Innovative Strategies for Less Common Thyroid Cancers

For 50 years, doctors have successfully treated most cases of thyroid cancer with a combination of surgery to remove the tumor and radioactive ^{131}I to eliminate residual cancer cells. Radioiodine has been effective against the two most common forms of thyroid cancer: papillary and follicular. Now, doctors are developing strategies for treating the less common medullary and anaplastic forms.

Cancer of the thyroid makes up only about 1.1% of all human malignancies, according to the University of Pennsylvania Cancer Center, Philadelphia, PA, but it is the most common cancer of the endocrine system. It also is much more common in women than in men.

The only known causative factor for thyroid cancer is exposure to radiation. People who receive radiation treatment for medical problems in the head and neck may have an increased chance of developing thyroid cancer, which might not occur until 20 years or more after the radiation treatment. Routine diagnostic radiographs have not been shown to cause thyroid cancer. Ironically, radiation is also a curative factor for most cases of thyroid cancer.

The conventional course of treatment is surgical removal of part or all of the thyroid, followed by the administration of radioactive ^{131}I. Iodine normally collects in the thyroid, which uses it to produce thyroid hormone. Radioiodine concentrates in any residual thyroid cells after surgery and destroys them. With the help of thyroid-stimulating hormone from the pituitary gland, even thyroid tumor cells that have spread to other parts of the body will take up enough radioiodine to destroy cancerous cells without damaging surrounding healthy tissue. External-beam radiation and chemotherapy also are sometimes used, but they are not very effective.

The conventional treatment is effective for the two most common forms of thyroid cancer, papillary and follicular, which make up about 90% of all cases of thyroid cancer.

Papillary thyroid cancer is the most common form and makes up about 70% of all cases, or about 12,000 new cases per year in the U.S. Papillary thyroid cancer tends to grow slowly and spread through the lymphatic system. However, metastasis to nearby lymph nodes usually does not alter the disease's excellent prognosis. With surgery and radioiodine therapy, the survival rate from papillary thyroid cancer is 85%–90% after 20 years.

Follicular thyroid cancer is the second most common form, occurring in about 10%–15% of thyroid cancer cases. Follicular thyroid cancer is more aggressive than the papillary type and may grow into blood vessels, through which it can metastasize to distant locations such as the lungs and bones. The survival rate for follicular thyroid cancer patients is about half that for papillary thyroid cancer patients.

Papillary and follicular thyroid carcinomas are referred to as well-differentiated tumors, meaning that they retain many of their normal, noncancerous functions.

Unfortunately, the two less common forms of thyroid cancer—medullary and anaplastic—ordinarily do not respond to conventional ^{131}I treatment. Medullary and anaplastic thyroid carcinomas are poorly differentiated. Anaplastic thyroid cancer cells no longer accumulate ^{131}I, and medullary thyroid cancer develops out of a totally different type of cell within the thyroid, C cells, which do not normally concentrate iodine. Because these types of thyroid cancer are more aggressive than the other types, grow fast and metastasize early, surgery is the only effective treatment.

Medullary thyroid cancer accounts for only 5%–10% of thyroid cancer cases. A genetic abnormality has been found in about 20% of patients with medullary thyroid cancer. The University of Penn-

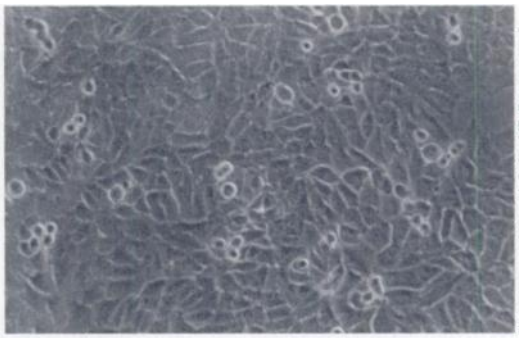
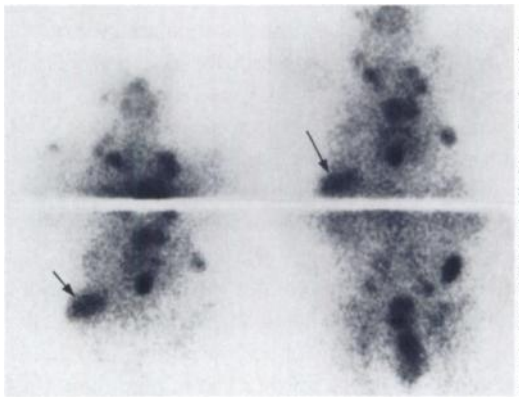


