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REPORT TO PHYSICIANS

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MD Anderson OncoLog

Newly Organized Ophthalmology Section Expands Treatment of Ocular Malignancies

by Kerry L. Wright

Bita Esmaeli, M.D., walks down a long hallway at The University of Texas M. D. Anderson Cancer Center and into one of the three rooms that house the institution's ophthalmology clinic. Several large cardboard boxes lie on the floor, holding inside them a brand new ophthalmic ultrasound machine, newly arrived and ready to be set up for a demonstration the next day.

Along with the ultrasound come new possibilities for the diagnosis of intraocular tumors and the promise of future expansion as the fledgling clinic settles into a permanent home.

"The goal—the vision—is to have this truly be a regional, and possibly a national, ocular oncology unit where we treat primary intraocular and periocular tumors," said Dr. Esmaeli, an assistant professor in the Section of Ophthalmology, Department of Plastic Surgery and director of the Ophthalmology Service. "We have all the components to be that."

Ophthalmologist **Bita Esmaeli, M.D.**, *(right) an assistant professor in the Department of Plastic Surgery, conducts an ocular examination in the ophthalmology clinic. Dr. Esmaeli directs the Ophthalmology Service, which provides treatment for ocular malignancies and other cancer- and treatment-related eye conditions.*

Establishing the Ophthalmology Service

Physicians in the ophthalmology clinic currently treat intraocular, periocular, and conjunctival malignancies, as well as orbital cancers,

(Continued on **next page***)*

Treatment and Support of Ocular Malignancies

(Continued from **page 1***)*

such as lymphomas, and paranasal sinus tumors. Patients are also seen for diagnosis and treatment of eye conditions that result from non-ocular cancers.

Dr. Esmaeli, an ophthalmologist who specializes in ophthalmic plastic and reconstructive surgery, came to M. D. Anderson only a year and a half ago as part of an experiment to see if a successful, free-standing Section of Ophthalmology could be created. Since the ophthalmology clinic opened in November 1998 under the auspices of the Department of Plastic Surgery, the number of patients who are treated at the clinic each month has increased by more than 400%.

The number of full-time faculty in the Section of Ophthalmology is expected to at least double by the end of 2000; a pediatric ophthalmologist and an ocular oncologist are among those joining the team. Many part-time and volunteer faculty from various subspecialties of ophthalmology are also involved in treating patients, and close collaborations exist with the Department of Ophthalmology at Baylor College of Medicine and with pediatric oncologists, radiation oncologists, head and neck oncologists, and plastic surgeons at M. D. Anderson.

Multidisciplinary approach to treating retinoblastoma

Among the clinic's main priorities is the treatment of retinoblastoma, the most common intraocular tumor in children. Retinoblastoma occurs at an estimated rate of 1 case per 18,000 to 30,000 births and is usually diagnosed before a child's second birthday. Approximately 40% of patients with retinoblastoma have inherited a defect in their retinoblastoma tumor suppressor gene, so they are also at increased risk for nonocular tumors throughout their lives. Retinoblastomas are known to metastasize quickly, so appropriate and timely treatment of primary tumors is essential.

"One of the ways to successfully treat retinoblastoma is to combine chemotherapy, radiation therapy, and local surgical measures such as cryotherapy or laser treatment," said Dr. Esmaeli. For large, unilateral tumors, complete removal of the affected eye may be the preferred method of treatment. For bilateral retinoblastoma tumors, however, the more diseased eye is normally enucleated, and the other eye is preserved. Recent trends in the management of retinoblastoma include the use of a combination of chemotherapy and conservative eye-preserving surgical techniques, even in unilateral cases.

"In both retinoblastoma and uveal melanoma, the trend is to preserve the eye whenever possible."

"In both retinoblastoma and uveal melanoma, the most common type of intraocular tumor in adults, the trend is to preserve the eye whenever possible," said Dr. Esmaeli.

Proton beam therapy for uveal melanomas

Radiotherapy often plays a pivotal role in the treatment of uveal melanoma, a disease that attacks the uveal tract of the eye (most often the choroid). Except for enucleation in the case of large tumors, plaque radiotherapy is currently the standard treatment for uveal melanoma. For plaque radiotherapy, a radiation oncologist, radiation physicist, and ophthalmologist design a gold-plated metal plaque with radioactive seeds placed inside. The plaque is sewn onto the eye for three to seven days, depending on the radiation dosage, then removed.

An alternative to radioactive plaque therapy—and a potentially more specific method of surgically applied radiation—is proton beam therapy.

"The key thing to recognize is that the eye is sensitive to radiation, and high radiation doses to the entire eye can be blinding," said Adam S. Garden, M.D., an associate professor in the Department of Radiation Oncology who works closely with Dr. Esmaeli to treat patients with uveal melanoma.

"Standard radiation uses electrons," said Dr. Garden, "either by themselves or to create therapeutic photons. The theoretical advantage of protons is based on their physical properties, not their biological properties." Protons conform well to narrow, exact beams and deliver most of their energy at the end of their range. These characteristics make it possible to treat the tumor while sparing a significant portion of adjacent normal tissues in the eye and, in many cases, saving the patient's vision.

"Another advantage of the proton beam is that you don't have to hospitalize the patient for several days while a radioactive plaque is on," said Dr. Esmaeli. M. D. Anderson is expected to complete construction of a proton beam treatment center within the next year, making it only the third center in the country to use the technique for the treatment of ocular tumors.

Using chemo-embolization to fight liver metastases

Approximately 30% to 40% of patients with uveal melanoma eventually develop distant metastases, most often to the liver, said Dr. Esmaeli. Systemic chemotherapy used for cutaneous melanoma has not proven beneficial in this patient population, and according to Agop Y. Bedikian, M.D., a professor in the Department of Melanoma/Sarcoma Medical Oncology, chemo-embolization is "the best therapy for patients with metastatic choroidal melanoma that is confined to the liver." For the procedure, a radiologist introduces a catheter into the patient's femoral artery and using fluoroscopic guidance, moves it up the aorta and into the hepatic artery that supplies blood to the tumor in the

Studies Aim to Detect and Treat Ocular Malignancies

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with ocular melanomas.

