Site Task Forces to Recommend Staging Revisions

The American Joint Committee on Cancer (AJCC) has organized the following 13 disease-site task forces to make recommendations for revised TNM staging criteria for the sixth edition of the *AJCC Cancer Staging Manual*:

Bone	Head and Neck
Breast	Lung and Esophagus
Central Nervous System	Lymphomas
Colorectal	Melanoma
Digestive System	Ophthalmic
Genitourinary	Soft Tissue Sarcoma
Gynecologic	

Each multidisciplinary task force consists of at least eight members who are governed by new policies and procedures that require them not only to review relevant literature before making their recommendations but also to prepare new data and to perform their own meta-analyses when sufficient data are available. The Melanoma Task Force is the first to have its recommendations approved by the executive committee of the AJCC and the International Union Against Cancer.



“We are still dealing with patients, and we try to get the best diagnosis and the best treatment possible for a particular patient. That is our goal.”

— Victor G. Prieto, M.D.,
associate professor,
Department of Pathology

Faculty and staff listen to a presentation during a weekly multidisciplinary melanoma conference at M. D. Anderson. Here, attendees from many departments discuss clinical and pathologic information to develop workup and treatment recommendations for patients with complex cases of melanoma.

Further analysis showed that patients with metastases to the skin, subcutaneous tissue, or distant lymph nodes had better prognoses than those with metastases to other sites. The staging committee concluded that the site of metastasis was more predictive of outcome and more reliable than the number of metastases. Thus, under the new criteria, a patient's M classification will be determined by location of metastases.

“In addition, for the first time in melanoma staging, a serum factor will be incorporated,” said Dr. Gershenwald, “because the presence of an abnormally high lactate dehydrogenase level in patients with distant metastatic disease seems to portend the worst prognosis.” In the new system, patients with distant metastases and elevated serum LDH levels will be assigned to the highest M subclass, regardless of where the metastases are located.

Information from the separate TNM classifications is also combined to identify stage groupings, traditionally

defined as stages I to IV. Since pathologic staging is more precise than clinical staging, in the revised system, patients will be assigned stage subgroupings based on ulceration, number of metastatic nodes, and type of metastases, as determined by microstaging and available data from lymphadenectomy or sentinel lymph node biopsy.

Sentinel node biopsies are now routinely performed on patients with tumors at least 1 mm thick, so most patients will have some type of pathologic information available, said Dr. Gershenwald. According to Dr. Prieto, biopsy specimens will continue to be evaluated by staining with hematoxylin and eosin, followed by immunohistochemical analysis, which recently has been shown to be more sensitive than traditional histology. Several members of the Department of Surgical Oncology, including Dr. Ross, Dr. Gershenwald, Associate Professor Paul F. Mansfield, M.D., and Associate Professor Jeffrey E. Lee, M.D., are currently involved in the

multi-institutional Sunbelt Melanoma Trial to compare the sensitivity of standard histologic examination with that of the polymerase chain reaction (PCR).

“Using PCR, we may be able to identify very early spread of melanoma to lymph nodes,” said Dr. Lee, adding that the technique could be able to detect a single melanoma cell in a pool of up to one million normal cells. Dr. Ross is the institutional study chairman of the Sunbelt trial, in which patients with a sentinel lymph node that is negative for melanoma by microscopic evaluation but positive for the possible presence of melanoma by PCR are randomized to receive one of three possible treatments: observation, lymph node dissection, or lymph node dissection plus interferon alfa-2b for one month.

“Only by doing these studies will we be able to determine if extra treatments are beneficial for patients with very early spread of melanoma,” Dr. Lee said.

(Continued on page 4)

New Melanoma Staging System

(Continued from page 3)

When standard histological and immunohistochemical analyses are used, the actual time spent making or confirming a diagnosis of melanoma varies depending on the complexity of a particular case. Pathologists can spend anywhere from 15 seconds to several hours examining a single slide, and a diagnosis can be made from just one slide—prepared from a standard punch biopsy, for example—or up to 200 slides for larger tumors and more difficult cases, said Dr. Prieto. However, knowing the clinical information for a specific case can also be of tremendous help in making a diagnosis.

