

REPORT TO PHYSICIANS

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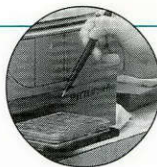
THE UNIVERSITY OF TEXAS
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MD Anderson **Oncology**

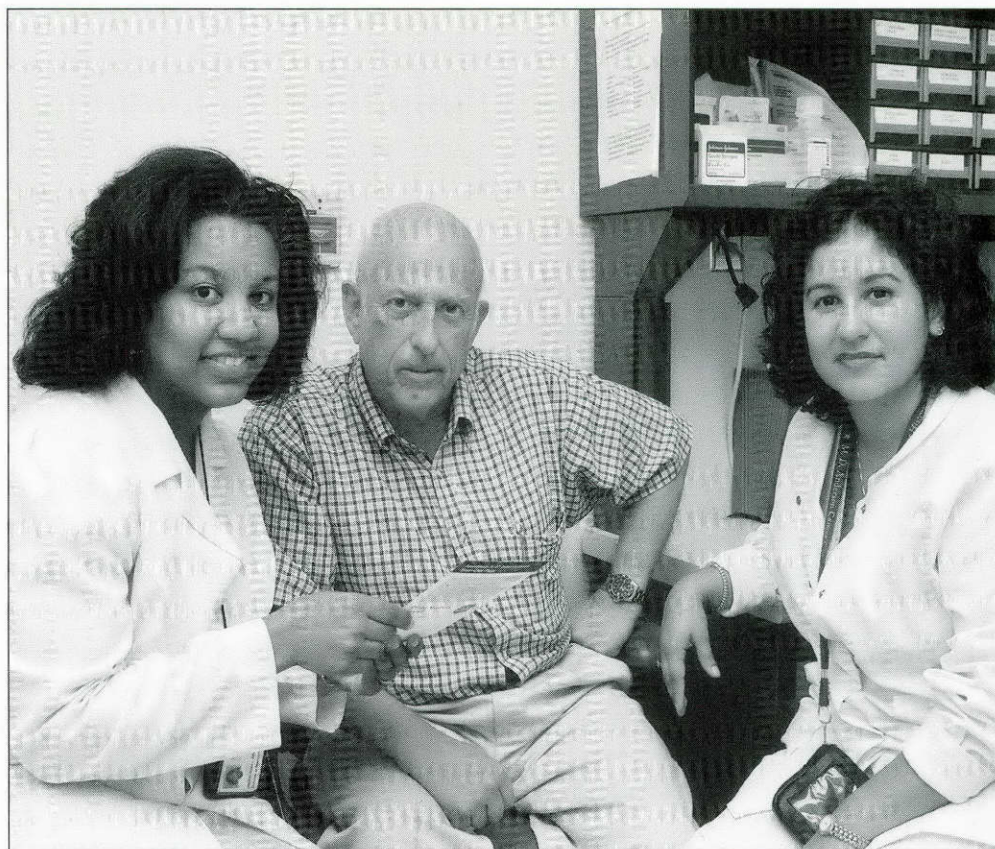
Rise in Incidence, Associated Diseases Complicate Screening for Esophageal Cancer *Multimodality treatment yields good results*

by Don Norwood

Esophageal cancer is one of the deadliest cancers, largely because it is usually not detected until it has reached an advanced stage. It is also an uncommon form of cancer in Western countries, but a steady rise in the incidence of one type of esophageal cancer over the past 15 to 20 years is threatening to change that.

“Adenocarcinoma of the esophagus has assumed increasing importance as a cancer in the United States because the rate of it is increasing dramatically,” said Stanley R. Hamilton, M.D., head of the Division of Pathology and Laboratory Medicine at

(Continued on next page)



Jackie Baker, B.S.N., (left) and Maria Keith, R.N., research nurses in the Department of Gastrointestinal Medical Oncology and Digestive Diseases, meet with patient John Amy, M.D., to explain the side effects of a chemotherapy drug. Chemotherapy is just one component of a promising multimodality approach to treating esophageal cancer.

Screening for Esophageal Cancer Can Be Complicated

(Continued from page 1)

The University of Texas M. D. Anderson Cancer Center. "In some of the studies that have been done, it looks like it is perhaps the fastest-increasing tumor type in the United States."