- A search for serologic markers for metastatic melanoma of the uveal tract (ID00-040). *Physician: Bita Esmaeli, M.D.*

  This study aims to identify serologic markers for earlier detection of metastasis in uveal melanoma. The serum of patients with end-stage melanoma and healthy control subjects will be analyzed at the molecular and protein levels. Participants must be older than 18 years and have metastatic uveal melanoma as proven by histological or imaging studies.

- Sentinel lymph node localization and biopsy for conjunctival melanomas: A pilot study (GSP00-106). *Physician: Bita Esmaeli, M.D.*

  This study is designed for patients at least 18 years old who have histologically documented malignant melanoma of the conjunctiva (greater than 1 mm in thickness) but have no clinical evidence of regional nodal disease or systemic metastasis by chest x-ray, liver function tests, and head and neck computed tomography. Patients must be able to undergo outpatient surgery under general anesthesia and return to M. D. Anderson approximately every three months for follow-up. Women who are pregnant, nursing, or not using reliable birth control measures may not participate.

- Phase II evaluation of temozolomide in metastatic choroidal melanoma (DM99-352). *Physician: Agop Y. Bedikian, M.D.*

  Participants must have metastatic choroidal melanoma with bidimensionally measurable disease and a life expectancy of at least eight weeks. Patients may not have undergone chemotherapy with a dacarbazine-containing regimen but may have received chemotherapy or radiation therapy three or more weeks prior to study entry if fully recovered from treatment. Patients with uncontrolled central nervous system involvement or a serious intercurrent illness cannot enroll.

- A randomized, parallel design, phase II study of paclitaxel administered weekly with or without the matrix metalloprotease inhibitor prinomastat (AG3340-022) in patients with metastatic melanoma (ID00-171). *Physician: Agop Y. Bedikian, M.D.*

  Participants must have metastatic choroidal melanoma with bidimensionally measurable disease and a life expectancy of at least eight weeks. Patients with cutaneous melanoma are eligible if they have had prior dacarbazine therapy; patients with ocular melanoma are eligible with or without prior chemotherapy. Patients with uncontrolled central nervous system involvement or a serious intercurrent illness cannot enroll. ●

FOR MORE INFORMATION *about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.*

liver. Starch particles and the chemotherapeutic agent cisplatin are then administered from a syringe through the catheter. The starch particles cause transient gelling of the blood, which not only deprives the tumor of oxygen and nutrition but also increases contact time between the cisplatin and the tumor cells.

"The combination of these effects results in necrosis of the tumor cells, which liquefy and are slowly absorbed and cleared by the body," Dr. Bedikian said. New chemotherapeutic agents are also being offered as investigational therapies to treat uveal melanoma metastatic to the liver and other organs.

Supportive care for patients with ocular complications

The ophthalmology clinic is also a full-time support center for patients with a wide range of ocular problems. Along with radiation oncologists, the ophthalmologists in the clinic treat ocular metastases in patients with breast and lung cancer and offer screening for retinal and corneal side effects of chemotherapeutic drugs. In addition, one of the largest populations requiring ophthalmologic assessment are patients who have undergone bone marrow transplantation. Ocular graft-versus-host disease and posterior subcapsular cataracts are fairly common in patients who have had a bone marrow transplant.

"We see quite a few cases of severe intraocular infection, including endophthalmitis, in our population of immunocompromised patients," Dr. Esmaeli said.

The operating room at M. D. Anderson recently acquired equipment that allows ophthalmic surgeons to perform procedures such as vitreoretinal surgery (for the diagnosis of intraocular lymphoma and infectious endophthalmitis) and cataract surgery.

"One of our immediate future goals is to reach out to the ophthalmologists in the community and nationwide and make them aware of the latest treatments available at M. D. Anderson. We hope to be able to set up an eye cancer registry in the near future that will likely help us identify trends in natural history and treatment options for some of the more rare eye malignancies," said Dr. Esmaeli. ●

FOR MORE INFORMATION, *contact Dr. Esmaeli at (713) 794-1247 or see the Section of Ophthalmology Web site at http://www/DEPARTMENTS/plastic/ophthal.htm.*

Ovarian Cancer

This case report of a patient with stage IV ovarian cancer is the first in a series of individual treatment summaries that correspond to and serve to illustrate the Clinical Practice Guidelines found in Compass.

As in most cases of ovarian cancer, [redacted] tumor was discovered in an advanced state, by chance—in this instance during a workup for pleural effusion prompted by a chest x-ray taken of the 75-year-old woman during outpatient evaluation for indigestion. Thoracentesis revealed numerous papillary clusters of malignant cells with psammoma bodies in the fluid and strong immunocytochemical activity to CA 125 (a tumor marker for ovarian cancer).

In light of these findings, [redacted] underwent computed tomography (CT) of the abdomen and pelvis that revealed an abnormal soft tissue density in the central pelvis, bilateral pleural effusions with pelvic ascites, and a large cyst on the right kidney. Subsequent ultrasonography of the abdomen showed a complex pelvic mass. Mrs. Newman was referred to The University of Texas M. D. Anderson Cancer Center for staging and treatment.

Physicians at M. D. Anderson discussed two treatment options with [redacted] initial surgery followed by chemotherapy and chemotherapy followed by exploratory laparotomy and tumor reduction surgery. Because [redacted] was in moderately good health and because initial surgery would allow for a definitive tissue diagnosis, it was agreed to first treat her with surgery, aimed at both confirming her disease stage and reducing the size of her tumor. Subsequent pathologic examination indicated that she had stage IV ovarian cancer, the most serious stage of the disease.

Because of the advanced stage of her cancer, surgery alone was not sufficient treatment, and doctors initiated a chemotherapy regimen of paclitaxel and cisplatin. She received six cycles of chemotherapy and, as in most patients, her disease responded well. After six months of treatment, her CA 125 level was 38 (normal < 35 units/ml), down from a preoperative level of 3,071.