“According to the old school, it had to be a blinded diagnosis so you would give the diagnosis with whatever material you had. But today, most of the time pathologists insist on having the clinical information,” Dr. Prieto said. For example, he continued, if an elderly person comes to the clinic with a pigmented lesion on the face and the biopsy results do not provide a distinction between melanoma and sun damage, then just knowing the size of the lesion can help in the differential diagnosis.

For more complex cases, however, it is important for physicians from many disciplines to meet and discuss all available clinical and pathologic information. At M. D. Anderson, surgeons, pathologists, oncologists, radiation therapists, nurses, and physician’s assistants meet once a week at a multidisciplinary planning conference, during which selected patients are examined and workup and treatment recommendations are made.

So, although the new melanoma staging system will rely heavily on pathologic data, “We are still dealing with patients,” said Dr. Prieto, “and we try to get the best diagnosis and the best treatment possible for a particular patient. That is our goal.” ●

FOR MORE INFORMATION, contact Dr. Gershenwald at (713) 792-6936, Dr. Prieto at (713) 792-3187, or Dr. Lee at (713) 792-7218.

Updated M. D. Anderson Web Site to Meet the Online Needs of

by Dawn Chalaire

Before launching its redesigned Web site in September 2000, The University of Texas M. D. Anderson Cancer Center conducted extensive marketing research, gleaning insights from patient focus groups and interviews with referring physicians, faculty members, and the public. What the researchers discovered was that patients and physicians often want very different things from a medical center Internet site.

According to Alan Powell, director of Internet Services, patients usually arrived at the M. D. Anderson Web site looking for information about their specific diagnosis and trying to make a decision about whether to seek treatment at M. D. Anderson. Physicians, on the other hand, wanted to know how the Web site could facilitate and support the referral process.

“For example,” Powell said, “they wanted to know if the new Web site could do a better job of helping them find a doctor to talk to about their patient.”

The physicians interviewed were also interested in viewing educational programs, using the Internet and e-mail in the referral process, and finding clinical trials for their patients.

The Web site’s new home page accommodates these divergent interests by immediately directing users to one of three categories—“Patients and Public,” “Cancer Professionals,” and “About M. D. Anderson.” The home page for cancer professionals contains clinical and educational resources and information about M. D. Anderson faculty

through a staff directory and the online *Research Report and Guide for Referring Physicians*.

Information about clinical trials at M. D. Anderson can be accessed through both the “Cancer Professionals” and “Patients and Public” home pages. In the coming year, a search engine will be added to the clinical trials site.

The site also makes it easier than ever for physicians to refer their patients to M. D. Anderson, with a revised online referral form that is simple to use. Since an online referral form was introduced with the original Web site in December 1997, about 2,000 patients have been referred to M. D. Anderson via the Internet.

“That’s been very effective, and it continues to grow,” Powell said. “We’ve seen a very dramatic increase in the number of patients referring themselves. We’ve seen a much steadier increase in the number of physicians and physician offices using the Web site.”