Photo courtesy of Kenneth B. Ain, MD, Department of Internal Medicine, University of Kentucky Chandler Medical Center, Lexington, KY.

FIGURE 1



Photos courtesy of Malik Juweid, MD, Garden State Cancer Center, Belleville, NJ.

FIGURE 2

FIGURE 1. Phase-contrast photomicrograph of confluent monolayer culture of human anaplastic thyroid carcinoma cell line, DRO-90. This cell line is one of several that provide model systems for investigations into cell biology and experimental therapeutics of anaplastic thyroid cancer.

FIGURE 2. Multiple planar views of head and neck (upper left), chest (upper right), abdomen (lower left) and pelvis (lower right) obtained 7 days after infusion of 8 mCi (0.7 mg) ^{131}I-MN-14 $F(ab)_2$ anticarcinoembryonic antigen antibody in patient with medullary thyroid cancer show multiple bony metastases in right humeral head, sternum, spine, ribs and pelvic bones in addition to cervical and mediastinal adenopathy and large soft-tissue mass in right lower thorax wall (arrow).

"Monoclonal antibodies against certain antigens on the surface of medullary thyroid carcinoma can function as vehicles to carry these isotopes to the tumor."

sylvania Cancer Center advises that any person with medullary thyroid cancer, along with his or her family members, should be tested for this genetic variation. Family members with the genetic mutation should undergo preventive thyroid removal.

Anaplastic thyroid cancer is even less common than the medullary form (fewer than 300 cases per year in the U.S.), but it is the most deadly of the primary forms. "It is the most aggressive solid tumor in the human body," according to Kenneth B. Ain, MD, associate professor of medicine, University of Kentucky, Lexington, KY. "It grows the fastest, spreads the most and kills the most." It does not respond to treatment with most chemotherapy drugs, and patients usually die within 4 months of diagnosis (Fig. 1).

Perhaps because of the historical success of ^{131}I in treating the most common forms of thyroid cancer, many treatments for the less common forms center on making the tumors vulnerable to ^{131}I treatment.

Monoclonal Antibodies—Malik Juweid, director of nuclear medicine, Garden State Cancer Center, Belleville, NJ, is working on a treatment for medullary thyroid cancer that binds ^{131}I to an antibody that specifically targets the tumor cells. Juweid explains, "Monoclonal antibodies against certain antigens on the surface of medullary thyroid carcinoma can function as vehicles to carry these isotopes to the tumor."

Because medullary thyroid cancer cells carry carcinoembryonic antigen (CEA) on their surfaces, Juweid uses anti-CEA antibodies to deliver ^{131}I to medullary thyroid cancer cells anywhere in the body (Fig. 2). The antibody can carry radioactive ^{111}In or ^{90}Y instead of ^{131}I, and Juweid is preparing to begin clinical trials with ^{90}Y. He says that using ^{90}Y should produce a twofold increase in the ratio of tumor-to-nontumor radiation dose. In addition, this will make this form of treatment possible on an outpatient basis.

Along with CEA, medullary thyroid cancer cells produce calcitonin. "Since many patients with established and occult [undetected] MTC [medullary thyroid cancer] express and release CEA," wrote Juweid in a 1996 article in the *Journal of Clinical Oncology* (Juweid M, Sharkey RM, Behr T, et al. Improved detection of medullary thyroid cancer with radiolabeled antibodies to carcinoembryonic antigen. *J Clin Oncol* 1996;14:1209–1217), "radiolabeled anti-CEA monoclonal antibodies (MAbs) may hold promise both for the detection and for the potential treatment of residual, recurrent or metastatic disease."