[redacted] had no evidence of disease during chemotherapy, but after the sixth cycle, a CT scan revealed a 2-cm peritoneal mass. Her CA 125 level had declined on paclitaxel/cisplatin chemotherapy, but [redacted] still had evidence of persistent cancer and required further chemotherapy. Unfortunately, doctors had to choose a new agent because, though successful, paclitaxel/cisplatin therapy had caused substantial side effects: hearing loss, lower extremity paresthesia, and hypomagnesemia. Physicians changed her regimen to carboplatin.

After six cycles of carboplatin treatment, [redacted] experienced a period of calm, with a falling CA 125 level and no sign of recurrence. She lived much of the year without chemotherapy, showing no evidence of disease and receiving medical care only for pneumonia.

Late in the year, a CT scan and subsequent biopsy revealed metastatic disease adjacent to an abdominal muscle, and doctors restarted chemotherapy with carboplatin. Because a significant period of time had elapsed since [redacted] was last treated with the drug, physicians had reason to believe carboplatin would still be effective. This time, however, the drug was not as effective, and she experienced a number of side effects. In addition, after four cycles of carboplatin, a rise in her CA 125 level was noted, and doctors discontinued the treatment.

Physicians at M. D. Anderson continued to search for a drug or drug combination to which [redacted] cancer would consistently respond without causing serious side effects. Topotecan treatment followed carboplatin therapy. After 10 cycles of topotecan, chemotherapy was postponed because of bronchitis and neutropenic fever. Topotecan treatment was then resumed with granulocyte colony-stimulating factor (G-CSF) support (aimed at decreasing the incidence of infection) for a total of 23 cycles. Side effects of topotecan were minimal and included fatigue and a recurring rash, but G-CSF caused significant bone pain. [redacted] responded to topotecan for approximately a year and a half, but her CA 125 level eventually began to rise once again.

Noting the rise in her CA 125 level and discovering further metastatic disease (this time in the left axillary node), M. D. Anderson physicians changed her treatment from topotecan to gemcitabine. This drug therapy lasted for eight months and caused her CA 125 level to decline. Chronic bronchitis and chronic cough often delayed chemotherapy and were treated with steroids, antibiotics, and inhalants. Though her CA 125 level declined with gemcitabine treatment, doctors discontinued it, suspecting a connection between the treatment and [redacted] pulmonary problems.

Hormonal therapy with tamoxifen was then attempted. Shortly after, metastatic disease was detected in her left breast, and tamoxifen use was discontinued in favor of liposomal doxorubicin (Doxil).

Now 80 years old, [redacted] remains on Doxil therapy. She continues to have numbness in her lower extremities, respiratory difficulties, and occasional problems with ambulation. Her chest x-rays have shown stable disease, and her CA 125 level was most recently calculated at 1718. This number is far from normal, but her disease's response to treatment has been, in general, remarkable. Patients with stage IV ovarian cancer have a median survival duration of approximately two years and a five-year survival rate of 1% to 2%. [redacted] has thus far lived five years from the time of her diagnosis.

Written by: Rebecca Gershenson Smith

**Name has been changed to protect the identity of the patient.*

THE UNIVERSITY OF TEXAS
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Compass

CLINICAL PRACTICE GUIDELINES
Quarterly Supplement to *OncoLog*
SUMMER 2000, VOL. 2, NO. 2

About These Clinical Practice Guidelines

These guidelines may assist in the diagnostic evaluation of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

M. D. Anderson Cancer Center's Practice Guidelines are continually updated as new information becomes available and are being expanded to include the entire spectrum of cancer management. New guidelines for screening and diagnosis are currently under development. Access the most current version of all M. D. Anderson Practice Guidelines from M. D. Anderson's Home Page at http://www.mdanderson.org.

Continuing Medical Education: An expanded version of these materials with CME category 1 credit is available on the Internet. Choose 'Practice Guidelines' from M. D. Anderson's Home Page at **http://www.mdanderson.org**

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CLINICAL DISCUSSION: Ovarian Cancer

Scope of This Guideline

This guideline addresses the evaluation and treatment of epithelial ovarian cancer, which accounts for approximately 90% of ovarian neoplasms.

Synopsis & Highlights

Overview

Two hallmarks of this lethal disease are that it is insidious, often producing no alarming symptoms even in advanced stages, and that it is by nature a disease that spreads readily throughout the peritoneal cavity on visceral and parietal surfaces and in abdominal fluids (ascites).

There is currently no effective screening measure for ovarian cancer. Early-stage disease is most often discovered as a pelvic mass during a routine examination. Patients may be entirely asymptomatic or may have only vague or seemingly minor symptoms: tumors may grow to a rather large size before producing symptoms such as urinary frequency or rectal pressure; in more advanced disease, patients may complain of abdominal bloating or distention related to ascites or of respiratory symptoms associated with pleural effusion. Occasionally, even in advanced disease, ovaries may be normal in size upon examination.

The definitive diagnosis of ovarian cancer is made by histologic study of tissues and fluids removed during the initial surgery, which is a comprehensive staging exploratory laparotomy. This surgery is a critical event in the management of this disease, as all treatment decisions, and therefore outcomes, are based upon accurate staging. According to NIH recommendations, a woman with suspected ovarian cancer should be given the opportunity to have the laparotomy performed by a gynecologic oncologist.

Chemotherapy is the other mainstay of treatment and is indicated as a primary postoperative treatment in all situations except for very early, well-differentiated, and limited disease

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Pull Out

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(stage IA). Chemotherapy also plays a major role in the management of recurrent or progressing disease.

Second-look surgery for the purpose of monitoring disease is not considered necessary unless it will change disease management, so it is not routinely recommended outside of select clinical trials or unusual clinical presentations. However, for patients with recurrent disease, a second laparotomy may be indicated for debulking (secondary cytoreduction).

At all points in the guideline where clinical trials are listed as an option, our authors recommend them as the best choice.

