Iodine-131 as an Oncology Agent

Judith M. Bender and Howard J. Dworkin

Nuclear Medicine Department, William Beaumont Hospital, Royal Oak, Michigan

This is the third article in a four-part series on nuclear medicine oncology procedures. Upon completion, the technologist will be able to (1) describe the evolution of iodine-131 ablation, (2) list rationale and indications for its use, and (3) discuss management of the patient before, during, and after treatment.

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Though controversy still exists regarding its efficacy, sodium iodine-131 (^{131}I) has become the oncologic treatment of choice for papillary and follicular thyroid carcinoma. This article will thoroughly discuss the technical aspects as well as the specific patient care management issues involved in ^{131}I ablation therapy.

I-131 was first introduced in the early 1940s as an oncologic agent in the treatment of papillary and follicular thyroid cancer. Over the past 50 years, this radionuclide has become a well accepted and often used therapy for thyroid malignancies. This article will describe the evolution of ^{131}I ablation as well as the rationale and indications for its use. The technical details of the drug's preparation and administration and the management of the patient before, during, and after treatment will be discussed. Finally, the use of ^{131}I for the treatment of other malignancies will be briefly addressed.

Prior to discussing the use of ^{131}I as a therapeutic agent, it is necessary to have some knowledge of the disease entity being treated. Thyroid cancer is a relatively rare malignancy occurring in approximately 12,000 new patients per year (*1*). This disease occurs with the highest frequency in the fourth and fifth decades of life and is twice as common in women as in men (*2,3*). Exposure to external beam radiotherapy to the head and neck causes an increased incidence of thyroid cancer as high as 5%–7% (*4*).

Thyroid cancer can be classified into four major groups. Papillary cancer is the most common type representing approximately two-thirds of all thyroid malignancies. This category includes those tumors which are purely papillary and those that contain both papillary and follicular elements, since these tumors biologically behave like a papillary cancer, even if the papillary component is the minor portion. Papillary cancers tend to be slow growing, multifocal, unencapsulated neoplasms that metastasize to local lymph nodes (*5*).

Follicular cancer of the thyroid accounts for 10%–20% of all cases. It is usually a solitary encapsulated tumor which occurs in an older age group than papillary cancer. This tumor tends to invade vascular structures and metastasize to the lung and bone (*5*). A subset of follicular cell carcinoma is the oxyphilic cell type or Hurthle cell tumor. This tumor behaves similarly to routine follicular thyroid cancer, but it does not concentrate ^{131}I (*6*).

Medullary cancer of the thyroid constitutes 6%–10% of thyroid cancers and originates in the parafollicular C-cells.

Anaplastic tumors make up 4%–6% of thyroid cancers and are the result of dedifferentiated papillary or follicular cancer. They are locally invasive with regional spread and early distant metastases.

The first sign of thyroid cancer is often a palpable asymptomatic thyroid nodule found on a routine physical examination. Two approaches have been advocated. Fine needle aspiration biopsy can be done as the initial step in evaluation, followed by radionuclide scanning only if the cytologic results are indeterminate or there is evidence of thyrotoxicosis (*1*). Alternatively, a radioiodine or technetium scan is carried out initially to determine if the nodule is hypofunctional (Fig. 1). If it is, a fine needle aspiration can then be done. Surgical removal of a nodule is suggested if the fine needle aspiration is positive or suspicious. Ultrasound may be helpful to determine the volume of a nodule but does not address its histology or function. Approximately 6%–20% of cold nodules prove to be malignant (*7*).

Once thyroid cancer is diagnosed, surgical removal is mandatory. The extent of the initial surgical resection is controversial. Some centers feel that a lobectomy and isthmectomy is sufficient for a solitary encapsulated papillary lesion that is <1.5–2.0 cm (*1*). Others feel that any cancer should be treated with a total thyroidectomy for several reasons: to remove multifocal cancer, to treat with sodium ^{131}I, for staging and diagnosis, or to determine prognosis. The rationale for total thyroidectomy is to remove multifocal cancers and ensure that ^{131}I goes to residual malignant cells and not to the remaining normal thyroid. If portions of healthy thyroid are not removed, then pretherapy ^{131}I scans

For reprints contact: Judith M. Bender, MD, St. Joseph Mercy Hospital, Dept. of Radiology, 900 Woodward, Pontiac, MI 48341.