Juweid found that radiolabeled anti-CEA MAbs did an excellent job of finding medullary thyroid cancer sites, even those not detected by any other imaging method, including MRI, CT, ultrasound and bone scans. "Our data are especially encouraging," wrote Juweid, "since the antibody scan was the only positive imaging study in 7 of 9 assessable patients with occult disease. These patients had disease suspected only by serum tumor marker studies [CEA and/or calcitonin], with negative findings by conventional imaging methods."

In one of Juweid's studies, 7 of 14 evaluable patients showed evidence of moderate antitumor effects that lasted up to 26 months (Juweid M, Sharkey RM, Behr T, et al. Radioimmunotherapy of medullary thyroid cancer with iodine-131-labeled anti-CEA antibodies. *J Nucl Med* 1996;37:905–911). Juweid also has seen promising results using higher radiation doses in combination with bone marrow or peripheral stem cell transplantation. Median tumor-to-nontumor radiation absorbed dose ratios ranged from 5.0 for the liver to 7.9 for the lung, two of the organs most vulnerable to radiation damage.

Gene Therapy—Leslie DeGroot, professor of medicine, University of Chicago, Chicago, IL, is working on treatment of medullary thyroid cancer using gene therapy. DeGroot has effectively destroyed medullary thyroid cancer tumors in mice using an adenovirus to insert a gene into the tumor cells. The inserted gene changes the tumor cell in such a way that the cell is killed by the body's natural immune system.

DeGroot is also experimenting with using the same adenovirus to insert a different gene into medullary thyroid cancer tumor cells. In this case, the genetically altered tumor cells produce calcitonin that is fused to thymidine kinase. If doctors then inject ganciclovir into the tumor, the ganciclovir will destroy the tumor cells.

Iodine Promoter—Ain and his colleagues at the University of Kentucky have successfully cloned the promoter, or control, part of the gene for the sodium iodide symporter (NIS). NIS codes the component of the membrane of thyroid cells that pumps iodine into the cells, making it possible to locate and treat thyroid cells with radioiodine. "What some of our research is involved in," says Ain, "is why, in some circumstances, thyroid cancers lose expression of NIS, so that they no longer can concentrate iodine and be detected or treated with radioiodine."

Anaplastic thyroid cancer cells express NIS, according to Ain, but a breakdown in translation from deoxyribonucleic acid to protein means that anaplastic thyroid cancer cells do not concentrate iodine. Ain is studying where the translation breaks down in anaplastic tumors.

Ain is also investigating how anaplastic tumor

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Thyroid Cancer

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cells resist chemotherapy drugs. He is gathering patients for a human trial of the drug paclitaxel, or Taxol, which is the only chemotherapy drug that has been shown to be active in anaplastic thyroid cancer. Just as there are mechanisms on the cell membrane that pump in iodine, there are mechanisms on some cancer cells that pump out chemotherapy drugs. Controlling these pumps could make the cancer cells more vulnerable to the drugs.

Potassium Iodide for Prevention—Along with successfully treating most thyroid cancer cases, iodine can also be effective in preventing thyroid cancer. Radioactive iodine is a product of fissioning uranium and could be released into the environment by a serious accident at a nuclear reactor, causing unintended thyroid damage or cancer. If a stable isotope of iodine, in the form of potassium iodide (KI) tablets, is administered before exposure to radioactive iodine, the stable isotope builds up in the thyroid, thus blocking entry of the radioactive iodine and limiting the damage.