The increased incidence of adenocarcinoma has made it more prevalent than squamous cell carcinoma of the esophagus in the United States. Tobacco, alcohol, and diet have been identified as risk factors for squamous cell carcinoma, but the risk factors associated with adenocarcinoma are less clear.

What investigators do know is that gastroesophageal reflux disease (GERD), a condition that is more common in obese people, is associated with the occurrence of esophageal cancer, especially adenocarcinoma.

"If you look at the surveys that are done about people's health symptoms," Dr. Hamilton said, "a very high percentage of the U.S. population has symptomatic gastroesophageal reflux. All you have to do is watch TV for the antacid commercials to realize how major this problem is in the United States."

Barrett's esophagus, or columnar epithelial metaplasia of the distal esophagus, is an adaptive response to GERD. As GERD continues over time, the squamous epithelium in the esophagus is gradually replaced by columnar epithelium like that in the lining of the stomach. This new epithelium protects the esophagus against the duodenal and gastric contents that are regurgitated. Over time, about 5% to 10% of people with Barrett's esophagus will develop esophageal adenocarcinoma—a significant number but only a tiny fraction of those who have GERD.

Therein lies a problem for clinicians whose patients may be at risk for esophageal cancer: screening. Deciding who should and should not undergo invasive procedures to detect esophageal cancer is a complicated issue, one that physicians should approach with great care.

Wholesale screening of people with GERD is impractical, said Jaffer

A. Ajani, M.D., a professor in the Department of Gastrointestinal Medical Oncology and Digestive Diseases, because esophageal cancer is so rare. Instead, physicians must keep close tabs on their patients who have chronic and progressive GERD.

"Doctors have to start thinking about this disease when the patient first presents with heartburn, also pain, a little bit of weight loss, and slight swallowing problems," Dr. Ajani said. "They have to be investigated quickly. Sometimes that doesn't happen because the diagnosis requires endoscopy. The threshold has to be lowered for high-risk groups."

Dr. Hamilton echoed those statements, adding that even greater care should be taken when Barrett's esophagus is thrown into the mix.

"A problem with this, in terms of trying to recognize patients who are at risk, is that the severity of reflux symptoms is not related to the risk of adenocarcinoma," Dr. Hamilton said. "In fact, a substantial minority of the patients with adenocarcinoma of the esophagus and Barrett's esophagus don't have a significant history of GERD. That's probably related to the fact that they started off with reflux when they were children and kind of got used to it so that the symptoms were really not something they recognized. Furthermore, when Barrett's mucosa developed, because that columnar epithelium is more resistant to acid, they were not as symptomatic. People in whom Barrett's esophagus develops often actually have less symptomatic reflux than they did before it developed."

Although screening remains troublesome, great strides have been made in the treatment of esophageal cancer. According to Dr. Ajani, clinical trials of multimodality therapy combining radiation therapy, chemotherapy, and surgery have shown good results in patients whose disease has not reached a very advanced stage. In addition, Dr. Ajani said that M. D. Anderson has been instrumental in organizing clinical trials of new, highly effective chemotherapy agents

such as paclitaxel and irinotecan for the treatment of esophageal cancer.

"If patients have localized cancer of the esophagus, then there are two options," Dr. Ajani said. "One is surgery, but then there is another equally effective option of using chemotherapy and radiation together."

A trial of preoperative induction chemotherapy followed by chemoradiotherapy in patients who eventually will undergo surgical resection of their cancer is under way at M. D. Anderson, and a nonoperative, combined-modality clinical trial will begin soon, Dr. Ajani said.

"In this trial, the goal is to achieve local and systemic control of cancer for prolonged periods of time without surgery," Dr. Ajani said.

If surgery is indicated, patients undergo a transthoracic esophagectomy (Lewis procedure) or transhiatal esophagectomy. Joe B. Putnam, Jr., M.D., an associate professor in the Department of Thoracic and Cardiovascular Surgery, attributes the high success rate and low mortality rate for esophageal resection to a surgical team focused solely on thoracic surgical oncology, particularly lung and esophageal cancer, and a multidisciplinary team of surgeons, medical oncologists, gastroenterologists, and radiation oncologists who provide consistent and timely care.