Primary Treatment

Pelvic mass at clinical presentation

Patients who present with suspected ovarian cancer manifested as a pelvic mass should undergo a thorough preoperative physical examination and medical history. Because surgery is anticipated, the evaluation usually also includes a chest x-ray, an ECG, and any additional preoperative workup indicated for individual patients. Imaging studies such as abdominal CT scans may help locate and assess the extent of disease, but extensive imaging is not necessary, particularly if it delays definitive management. For the same reason, no preoperative biopsies to obtain material for cytologic or histologic evaluation are recommended, nor is paracentesis for abdominal ascites or effusions, as material for pathological examination will be obtained at the time of surgery.

An exploratory laparotomy for comprehensive staging and cytoreduction is the initial intervention, except in patients who are medically unstable. The latter patients may benefit from chemotherapy first. According to Dr. Gershenson, the initial surgery should be done through a vertical midline incision to provide an adequate field for biopsy and resection. Laparoscopy is not appropriate or adequate for the initial surgery. The procedure should include:

- evacuation of ascites if present, with submission of samples for cytologic evaluation
- cytologic washings of the pelvis, bilateral paracolic gutters, and subdiaphragmatic areas performed prior to manipulation of intraperitoneal contents
- careful systematic inspection and palpation of the entire peritoneal cavity with excision or biopsy of any suspicious area
- assessment of both ovaries for size, evidence of tumor involvement, or adhesion
- removal of the primary ovarian tumor intact
- generous random biopsies of all peritoneal surfaces
- where gross metastatic disease is encountered, an aggressive attempt to remove it should be made; where removal is not possible, it should be sampled to document the extent of disease
- careful examination of para-aortic and bilateral pelvic lymph node–bearing areas, including those in the retroperitoneum, with biopsy or removal of suspicious nodes
- thorough documentation of the entire procedure

Based on intraoperative findings and frozen section analysis, hysterectomy and bilateral salpingo-oophorectomy and omentectomy may be performed. Conservative surgery may be possible in patients who want to preserve childbearing ability if they are found to have limited and early (stage I, grade 1) disease. Although this is not frequently an issue in epithelial ovarian cancer, Dr. Morris points out that the surgeon should always understand its importance to the patient and stresses the need for good preoperative counseling; the options and decisions that will be made intraoperatively should be discussed with the patient beforehand.

Following surgery, further treatment is directed by disease stage. In patients with low-grade (stage IA), well-differentiated tumors limited to the ovary and no residual disease, surgery alone produces a long-term survival rate of >90%. In this setting, additional chemotherapy is not warranted, nor has it been shown to increase the long-term survival rate.

All others should receive primary adjuvant chemotherapy. According to Dr. Bast, for patients with stages II-IV disease, combination therapy with a taxane-based agent (paclitaxel or docetaxel) and a platinum derivative (cisplatin or carboplatin) is standard. For patients with low-grade, early-stage disease (stage IB-IC), more study is needed to determine the optimal agent or combination of agents to use. Currently, paclitaxel with cisplatin or carboplatin is recommended; single-agent carboplatin is considered by some experts to be as effective as the combination, but this issue is quite controversial.

The serum tumor marker CA125 is an important prognostic factor, and its levels should be monitored prior to therapy, after cytoreduction, and between cycles of chemotherapy. "We hope to see CA125 levels normalize by the third cycle, as studies suggest that this is associated with a better prognostic outlook," says Dr. Gershenson. Measurement of CA125 should be repeated at each follow-up visit after treatment; a progressively rising level is strongly predictive of disease recurrence and can precede physical exam findings and radiographic studies by as much as 3 months.

Ovarian cancer diagnosed by previous surgery

When a patient presents with ovarian cancer diagnosed during a previous surgical procedure, the first challenge is to determine the adequacy of the initial surgery with regard to staging. Where staging is incomplete, re-staging surgery or chemotherapy may be recommended.

Consolidation Treatment

Following six cycles of primary chemotherapy, patients with stage I-II disease should receive follow-up care as shown in the surveillance recommendations. Patients with more advanced (stage III-IV) disease may be considered for further (consolidation) treatment.

■ *Patients with partial remission of disease* after initial therapy are at high risk for relapse and should receive additional chemotherapy, with the choice of agent based upon earlier responses: paclitaxel or carboplatin are continued if response to either was noted; carboplatin or cisplatin may be tried if they were not previ-