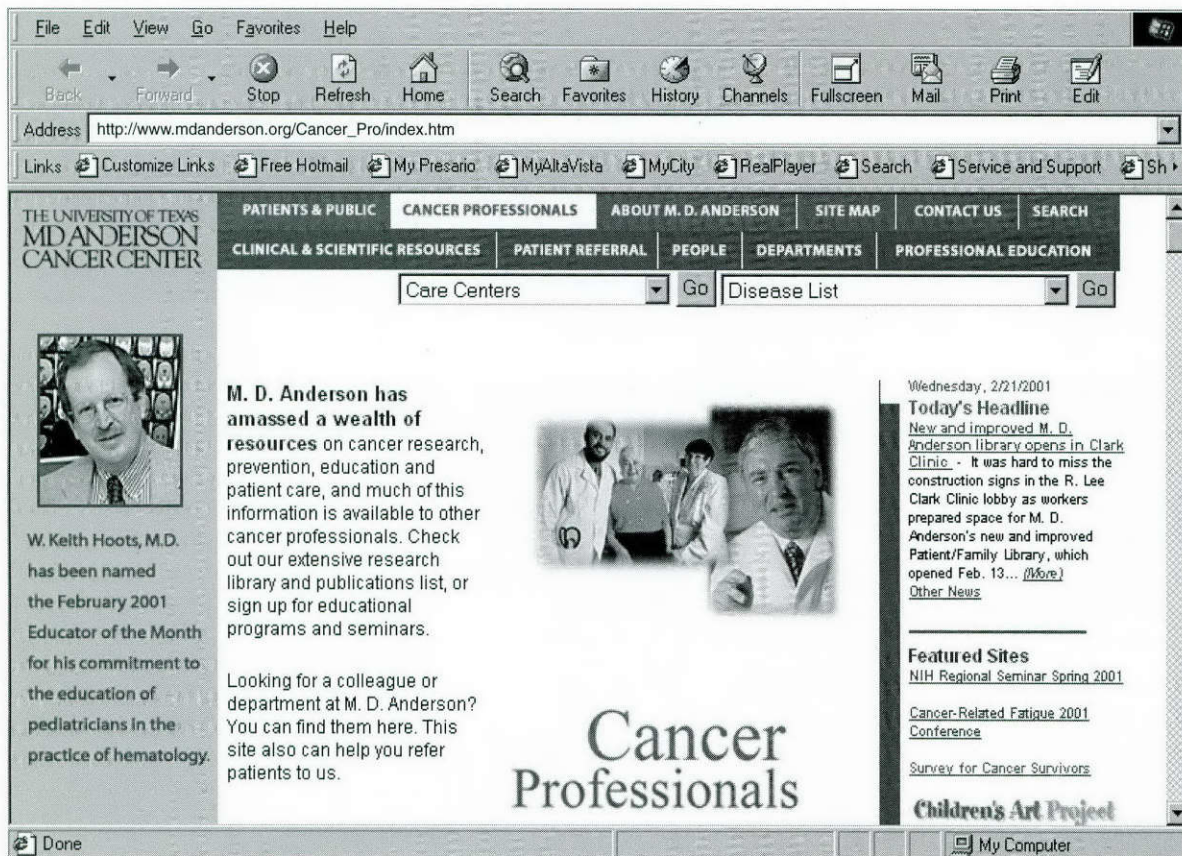
Physicians who explore the Web site will discover a new physician relations page (www.mdanderson.org/PhysicianRelations) that provides referring physicians with easy, comprehensive access to the M. D. Anderson programs and services that are designed to support physicians in the community.

Mitchell Morris, M.D., senior vice president and chief information officer at M. D. Anderson,* said that one of the most important new features of the redesigned site is a content management tool that allows many different departments within the institution to simultaneously create content for the site.

“That is going to give us the potential to add many more kinds of features and functions over the coming months and years,” Dr. Morris said.

In the future, physicians will be able to earn continuing medical education (CME) credits online through Net Grand Rounds, a program that replays a videotape from M. D. Anderson Grand

Site Designed Physicians and Patients



From the "Cancer Professionals" home page on the updated M. D. Anderson Web site, physicians can find links to clinical and scientific resources, information about patient referral, professional education, and lists of faculty and staff.

Rounds presentations and includes a transcript of the presentation, slides, and links to related information.

"Very often, doctors don't have the time to go to a meeting but can take 10 minutes to come online and view some of this content, take a test, and get some CME credit," Dr. Morris said.

A similar approach to patient education is in the works. Soon, patients will be able to view patient education content about cancer prevention and detection, cancer treatment, managing side effects, and supportive care issues.