"Our department does more surgery for esophageal cancer than probably any other department in the United States, with results that are much better than the national averages," Dr. Putnam said. "The patient has the advantage of input from many specialists."

According to Dr. Hamilton, many patients already have Barrett's esophagus at the time they are first seen for symptomatic reflux disease. For those patients, aggressive treatment of the reflux disease has been suggested in some studies to decrease the frequency of dysplasia and adenocarcinoma.

"That's not a universal finding," Dr. Hamilton said, "but presumably because the injury to the epithelium

Clinical Trials for Esophageal Cancer

is one of the factors that helps to drive the process of dysplasia and adenocarcinoma, there certainly can be no argument against treating the reflux disease aggressively.”

Fifty percent to 75% of patients with severe dysplasia will have adenocarcinoma identified in the resected specimen. Patients with severe dysplasia are usually treated with transhiatal esophagectomy, including gastric interposition and a cervical anastomosis, which spare patients from having to undergo a thoracotomy.

“Most patients are cured, if the disease is early stage and limited to the mucosa,” Dr. Putnam said.

People with Barrett’s esophagus should also undergo regular surveillance, including an endoscopy at regular intervals (every one to two years) with multiple biopsies to sample the Barrett’s mucosa, which is examined by a pathologist for evidence of dysplasia in the epithelium. Evidence indicates that a rigorous sampling of the segment of Barrett’s epithelium has a greater likelihood of detecting dysplasia or cancer.

Another area of progress at M. D. Anderson has been palliative care for patients with esophageal cancer, which is especially important because these patients so often present with advanced-stage disease. New palliative procedures to improve patients’ quality of life include photodynamic therapy, laser therapy, and stent placement.

“One of the biggest problems patients with esophageal cancer have is they cannot eat,” Dr. Ajani said. “When you cannot eat, only then do you realize how important it is and how much we take it for granted. These patients desperately want to eat. They want to taste food that goes down their throats. These are the techniques that can really help patients eat again, and they are so appreciative.”

In the end, the key to avoiding the ravages of esophageal cancer lies in prevention. One strategy is to focus on preventing the progression of Barrett’s esophagus to cancer.

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for esophageal cancer.

- Phase I study of irinotecan and concurrent radiation therapy in patients with locally advanced, unresectable, or metastatic gastric, gastroesophageal junction, or esophageal carcinoma (ID97-311). *Physician: Jaffer A. Ajani, M.D.*

Participants must have histologic confirmation of advanced, unresectable, or metastatic gastric, gastroesophageal, or esophageal carcinoma, including unresectable cervical carcinoma of the esophagus, with no prior radiation therapy to the target. Patients may have undergone up to two prior systemic chemotherapy regimens or radiation therapy to areas other than the primary tumor. However, patients with prior malignancies (except for basal cell or squamous cell skin cancer, in situ cervical cancer, or another cancer of which they have been disease-free for at least five years) are excluded.

- A phase II prevention trial of eflornithine (DFMO) in patients with Barrett’s esophagus with dysplasia (DM98-204). *Physician: Frank A. Sinicrope, M.D.*

Patients with histologically confirmed or suspected Barrett’s esophagus with any degree of mucosal dysplasia are eligible, and patient consent for three endoscopic exams and esophageal biopsies is required. Participants must not have received chemotherapy or

radiotherapy for prior malignancies within the past six months and must have no prior history of esophageal surgery, photodynamic therapy, or electrocautery or laser treatment for Barrett’s esophagus.

- A phase I study of continuous infusion low-dose paclitaxel and concurrent radiotherapy for unresectable esophageal cancer (ID95-071). *Physician: Ritsuko Komaki, M.D.*

To determine the tolerance dose of paclitaxel given during 21-day infusion, biological endpoints will be evaluated by several biomarkers. This study is designed for patients between the ages of 15 and 75 who have histologic or cytologic proof of stage T1-4, NX, M1 or recurrent carcinoma of the esophagus. Participants must sign an informed consent and be willing and able to care for an infusion pump, either alone or with social support. Participants must not have undergone previous irradiation in the proposed or adjacent irradiation fields and must not be currently undergoing chemotherapy with other agents. ●

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.