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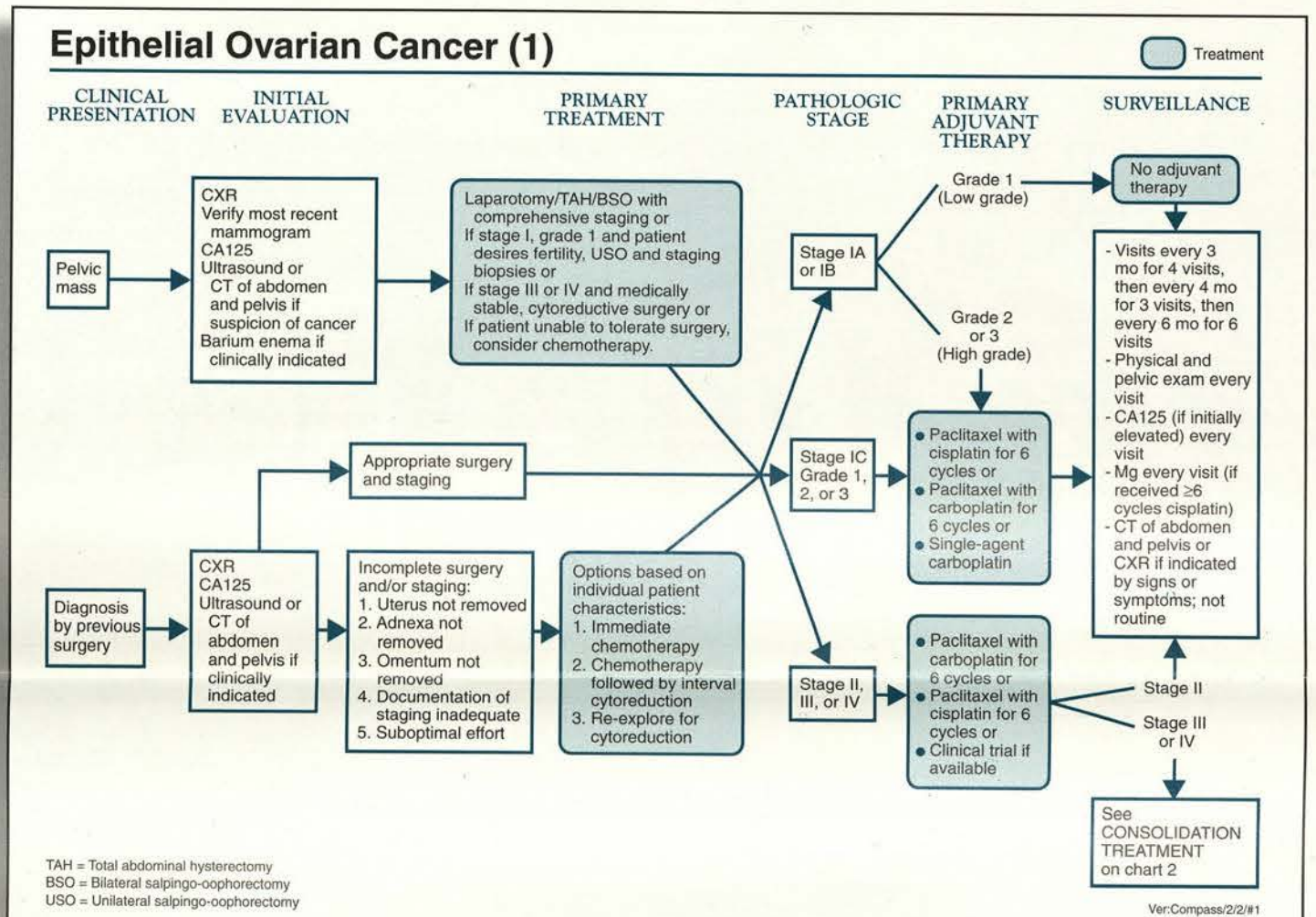

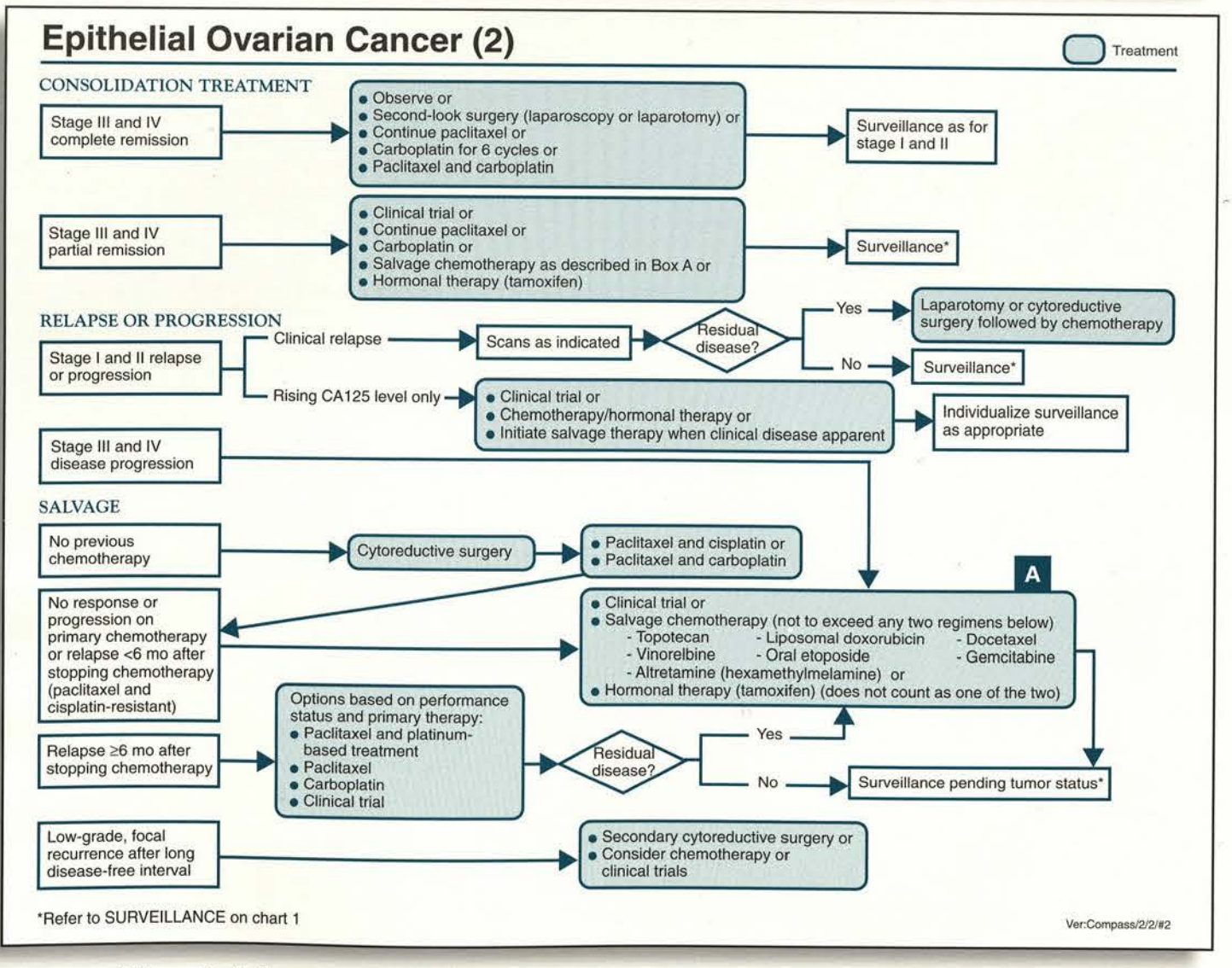

This practice guideline was developed in a collaborative effort between the physicians and nurses at The University of Texas M. D. Anderson Cancer Center and the National Comprehensive Cancer Network. The core development team at M. D. Anderson working on this practice guideline included Dr. Robert C. Bast, Jr., Dr. Thomas W. Burke, Dr. David M. Gershenson, Dr. John J. Kavanagh, and Dr. Mitchell Morris.