The American Thyroid Association's Public Health Committee recommends stockpiling KI tablets for prophylaxis in the event of a nuclear reactor accident. Peter Crane, who had petitioned the U.S. Nuclear Regulatory Commission (NRC) to change its policy to endorse KI stockpiling in addition to evacuation and sheltering after a nuclear reactor accident, spoke at a November 5, 1997, meeting of the NRC commissioners. He stated, "Potassium iodide is an effective, safe and cheap medicine, with a long shelf life. It prevents thyroid cancer and other thyroid diseases by blocking the absorption of inhaled or ingested radioactive iodine....In fact, 3 years ago the NRC's technical staff calculated that it would be cheaper to buy a national stockpile of KI—for a total of a few hundred thousand dollars, or $1100 for the average plant—than to go on studying whether to do so."

Crane argued that the accident at the Chernobyl nuclear power plant showed that thyroid cancer is indeed a major result of a large reactor accident, even when evacuation is carried out. Experience in Poland, where KI is stockpiled, shows that large-scale deployment of KI is safe, he said, and that the accident at the Three Mile Island nuclear power plant showed that it is difficult to obtain a sufficient supply of KI in an emergency.

The NRC does not require the stockpiling of KI tablets, even though in March 1994 NRC staff advised doing so. "It appears prudent to stockpile KI for limited populations located close to the operating nuclear power plants. This option represents an interoffice consensus and is recommended by the [NRC] staff. While NRC encourages the stockpiling of KI, the decision to stockpile, distribute and use KI would be the responsibility of the individual states."

—Allen Zeyher

Annual Meeting Press Coverage

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by two national Canadian daily newspapers.

In the U.S., SNM received two first-time media hits. In coverage from June 19 through June 21, CNN aired a story about the use of lymphoscintigraphy to detect the spread of breast cancer less invasively and in a less costly manner than conventional surgery. The segment featured a pre-Meeting interview with co-spokesperson Naomi Alazraki, MD, Emory University, Atlanta, GA. Millions of CNN viewers worldwide learned how nuclear medicine can spare women with breast cancer the complications of unnecessary surgery to learn if their cancer has spread to the lymph nodes. In addition, several Atlanta television stations aired similar stories featuring Alazraki. This coverage was achieved with contacts and assistance from the Public Affairs Office of the Emory University Health and Sciences Department.

The other first-time media opportunity SNM realized was having its news posted on a popular World Wide Web news site. Reuters Health Information Services featured a story about the use of SPECT in emergency departments to diagnose heart disease and another story about lymphoscintigraphy. The reporter from Reuters Health online attended the press conference via teleconferencing, which was offered for the first time at the 1998 Meeting. This online media coverage was achieved with contacts and assistance from the Public Relations Department at Miami Cardiac and Vascular Institute.

The Annual Meeting also received some first-time coverage in the trade press. In addition to coverage by *Advance, Diagnostic Imaging* and *Applied Radiology*, reporters from *The Medical Post, Oncology News International* and *Administrative Radiology* also attended the press conferences and many scientific sessions. At the trade press conference, Robert F. Carretta, MD, Roseville Community Hospital, Roseville, CA, served as spokesperson and moderated a roundtable discussion between reporters and Daniel S. Berman, MD, Cedars-Sinai Medical Center, Los Angeles, CA; Hans J. Biersack, MD, University of Bonn, Germany; R. Edward Coleman, MD, Duke University Medical Center, Durham, NC; and Donald A. Podoloff, MD, Houston, TX. In addition, *Radiology Imaging Letter, Health Technology Trends* and *RT Image*, which were unable to be represented at the Annual Meeting, are expected to publish articles on the new nuclear medicine research.

Post-Meeting coverage will continue for several months as a result of nationwide syndicated release of three newspaper articles and one radio public service announcement (PSA). The articles and PSA address breast lymphoscintigraphy, SPECT in emergency departments and nuclear cardiology's applications in women's heart disease. These pieces will be running in small- to medium-sized markets and will list SNM's phone number and web site to contact for more information. This is SNM's first time using this newspaper syndication service.

Although this year's coverage was more limited than in 1997, the news coverage achieved in both the consumer and trade press is valuable to the Society's efforts to educate the public and referring physicians about the value and benefits of nuclear medicine.

—Carolyn Pemberton