Studies are ongoing to evaluate drugs that might be effective at preventing progression of Barrett’s esophagus with dysplasia to cancer. These drugs include eflornithine (DFMO) and aspirin-related agents, which are also being studied in patients with a history of precancerous colon polyps.

Another strategy is to stress to patients the importance of maintaining a healthy weight, not using tobacco, and drinking only in mod-

eration. Also, anyone who regularly experiences symptoms of heartburn should visit a doctor.

“If an informed patient at high risk for esophageal cancer demands an endoscopy, I would say it is okay to do it,” Dr. Ajani said. ●

FOR MORE INFORMATION, contact Dr. Hamilton at (713) 792-2040, Dr. Ajani at (713) 792-2828, or Dr. Putnam at (713) 792-6934.

Preclinical Studies Examine Strategies to Fight

by Kerry L. Wright

Among cancers, thyroid cancer has a better reputation than most—a reputation that comes from demonstrating a good response to treatment and having a high overall survival rate. Even so, the rarest forms of the disease are often the most aggressive and the least responsive to current treatments, creating a small subset of patients who have a much poorer prognosis than the more fortunate majority.

By taking a closer look at the biology of these rare tumors, physicians at The University of Texas M. D. Anderson Cancer Center are developing new treatment strategies that could one day end this disparity and lead to good outcomes for all patients with thyroid cancer.

“In general, thyroid cancer is one of the types of cancer that people do well with,” said Rena Sellin, M.D., a professor in the Section of Endocrine Neoplasia and Hormonal Disorders, Department of Internal Medicine Specialties. “However, there are some groups of patients who have a much more aggressive disease, and this is where most of the innovations and new directions are.”

At M. D. Anderson, the Section of Endocrine Neoplasia and Hormonal Disorders collaborates closely with the departments of Head and Neck Surgery, Nuclear Medicine, and Melanoma/Sarcoma Medical Oncology to treat patients with thyroid cancer. According to Dr. Sellin, nearly all patients with papillary or follicular thyroid carcinoma (the two most common forms of the disease) are treated with surgery alone or surgery plus radioactive iodine. These types of thyroid cancer are well-differentiated and yield the highest survival rates among patients with thyroid cancer.

Two physicians at M. D. Anderson are focusing their laboratory research on the less common but more life-threatening forms of thyroid cancer: Robert F. Gagel, M.D., chairman of the Department of Internal Medicine Specialties, is studying how hereditary medullary thyroid carcinoma

(MTC) originates, and Assistant Professor of Internal Medicine Specialties Sai-ching J. Yeung, M.D., Ph.D., is investigating new treatments for anaplastic carcinoma. Though the two diseases differ in many respects, the mechanisms behind their causes are similar—both involve misregulation of receptor tyrosine kinase pathways.

Receptor tyrosine kinases are just one type of receptor involved in normal cellular growth and differentiation. Most of these receptors are composed of three domains: an extracellular domain that receives signals, an intracellular domain that helps transmit signals, and a transmembrane domain, a region that crosses the cell membrane. Cell signals, or ligands, bind to the extracellular domain and induce a conformational change that causes the receptor to self-phosphorylate. A complex of proteins can then go to the plasma membrane to help transmit the growth signals throughout the cell. Mutations in any component of the pathway can lead to continuous growth signaling and thus to cancer.