(Continued from **previous page**)

ously used. In situations where disease is judged resistant to these first-line agents, other drugs are used (see Box A on guideline).

The use of hormonal therapy (tamoxifen) in consolidation treatment is somewhat controversial: no trials have shown it to be more effective than chemotherapy, and there is no evidence that it prolongs disease-free survival. In the treatment of recurrence, however, tamoxifen may provide an alternative to more toxic agents in certain patients, particularly where there is indolent disease, provided the patient is carefully monitored.

■ *For patients with complete remission of disease* after initial therapy, the decision to continue treatment is less clear cut. The options are observation alone, continued chemotherapy, and second-look surgery. In this setting, the evidence is not conclusive that continued chemotherapy is superior to observation alone, so it is a situation in which clinical judgment must be based on the individual patient, and close consultation with her is part of this decision.

Similarly, second-look surgery is somewhat controversial. "We honestly don't know which of these options is better," says Dr. Gershenson, "because there have been no prospective randomized trials, and retrospective data don't show surgery to be better, although we know that information obtained surgically is more accurate than that imparted by CT scan or by measurement of CA125 levels." At M. D. Anderson, second-look surgery is included in some protocols for study purposes. "At this time we feel it's best done in the setting of a clinical trial or as part of an unusual patient presentation where the information is used to make treatment decisions," says Dr. Morris. " If the second look will not change those, then it is more controversial, particularly in cases where CA125 levels and CT scans are normal."

It should be noted, however, that the patient's personal choice is an important factor. "Many women feel strongly about having the second surgery," says Dr. Gershenson. "We don't have a personal bias either way but try to present the patient with a balanced view."

Management of Relapse or Progression of Disease

Management decisions in recurrent or progressing disease are based upon disease stage and the presence of clinical signs. Patients with stage I-II disease whose CA125 levels rise should be examined by CT scan to confirm the presence and extent of residual disease. For these patients, cytoreductive surgery may be indicated and should be followed by chemotherapy. Whether to treat a rising CA125 level with chemotherapy in the absence of other evidence of recurrence remains controversial.

Patients with stage III-IV disease that relapses or progresses during chemotherapy should be considered for clinical trials or for chemotherapy with another agent. When relapse occurs six months or later following the end of treatment, there is an approximately 45% chance that disease may be considered sensitive to the original agent (paclitaxel, cisplatin, or carboplatin) and will respond to it. When relapse occurs in less than six months, there is reduced chance of response to these agents (i.e., resistance is likely), and another drug should be tried. Of the agents listed (see Box A on guideline), there are few studies or reliable tests to help predict which one will produce a response.

"In most patients (80%), disease responds to chemotherapy initially," says Dr. Gershenson. "The problem is maintaining response, or achieving 'durable response.' The problem is development of resistance and relapse."

Authors' Perspectives

The first surgery is the most critical event in the course of a patient's treatment. "One of the major issues for us is that only a small percentage of women have undergone cancer surgery where comprehensive staging was achieved," says Dr. Gershenson. He notes that one should always consider the possibility of malignancy, even in young patients. It is always appropriate to include a gynecologic oncologist in consultation and surgical planning when there is suspected cancer.

Ovarian cancer, though curable, remains a lethal disease for most women in spite of advances made in treatment over the past few decades. According to Dr. Morris, "In the past 20 years, the strides made in ovarian cancer treatment have been significant increases in life expectancy and survival rates, along with a dramatic reduction in the side effects of treatment, which has greatly enhanced quality of life for our patients. Our biggest continuing challenge is that 70% of patients with ovarian cancer present with advanced disease."

Clinical trials offer the best hope for improving therapy, says Dr. Bast. What is badly needed, he says, are accurate tests for predicting drug responses that will enable clinicians to select those drugs that are the most appropriate agents for individual patients. There is research under way to develop assays for this purpose.

Find more information about clinical trials and current protocols available at M. D. Anderson at *http://www.mdanderson.org/research/*

Compass

Quarterly Supplement to *OncoLog*

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References & Suggested Reading

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NCCN Ovarian Cancer Guidelines. Oncology, Vol 11, No 11A, November 1997

HOUSE•CALL

Virtual Health: Finding Reliable Medical Resources on the Internet

The popularity of the Internet has made obtaining medical information easier than ever before, but it is important to keep in mind that not all of the information available on the Internet is useful or accurate.

How can you ensure that the medical information you're reading about on the Internet is reliable?

Ask your doctor

When in doubt, always discuss the information you have found with a medically trained professional. Even information from a well-respected source should supplement, rather than replace, the advice of your physician.

Consider the source

If an Internet site is reputable, it should clearly state who is responsible for the information presented. Look to see if the person or organization in charge of the site created the information. If not, the original source should be documented. It is also helpful to know how the Internet site is funded. For example, an Internet site funded by a drug company could potentially create a bias in the site's information.

Is the information supported?

A good Internet site should clearly differentiate between facts and opinions. Material presented as fact should be referenced, i.e., should refer the reader to the results of a study, to a reference in a medical journal, or to specific Internet sites.

How is the information selected?

An Internet site that selects the information presented via consultation with medically qualified individuals or an editorial board is more reliable than other sites.

Is the information current?

A useful Internet site should post the date of the most recent review or update of its material. It is important that the person or organization running the site reviews the material regularly to ensure that it is still valid and current. Broken links are an indication that a site is not being updated regularly.

Is the advertising responsible?

Many reputable Internet sites contain advertising, but beware of those that allow advertising of products next to news articles about the product. Also, a reliable site will clearly differentiate between advertising and medical information. ●

The sites below were selected because reputable medical Web sites frequently provide links to them and because they meet the criteria for a good Internet site.