Also under development is a highly secure Web site for M. D. Anderson patients. Called "mymdanderson.org," the site will allow patients to access information using a password and identification code that will be given to them upon admission. (The information on the Web site will be encrypted, and the software used will meet all

"We've always felt that the more patients know about their treatment and their disease, the better they do with their treatment program."

**— Mitchell Morris, M.D.,
senior vice president
and chief information officer***

federal and state regulations governing patient privacy.) Patients will be able to use the site to refill prescriptions, check their schedule and request changes, view their billing and insurance information, and make payments

online. They will also be able to request customized patient education materials to be delivered to their home.

"We've always felt that the more patients know about their treatment and their disease, the better they do with their treatment program," Dr. Morris said.

Dr. Morris stressed that redesigning and adding content to the Internet site is an ongoing, collaborative project.

"It really is a team effort. So many people have put their time into this and their expertise and their talent. It's been fun to watch it grow," he said. ●

The M. D. Anderson Internet site address is www.mdanderson.org.

**Effective January 31, 2001, Dr. Morris resigned as senior vice president and CIO to become vice president for the First Consulting Group. As a consultant with M. D. Anderson, he will continue to contribute to the development of mymdanderson.org.*

Educational Conferences Explore Issues Related to Cancer Care and Research

The Office of Continuing Medical Education and Conference Services at The University of Texas M. D. Anderson Cancer Center will be sponsoring several educational conferences from late March through early October 2001. Topics include fatigue, cancer biology, mechanisms of cell death and disease, and leukemia in adolescents and young adults.

Many conferences offer continuing education credit, including American


Medical Association/Physicians Recognition Award (AMA/PRA) Category 1 and other professional certifications (approved according to the criteria of the Accreditation Council for Continuing Medical Education).

For additional information and updates about these conferences, as well as other conferences and in-house educational events at M. D. Anderson, see the Continuing Medical Information and Conference Services Web site at www.mdanderson.org/~meetings or

contact Conference Services by phone at (713) 792-2222, facsimile at (713) 794-1724, or e-mail at sroy@mdanderson.org.

Other events of interest to oncologists include the 92nd Annual Meeting of the American Association for Cancer Research, scheduled for March 24–28 in New Orleans, and the 37th Annual Meeting of the American Society of Clinical Oncology, which will be held May 12–15 in San Francisco. ●

Professional Conferences Sponsored by The University of Texas M. D. Anderson Cancer Center

Date	Conference (Location)	Chairpersons (Contact)	Continuing Education Credit (Credit Hours) 
March 23–24	Management of Cancer Treatment–Induced Diarrhea and Carcinoid Syndrome (New Orleans)	Jaffer A. Ajani, M.D. (Veronica Moreno, 713-792-4421)	AMA/PRA Category 1 (4.0)
March 24–25	2nd Annual Cancer-Related Fatigue Conference (Houston)	Charles S. Cleeland, Ph.D.	AMA/PRA Category 1 (12.5)
April 24–25	Japan/U.S. Cancer Therapy Symposium (JUCTS) New Concepts in the Biology and Treatment of Cancer (La Jolla, CA)	Ritsuko Komaki, M.D.	AMA/PRA Category 1 (12.0)
April 28	Houston Society of Clinical Pathologists 41st Annual Conference “Tumors of the Kidney, Urinary Bladder, and Testis: Recent Advances in Diagnosis and Classification” (Houston)	Jae Y. Ro, M.D., Ph.D.	AMA/PRA Category 1 (6.5)
May 5–6	6th Annual Hands-On & High-Tech Workshop for the Difficult Airway (Houston)	Joseph S. Chiang, M.D. (Mary Ann Schneider, 713-792-6911)	AMA/PRA Category 1 (12.5)
May 16–18	Conferencia Internacional de Hemato-Oncología Médica (Houston)	Sergio Giralt, M.D., and Jorge E. Cortes, M.D.	
June 1–2	6th Human Dimensions Conference (Houston)	Eduardo Bruera, M.D.	
June 2–5	2nd Mechanisms of Cell Death and Disease: Advances in Therapeutic Intervention (Falmouth, MA)	Timothy J. McDonnell, M.D., Ph.D.	AMA/PRA Category 1 (18.5)
September 7–8	AYA 2001: Issues in Adolescent and Young Adult Leukemias (Houston)	Sima Jeha, M.D., and Hagop M. Kantarjian, M.D.	AMA/PRA Category 1 (12.0)
September 20–22	Ovarian Cancer Conference (Houston)	David M. Gershenson, M.D.	AMA/PRA Category 1 (16.0)
September 30– October 2	23rd Annual Pharmacy Symposium (Houston)	Sharon Bronson, M.S., and William Dana, Pharm.D.	
October 2–5	54th Annual Symposium on Fundamental Cancer Research: Mechanisms for Cell Growth & Differentiation (Houston)	Richard Behringer, Ph.D., and Sharon Roth, Ph.D.	AMA/PRA Category 1 (15.5)