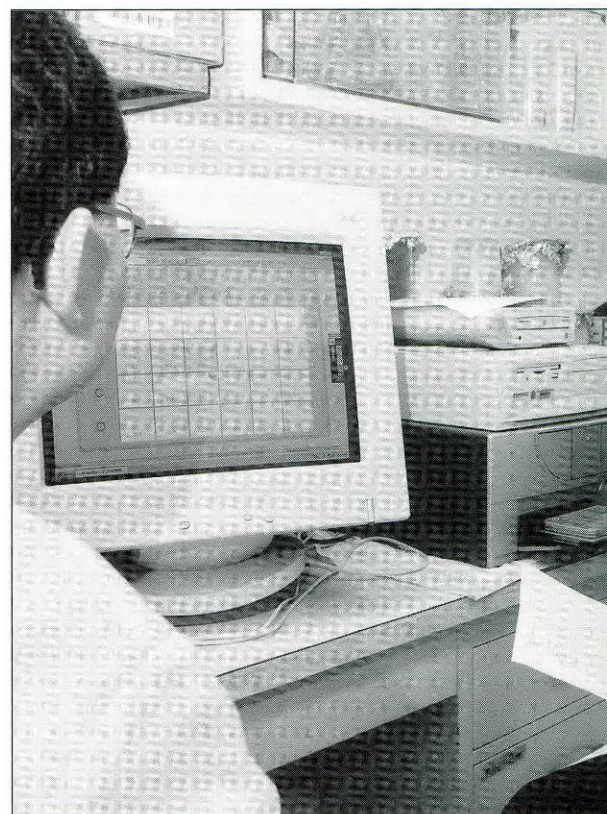
What is particularly intriguing, Dr. Gagel said, is that mutations of a single proto-oncogene, *RET*, are involved in two different types of thyroid cancer. Rearrangements of *RET*, which encodes the RET tyrosine kinase receptor, are found in 20% to 35% of papillary thyroid carcinomas, and point mutations in the gene account for approximately 20% of all cases

of hereditary MTC. All of the point mutations are activating mutations, and all lead to formation of a constitutively active RET receptor. According to Dr. Gagel, physicians can tell how aggressive a cancer is going to be and can also tell something about the biology of a tumor just by knowing which *RET* mutation is present.

MTC is the only cancer at present where a decision to treat the cancer can be based on a genetic test. There is evidence that early intervention can lead to cure, and therefore, it is often the decision at M. D. Anderson to remove the thyroids of children between the ages of four and six who have tested positive for mutations in *RET*.

While surgical removal of the thyroid is currently the standard treatment for MTC, if mutations that cause hereditary MTC could be identified and either reversed or inactivated, perhaps thyroid removal could be avoided in these patients. Dr. Gagel and colleagues are currently involved in preclinical studies that attempt to inactivate mutant *RET* genes in cultured cells.

“We’re using small RNA molecules



Rare Forms of Thyroid Cancer

that basepair with a target RNA and then cleave the target RNA to inactivate RET," said Dr. Gagel. The RNA that binds and cleaves the target is called a ribozyme, or RNA that has enzymatic activity. The target RNA in this case encodes the RET receptor tyrosine kinase; when it is cleaved, RET is essentially inactivated.

"In patients with hereditary medullary carcinoma, one copy of their *RET* gene is normal, and the other copy is abnormal," said Dr. Gagel. "So, our original thought was maybe we could selectively inactivate only mutant genes," he said. Dr. Gagel and colleagues designed a ribozyme that selectively cleaves RNA containing the most common *RET* mutation in MTC. Using this ribozyme de-

creased the number of transformed cells in culture by over 70%, said Dr. Gagel. However, an even more pragmatic approach is currently being developed in his laboratory.

"We're actually going back to a ribozyme in which we inactivate all the *RET* genes," said Dr. Gagel. His plans are to use a calcitonin-specific promoter that will be expressed only in C-cells, the cells in which MTC occurs. With this approach, a single construct could be used to inactivate *RET* genes carrying a variety of mutations, and therapy could be targeted specifically to cancer cells.

While Dr. Gagel's research aims to directly inactivate a receptor tyrosine kinase involved in hereditary MTC, research in Dr. Yeung's laboratory aims to disrupt another component of a similar pathway in anaplastic tumor cells.

Anaplastic thyroid carcinoma is the most aggressive of all the thyroid cancers, and metastasis is virtually guaranteed by the time of diagnosis, according to Dr. Yeung. Surgery is of little benefit to these patients, and though hyperfractionated radiation and chemotherapy are often applied for local control, most patients do not live more than a year after diagnosis.

Dr. Yeung, who refers to anaplastic thyroid carcinoma as an "orphan disease," heads one of only two research groups in the United States who are working to develop new treatment strategies for the disease. He and colleagues are studying the combined effects of paclitaxel, a common chemotherapeutic drug, and the new farnesylation inhibitor manumycin on anaplastic tumor cells in culture. This is the first time that manumycin has been examined in anaplastic cell lines, and it is the first time that it has been used in combination with paclitaxel.