Address Go

Links MyAltaVista MyCity Search

Recommended Cancer-Related Sites

American Cancer Society: www.cancer.org
A comprehensive site covering types of cancer, treatment options, and news articles.

cancerfacts.com: www.cancerfacts.com
Provides personalized, interactive treatment options and survival and recurrence rates for people with cancer, news articles, and articles written by people with cancer.

CancerSource.com: www.cancersource.com
Contains general information about cancer and links to news articles.

Cancer Survivor's Network: www.cancersurvivorsnetwork.org
Covers a wide range of topics important to patients with cancer and those close to them, including coping with fear, financial planning, and long-term effects of treatment.

Healthfinder: www.healthfinder.gov
A general health site that provides a medical dictionary, a link for cancer information, and links to on-line medical journals and health-related sites.

M. D. Anderson Cancer Center: www.mdanderson.org
Explains clinical trials, offers advice on cancer prevention, provides a glossary of terms, and gives information about M. D. Anderson's services and activities.

National Cancer Institute: www.nci.nih.gov
A comprehensive site with information on types of cancer, clinical trials, statistics, etc.

National Library of Medicine: www.nlm.nih.gov
Offers information on clinical trials, allows the user access to abstracts from medical journals, and provides a directory of health organizations.

oncology.com: www.oncology.com
Includes information for patients and caregivers.

RxList: www.rxlist.com
Provides information about prescription drugs and drug interactions.

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

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

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June 2000

New DNA Microarray Technology Could Speed Up Discovery of the Genetic Causes of Lung Cancer

by Maureen E. Goode, Ph.D.

With initial sequencing of the entire human genome now complete, discovering how heredity influences health seems only a step away. Armed with the human genetic code, researchers are testing a series of new technologies such as DNA microarrays, or "chips," that could exponentially speed up the process of identifying disease genes, enabling researchers to more easily evaluate individual disease risk based on the analysis of several genetic variables.

Changes in some genes have already been associated with an increase in cancer risk. But although some people seem to carry in their genes an increased risk for cancer, it is unlikely that any one gene by itself causes cancer. "Even the highly penetrant BRCA1 and BRCA2 gene mutations, which have been identified as strong components in some familial breast and ovarian cancers, are now believed to interact with other factors to modify the individual risk of breast and ovarian cancer among carriers," said Patricia A. Thompson, Ph.D., an assistant professor in the Department of Epidemiology at The University of Texas M. D. Anderson Cancer Center. "Many other genes and the environment may play a role, too. Lung cancer is another good example of this. Although smoking increases the average person's risk, some people smoke for years without getting lung cancer, and some nonsmokers get lung cancer."

Thompson, Margaret Spitz, M.D., M.P.H., chairman of the Department of Epidemiology at M. D. Anderson, and Michael Hogan, Ph.D., chief scientific officer of Genometrix, Inc. and professor of biophysics at Baylor College of Medicine, are using DNA microarray technology (see sidebar) to develop a rapid automated system for assessing an individual's risk for lung cancer.

It is already possible to determine individual risk for some diseases. "Cardiovascular disease is a good example of a multifactorial disease for which we have identified some of the contributing factors," Dr. Hogan explained. "Both clinicians and patients know that to determine your risk for cardiovascular disease, you should be tested for LDL, HDL, and cholesterol. But we just don't know that much about the factors that cause cancer." Some factors may not have the same effect in each person. "The body has numerous redundant capacities to clear the genetic damage that leads to cancer, and when it doesn't do a good enough job in one area, it sometimes can in another." So, the goal of current cancer risk-assessment studies is to identify groups of factors that affect the probability that a particular cancer will develop in a person.

Finding these factors is the rate-limiting step in risk assessment. Years of research by scientists have revealed about 33 common genetic variants (carried by more than 2% of the population) that may be involved in individual susceptibility to lung cancer. Some of these genes were singled out by their known roles in the metabolism of select therapeutics and tobacco carcinogens. For instance, people with certain genetic variants of the enzyme *N*-acetyltransferase have long been known to be "slow acetylators," that is, to break down some drugs and carcinogens more slowly than other patients do. The Genometrix microarray platform enables rapid identification of such patients, who should be given lower doses of certain drugs and who may be more sensitive to carcinogens found in tobacco products.

These gene variants represent the genetic diversity in the human population and are common, unlike mutations such as BRCA1 and BRCA2. To prove a role for these genes in disease, scientists need to show that a gene has an effect in 10,000 to 100,000 people—at least 100 times the number of people usually studied. Using current techniques to identify these variants, commonly referred to as genotyping, these large studies can take years, but by applying DNA chip technology, a miniaturized version of these techniques, researchers can test blood samples from 2000 people for the 33 genes in only two days. This new methodology promises to speed up both identification of new disease genes and confirmation of suspect genes.

Dr. Hogan's interest in screening for genes that cause lung cancer began in 1997, when he met Dr. Spitz, a well-known expert in the epidemiology of lung cancer, at a scientific meeting in Liverpool, England. Dr. Spitz and her colleagues have shown that patients with lung cancer have a lower than normal capacity for repairing the DNA damage from cigarette smoking that leads to lung cancer. However, many genes help repair DNA damage, and singling out the ones involved in lung cancer is a daunting proposition. "I realized from talking to Dr. Spitz," said Dr. Hogan, "that the Genometrix automated DNA microarray technology was the way to go for such large-scale population studies." Dr. Spitz suggested that Dr.

Many genes help repair DNA damage, and singling out the ones involved in lung cancer is a daunting proposition.

Hogan also speak to Dr. Thompson, who was then studying genetic susceptibility to disease at the National Center for Toxicological Research. Drs. Thompson and Hogan began collaborating, and Dr. Thompson joined the faculty of M. D. Anderson in July 1999.

The team's immediate goal is to validate the microarray by assessing whether the microarray process and conventional genotyping produce the same results in 1000 DNA samples from healthy individuals and patients with cancer. If this validation test is successful, Genometrix will mass-produce the optimized chip, and Drs. Thompson, Hogan, and Spitz will use it to screen DNA samples from patients with lung cancer to determine whether their genes are different from those of healthy people. The study will most likely show that certain gene variants are more common in, but not exclusive to, patients with lung cancer. These data, in combination with exposure data such as whether or not the person uses tobacco products, will eventually be used to determine the probability that lung cancer will develop in a given person.