Preventing Cancer: Food for Thought

We've all heard about the importance of a healthy diet, but did you know that the foods you eat—or don't eat—can affect your risk of cancer? According to the American Cancer Society (ACS), approximately one third of the 500,000 cancer deaths in the United States each year are linked to diet and nutrition. But changing the way you eat now and incorporating more healthy foods into your diet can actually help reduce your risk of cancer.

Certain nutrients such as vitamins can protect DNA from damage and can prevent or delay the development of cancer, even in people with increased genetic risk. A low-fat, plant-based diet—including ample servings of vegetables, fruits, whole grains, and beans—seems to offer the best protection against many kinds of cancer, including those of the esophagus, oral cavity, stomach, colon, rectum, and lungs.

Eating five or more servings of fruits and vegetables every day is the “single most important dietary factor for lowering risk of cancer,” according to the ACS. Unfortunately, this is not the way many Americans eat. Surveys show that most people eat an average of only two to three servings of fruits and vegetables per day and consume too many high-calorie, high-fat foods. Researchers from the National Cancer Institute determined that only 1% of American children meet all the national dietary recommendations for daily servings of grains, vegetables, fruits, meat, and dairy foods, and 16% meet none of the recommendations.

Improving your diet may seem daunting, but it doesn't have to be. A series of small changes—substituting a low-fat food for a high-fat one and including fruits and vegetables in your meals, for example—can reap big rewards. Here are some dietary guidelines, along with suggestions to help you put them into practice.

■ **Eat five to nine servings of fruit and vegetables each day.**

(A serving is a 1/2 cup of cooked fruit or vegetable or one medium-sized raw fruit or vegetable.) It's not as hard as you think. Try to include one or two servings with every meal or snack. Have fruit available for healthy snacks and pre-cut vegetables in the refrigerator ready to eat with a nonfat dip. Add some extra grated or chopped vegetables to your casseroles.



■ **Eat six to 11 servings of whole-grain foods each day.**

(A serving is one slice of bread, 1/2 cup cooked pasta or rice, or one ounce of cereal.) Look for foods that list whole grain as their first ingredient. These are rich in dietary fiber, which may reduce your risk of colorectal cancer.



■ **Eat a low-fat diet.** High-fat diets are associated with cancers of the breast, colon, and prostate.

Switch to low-fat (1% fat or less) or nonfat dairy products. Remove fat from all meat and skin from chicken before cooking, or substitute beans for meat in your meals.



■ **Limit alcohol consumption.**

If you drink at all, don't have more than two drinks per day (no more than one drink per day for women). Drinking is linked to breast, colon, and liver cancers and, when combined with smoking, greatly increases the risk of lung cancer and head and neck cancers.



■ **Remember, calories do count.**

Obesity is defined as being 20% or more above your ideal weight. Being obese can increase your risk of certain types of cancer (including breast and colon cancer) as well as cause a myriad of other health problems including diabetes, high blood pressure, stroke, and coronary heart disease.