Like initial events in MTC, some initial events in anaplastic carcinoma may involve mutations in growth receptors, but

many instead involve mutations in the *ras* proto-oncogene. The *ras* gene encodes an intracellular protein that works at the cell membrane to help transmit growth signals received by receptor tyrosine kinases. For *ras* to anchor itself to the plasma membrane, it must undergo post-translational modification in which a lipophilic tail, often composed of a farnesyl group, is attached to the protein. The process is catalyzed by an enzyme called farnesyl protein transferase, and farnesylation inhibitors (such as manumycin) prevent tumor growth by blocking activity of this enzyme.

"What we have shown is that the anticancer effect of paclitaxel is enhanced by manumycin. The two drugs potentiate the action of each other, and the possible mechanism for antitumor activity is induction of apoptosis," Dr. Yeung said. The drug combination is similarly effective against human tumors implanted into nude mice.

There are at least 13 other proteins that work in the same fashion as *ras* to regulate cellular growth and differentiation, and effects of paclitaxel and manumycin on these proteins may also contribute to the drugs' anticancer activity. However, researchers still need to determine the kinetics of the drug combination and understand how the drugs interact before clinical trials for thyroid cancer and other aggressive tumors can be planned.

"Although anaplastic thyroid carcinoma is rare, I think it is a good model of an extremely aggressive tumor," said Dr. Yeung. "Therapeutic interventions that would work against anaplastic thyroid carcinoma would also be likely to work against other aggressive tumors," he said. ●

FOR MORE INFORMATION, contact Dr. Sellin at (713) 792-2841, Dr. Gagel at (713) 792-6517, or Dr. Yeung at (713) 792-3722.

See page 6 for a related article.

*Assistant Professor of Internal Medicine
Specialties* **Dr. Sai-ching J. Yeung** uses a fluorometer to measure the effects of manumycin, a new farnesylation inhibitor, on cell migration. Dr. Yeung leads one of two research groups in the United States who are working in the laboratory to develop new treatment strategies for anaplastic thyroid carcinoma.



Efforts in Thyroid Cancer Treatment Include Initiation of Multicenter Clinical Trials

by Kerry L. Wright

Clinical trials of treatments for thyroid cancer have been few and far between, but current national efforts are helping to ensure that the future of thyroid cancer research will not be a reflection of its past.

"The future for thyroid cancer will be improving prognostication and emphasizing and initiating clinical trials to determine optimal therapeutic approaches," said Steven I. Sherman, M.D., an associate professor in the Department of Internal Medicine Specialties at The University of Texas M. D. Anderson Cancer Center.

Dr. Sherman leads The National Thyroid Cancer Treatment Cooperative Study Group, an assembly of 13 institutions that have formed a database to record prospective diagnostic, treatment, and follow-up data from patients with thyroid cancer. The database was created in 1987 at the University of Cincinnati in response to a lack of support for clinical trials. Its headquarters moved to M. D. Anderson in 1999, shortly after Dr. Sherman took over leadership of the study group.

Because thyroid cancer is rare and its long-term survival statistics are good, a high percentage of patients must be recruited to produce meaningful data in a clinical trial. For this reason, even current treatments including surgery, radioactive iodine, and thyroid hormone have never been studied in randomized, prospective trials.

Analysis of the study group's database has already shown that the current staging systems for thyroid cancer are not very predictive, that radioactive iodine treatment can improve outcomes for patients at high risk for death, and that thyroid hormone suppression therapy is

associated with an improved disease-free survival rate. Current analysis is focusing on physician practice patterns and how various therapies and diagnostic tools, such as recombinant thyroid stimulating hormone (TSH), are being used at different institutions.

M. D. Anderson was involved in an international phase III clinical trial that led to the Food and Drug Administration's approval in 1998 of recombinant TSH as a diagnostic tool for thyroid cancer. Recombinant TSH can now be given to patients by injection, in lieu of induction of hypothyroidism, to more quickly facilitate the thyroid's absorption of radioactive iodine so that radioactive scanning can be used to diagnose disease.

"These studies will do things like examine the role of adjuvant radiation therapy for older patients with invasive thyroid cancer and examine new approaches to chemotherapy."