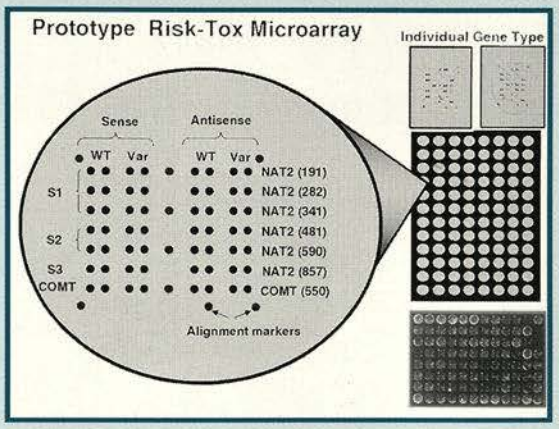
With these individual risk profiles, health care practitioners will someday be able to give patients personalized instructions on how to reduce their risk for complex diseases like lung cancer. For instance, a person with a mutation in a gene that detoxifies a particular carcinogen will be told to avoid that carcinogen, just as now a person whose parents have heart disease is told to lower his cholesterol level. "The DNA microarrays," said Dr. Hogan, "are just a way of taking a family history in excruciating detail." ●

FOR MORE INFORMATION, *contact Dr. Thompson at (713) 795-2492 or Dr. Spitz at (713) 792-3020.*

Microarrays Reduce Time, Labor, and Cost of DNA Analysis

by Maureen E. Goode, Ph.D.

DNA microarrays, which are being developed by several research groups, are miniaturized forms of current DNA screening procedures, bettered by improved DNA storage, more rapid processing, and automation. In most research laboratories, liquid DNA is isolated from blood samples and stored in huge freezers. The freezers are expensive and take up a lot of room, and a power outage that thaws the samples can ruin years of work. Dr. Hogan and colleagues have circumvented these problems by developing an automated technology for storing blood samples at room temperature, spotted on special papers about 5 by 5 cm square.



The DNA chip layout for the normal (WT) and mutant (Var) forms of six regions of the NAT2 *gene and one region of the* COMT *gene are shown. The results of an actual screening are shown in the upper right.*

Genes in the spotted blood samples are amplified by the polymerase chain reaction (PCR), a technique commonly used to replicate genes in vitro. PCR makes a small DNA sample detectable by copying a specific gene or part of a gene over and over until there are enough copies to analyze. In PCR, artificial, short pieces of the gene, called primers, are added to a DNA sample along with amplifying enzyme.

The standard procedures for analyzing sequences of the resulting products and determining the presence of variants are numerous and include several methods of sequence and fragment analysis. The major limitations to these existing technologies are the time, labor, and costs involved in analyzing, at most, five genes simultaneously in a single DNA sample. In contrast, the Genometrix technology allows the procedure to be performed at room temperature for several hours and can evaluate up to 50 genes in thousands of samples. The key improvement is the use of the DNA chip, in which synthetic DNA segments (probes) that bind up to 50 genes and their mutants are spotted to form an array within a 4 by 4 mm square of siliconized glass. One such array is formed in each well of a 96-well microtiter plate, to which an individual's PCR-amplified DNA sample is added. Each amplified gene (or its mutant variant) binds to the array at the site of its complementary probe, and a fluorescent marker is incorporated into the bound, amplified DNA. Whether a person has a normal gene or a mutant one is determined by examining the fluorescent pattern on the chip, which is detected and analyzed numerically.

Overall, Genometrix's system is 10 times faster than conventional genotyping methods and is almost completely automated. Ironically, these advances have created their own problem: they generate more data points than can be evaluated by conventional data analysis methods. Information specialists at Genometrix and M. D. Anderson, under the direction of Dr. Christopher Amos, a professor in the Department of Epidemiology, are therefore developing new statistical techniques to handle the large volume of data. ●

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Turning Knowledge Into Effective Gene Therapies

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Over the last 20 years, many of the mysteries underlying the origins of cancers have been solved, and a large body of evidence implicates alterations in normal genes.

Oncogenes and tumor suppressor genes are especially susceptible to acquiring mutations and deletions that predispose a cell to becoming cancerous. Oncogenes become hyperactive when mutated or overexpressed. Tumor suppressor genes normally function to regulate the cell cycle and repair DNA damage, but they are frequently inactivated by mutations or promoter silencing.

The challenge clinicians face is to turn the wealth of information about genes into useful therapies. Their task is made easier by the advantages that gene therapy offers: genes are readily available and easily expressed, and the effects of therapeutic gene expression may be highly selective, with a wide therapeutic window. For example, the *p53* tumor suppressor gene, which can cause apoptosis in cancer cells, does not affect normal cells, even when overexpressed.

The biggest problem facing cancer gene therapy has been developing vectors that can efficiently deliver genes to a sufficient number of cancer cells. Current vectors utilize retroviruses and adenoviruses that are rendered replication-defective and incapable of causing disease. Despite their limitations, in specific clinical situations these vectors can deliver, by intratumoral injection, therapeutic genes in sufficient quantities to mediate clinically relevant tumor regression.

A replication-defective adenovirus expressing the normal *p53* gene (Ad-p53) has been shown to enhance local tumor control and sensitize cancer cells to the cytotoxic effects of chemotherapy and radiation therapy. In phase I and phase II studies, serious vector-related adverse events have been seen in fewer than 5% of patients, and no vector-related deaths have occurred. At this institution, protocols with intratumoral injections of Ad-p53 are now enrolling patients with lung, head and neck, bladder, and brain cancers.

Research in the field of gene therapy is moving rapidly, and with the completion of the Human Genome Project, identification of cancer-related genes will accelerate. Techniques that reveal the genetic signatures of particular cancers may then be used to identify critical target genes. Already, clinical trials of vectors that can deliver genes to distant metastatic sites will begin this year, expanding the use of gene therapy to the treatment of both local and metastatic disease.

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