Changing your eating habits at any age can improve your health and reduce your cancer risk. Start embracing these recommendations today, and share them with those you care about. ●

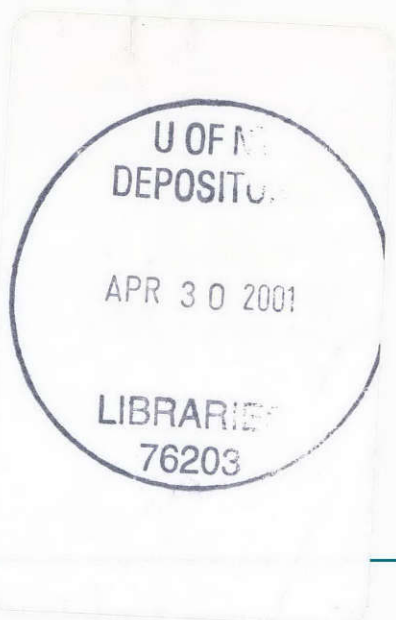
For more information, contact your physician or contact the M. D. Anderson Information Line:

☎ (800) 392-1611 within the United States, or

☎ (713) 792-6161 in Houston and outside the United States.

January 2001

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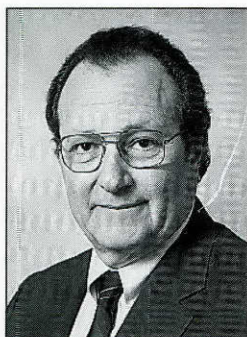


DiaLog

Leukemia: Setting the “Stage” for Effective Treatments

Emil J Freireich, M.D.
Professor, Department of Leukemia

The correct staging of a malignant disease is a powerful tool for estimating prognosis, which has a major impact on the choice of treatment. Most staging systems discriminate between local, regional, and systemic disease, but leukemia almost always presents as a systemic illness. Therefore, the staging systems developed for leukemia have been used as models for developing staging systems for systemic disease in other malignancies.



As with every malignancy, histopathologic morphology is a major prognostic factor for leukemia. The separation between poorly differentiated (acute) and well-differentiated (chronic) forms of leukemia was appreciated at the turn of the century. Next, it was noted that leukemia could emerge from myeloid, or bone marrow-derived, cells or from lymphoid-derived cells.

With the introduction of combination chemotherapy in the 1960s, the first cures of a systemic, syngeneic tumor—childhood acute lymphoblastic leukemia—were described. This therapy identified a new prognostic factor, the age of the patient. The older the patient, the more poorly the disease responded to treatment and the less likely a curative outcome would be achieved.

The major breakthrough in the staging

of systemic illnesses was the description in 1960 of the Philadelphia chromosome. This discovery revealed that hematological remissions did not change the cytogenetic pattern in the marrow. Treatment with interferon, however, made it possible to achieve cytogenetic remissions in patients with chronic myeloid leukemia (CML), and this was demonstrated to be associated with a significant increase in survival. Thus, the major prognostic factor for staging CML became the percentage of bone marrow metaphases in which the Philadelphia chromosome was present.

With the opening of the cytogenetic era, nonrandom chromosome abnormalities were identified in the acute myeloid leukemias, and these abnormalities became the most important prognostic factor. Another important advance was the description of monoclonal antibodies, which identified antigens on the surface of leukemic cells that were unique to leukemias. New molecular biological techniques that characterize cytogenetic abnormalities at the molecular level have proven extremely useful in identifying patients who are likely to have their disease eradicated in contrast to those who have residual disease and require additional treatment.

Clearly, now and in the future, the staging of systemic disease will increasingly rely on the molecular characterization of the genetic abnormality associated with that malignancy and its phenotypic consequence, and the objective measurement of degree of residual disease will be the most important way to identify treatments that prolong survival or bring about a cure.

OncoLog

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