Patients must often be taken off thyroid hormone for five to six weeks before they can produce enough of their own TSH for radioactive iodine treatment, and this not only causes fatigue but can also stimulate tumors to grow and can temporarily worsen medical conditions such as heart failure. Although radioactive scanning performed after recombinant TSH treatment is not as sensitive as scanning via the traditional method, it can benefit many patients whose quality of life may have otherwise been severely compromised.

"This is the first drug that has been approved for thyroid cancer in about 15 years," said Dr. Sherman.

"It is also the first time in about two decades that anybody has successfully organized a cooperative clinical study in thyroid cancer." According to Dr. Sherman, the TSH trial shows that patients can be successfully recruited for trials and that the trials can lead to improvements in thyroid cancer treatment.

"Our long-term priority is to get back to having ongoing cooperative trials," said Dr. Sherman. "These studies will do things like examine the role of adjuvant radiation therapy for older patients with invasive thyroid cancer and examine new approaches to chemotherapy."

Though support for clinical trials is still being garnered, trials are being initiated, even in the absence of sponsors. Michael A. Burgess, M.D., deputy chairman of the Department of Melanoma/Sarcoma Medical Oncology, is the principal investigator for a pilot study of paclitaxel in patients with thyroid cancer or adrenal cortical cancer that has not been controlled by surgery or radiation therapy. Dr. Burgess is also studying the use of gemcitabine to treat patients with progressive thyroid or adrenal malignancies.

To initiate large sponsored trials of thyroid cancer, the National Cancer Institute (NCI) recently granted the American College of Surgeons a cooperative oncology group with an Endocrine Tumor Working Committee that includes physicians from M. D. Anderson.

"We are trying to address really fundamental therapy questions, and it is going to take a long time and a lot of work to do it, but the NCI is viewing this as a model for how to develop cooperative group trials for rare or uncommon diseases," said Dr. Sherman. "Clinical trials: this is now the buzzword in thyroid cancer." ●

FOR MORE INFORMATION, contact Dr. Sherman at (713) 792-2841 or Dr. Burgess at (713) 792-3626.



Gene Therapy: Changing the Way Cancer Cells Behave

New treatments for cancer are constantly being developed. Most focus on new drugs or new ways of administering drugs, advances in surgery, or improvements in radiation therapy. One innovative approach to treating cancer that is currently being tested in clinical trials is called gene therapy.

What is gene therapy?

Gene therapy is the process of transferring genes into target cells in a patient's body for therapeutic purposes. The human body is composed of countless numbers of cells, each containing the same genetic material, including approximately 100,000 genes. However, different genes are expressed or activated in different cell types, so many genes lie dormant and do not contribute to how a specific cell functions. (Cells in the heart, for example, do not behave the same as those in the lungs, and tumor cells act differently than healthy ones, partly because of which genes are expressed.) In cancer, abnormal gene expression is a result of mutations in important genes. The aim of gene therapy for cancer is to transfer specific genes into a patient's tumor cells to either alter abnormal gene function, express a missing or new gene function, or inhibit abnormal gene function so that tumor cells function normally or are forced to undergo cell death.

Not all genes are good candidates for gene therapy, so many factors must be considered before a new therapeutic gene is tested, including the mechanism by which it works, its size, how and when it is expressed, and the expected effect of targeting that gene to a specific cell type. Most genes are transferred into the body through a vector, or carrier. Genetic

material can be carried by a virus or delivered by nonviral methods. If a virus is used, it can be manipulated so that it will not cause sickness in a person. The human therapeutic gene can be inserted directly into the viral genetic package, which is then introduced into a patient's body where it enters the cell type for which it was designed.

Types of gene therapy

There are many types of gene therapy for cancer, and each has been developed with a specific focus. These are some of the more common types:

Replacement gene therapy aims to replace a mutated gene with a normal version of the gene. This approach is currently being tried with the tumor suppressor gene *p53*, the most commonly mutated gene in cancer. *p53* normally functions to suppress cell growth, so cells are more likely to grow out of control and form tumors when it is mutated. If gene therapy can replace mutated *p53* and similar genes, then it could be used to treat patients with a variety of cancers.

In **pro-drug gene therapy**, patients are treated with drugs that are harmless to normal cells but kill cancer cells expressing the transferred gene. A gene that is mainly active in malignant cells is delivered into a patient's tumor cells. When a particular drug is administered to the patient, the tumor cells specifically metabolize it and produce analogues that are toxic to the tumor cells, causing them to die.

Chemosensitization gene therapy utilizes the expression of a therapeutic gene, often *p53*, in a tumor cell to make the cells more sensitive to chemotherapy or radiation therapy. Radiation therapy and many chemotherapy drugs work by damaging the DNA of tumor cells and causing the

cells to die. *p53* normally functions to suppress cell division or to kill cells if the cell's DNA is damaged. In some tumors, when these therapies are combined, the expression of *p53* in the tumor cells can cause increased sensitivity of the cells to chemotherapy and radiation therapy.

Immunomodulatory gene therapy delivers specific genes to tumor cells where they are expressed on the cell surface. The body's immune system then recognizes the molecules as foreign and attacks the tumor. This method acts to increase the body's own immune response against cancer.

The future of gene therapy

While the goals of gene therapy are simple, it is still a highly complicated process with many hurdles to get over before it becomes a standard treatment. Scientists are working diligently in the laboratory to make gene therapy as selective and efficient as possible. In addition, review committees are working to ensure the safety of all gene therapy protocols before they are used in the clinic.

Though standard use of gene therapy for the treatment of cancer is likely years away, it has been effective in laboratory settings and shows promise for the future of human cancer treatment.

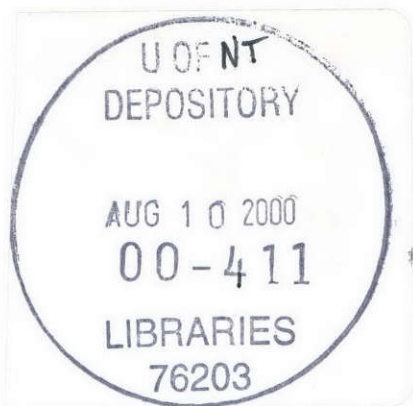
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Preventing Cancers of the Upper Aerodigestive Tract: Challenges for Clinicians

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Cancers of the upper aerodigestive tract significantly contribute to cancer-related morbidity and mortality in the United States (an estimated 52,900 new cases and 24,500 deaths in 1999 alone). From the early 1970s to the early 1990s, the death rates from esophageal cancer increased 24% among men and 7% among women.

The use of tobacco and alcohol are considered to be the most important risk factors for these cancers (oral cavity, pharynx, larynx, and esophagus). Studies have shown that alcohol and tobacco appear to be independent and synergistic risk factors. Consumption of tobacco and alcohol are frequently concomitant behaviors; tobacco use is higher among those who drink alcohol, and the consumption of alcohol is higher among tobacco users.

Findings from a French investigation suggest that even heavy smokers may reduce their risk of cancer by quitting smoking.

Clinicians are in an excellent position to help their patients quit smoking, but to

do so effectively requires familiarity with the basic principles of smoking cessation counseling and pharmacological treatment. Nicotine gum and patches have been proven to increase smoking cessation rates by 60% and 100%, respectively. The nicotine inhaler and nasal spray are also now available by prescription, and the Food and Drug Administration has recently approved the smoking cessation drug bupropion.

This year, a revised edition of *The Smoking Cessation Clinical Practice Guideline*, which summarizes the most effective methods of treating nicotine dependence, will be published by the Agency for Healthcare Research and Quality (AHRQ), and we highly recommend that every clinician become familiar with it. The guideline urges clinicians to follow five steps: (1) systematically identify all smokers; (2) strongly advise all smokers to quit; (3) determine a smoker's willingness to quit; (4) motivate smokers who are not willing to quit smoking immediately and assist those who are willing to quit by having them set a quit date, offering pharmacological quitting aids, and providing self-help materials and skill training; and (5) schedule a follow-up contact. More information about the AHRQ guideline can be found on the World Wide Web (<http://www.ahrq.gov/research/apr96/dept8.htm>).

Helping patients stop smoking is the single most important step physicians can take to reduce the burden of cancer mortality.

The University of Texas
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