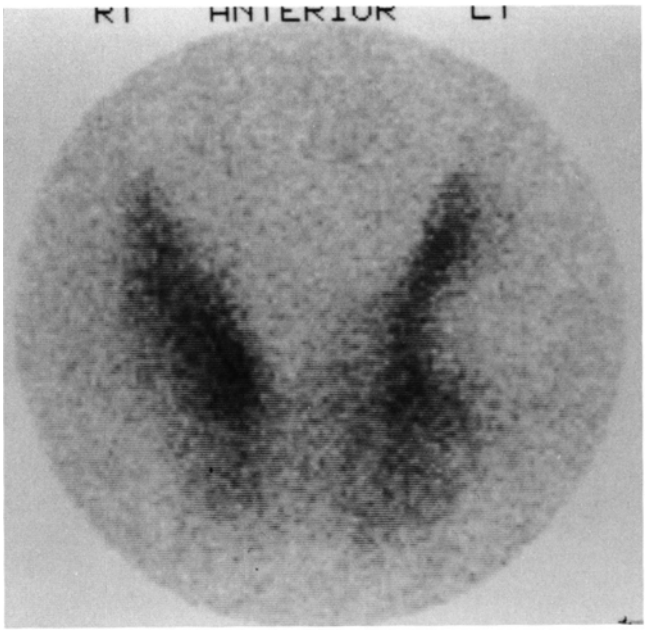

FIG. 1. Technetium thyroid image obtained 10 min after administration of 10.7 mCi of ^{99m}Tc pertechnetate shows a hypofunctional area in the midpole of the left lobe. On palpation, this area corresponds to a 2-cm firm discrete nodule, which on biopsy proved to be a follicular carcinoma.

will not be as likely to pick up residual disease. Resection of any involved cervical nodes is also advocated.

Because many variables effect the course of this uncommon disease, there is a lack of consensus on the proper therapy and follow-up care for papillary and follicular thyroid cancer. To make an intelligent decision regarding treatment options, attention must be paid to prognostic factors, specifically those that affect the outcome of well-differentiated thyroid cancer. The single, most important factor is age at the time of initial diagnosis; young patients, ages 20–40, have an excellent outcome. Local cervical node involvement increases the rate of reoccurrence, but not death. Multifocal disease, extracapsular extension, primary lesions >3.0 cm, or distant metastases are known to raise the risk of reoccurrence and death (*8*).

HISTORICAL OVERVIEW

For many years, primary thyroid cancers were treated with surgical resection and therapy for documented metastatic lesions was limited to external beam radiation. Keston et al. of Columbia University first described the uptake of radioiodine in metastatic lesions of thyroid cancer in 1942 and in later work suggested that this agent might be helpful in the treatment of such patients (*9*). Seidlin and associates at Montefiore Hospital in New York City were the first to actually use ^{131}I as an oncologic agent.

The initial patient was a middle-aged man who developed thyrotoxicosis secondary to extensive functional metastatic disease from thyroid cancer. The first course of radioiodine in 1943 consisted of a total of 102 mCi (3774 MBq of Na-^{130}I) and 20.5 mCi (758.5 MBq of Na-^{131}I), from which the patient experienced pain palliation and a decrease in his basal metabolic rate. The patient was subsequently treated with two additional doses of Na-^{130}I and Na-^{131}I in 1944 and 1945. Following each of these later doses, the patient was given "refeeding doses." These doses were actually Na-^{131}I that had been extracted from the patient's urine and re-fed to the patient 1–3 days after his initial dose (*10*). Publication of Seidlin's work in 1946 prompted public and monetary support for further investigation of this "cancer cure" (*11*). Fifty years later, Na-^{131}I is the oncologic treatment of choice and is available at virtually every large medical center.

Many arguments have been made both for and against the use of ^{131}I ablation therapy following surgical resection. There are still many centers that feel that young patients with well differentiated solitary tumors have an excellent prognosis and have similar outcomes with or without ^{131}I treatment (*12*). Other groups put forth strong arguments and cite multiple studies showing lower rates of reoccurrence and prolonged survival rates for patients treated with ^{131}I compared to those who do not receive treatment (*13*) (Fig. 2). Generally, patients with well differentiated papillary or follicular thyroid cancer, possessing one or more of the characteristics listed in Table 1, are felt to be candidates for ^{131}I ablation therapy (*8*).

PATIENT PREPARATION

Prior to I-131 ablation therapy, the patient must undergo an extensive workup and a near total thyroidectomy. Exogenous thyroxine containing hormone must be discontinued 6 wk prior to treatment to allow optimal endogenous thyroid-stimulating hormone (TSH) elevation. Some physicians place their patient on the shorter acting triiodothyronine (T3) for the first 3–4 wk, and then discontinue it for 12–14 days prior to treatment. Others feel that patients have a greater increase in their endogenous TSH and a better uptake of ^{131}I if they are off thyroid replacement completely for at least 6 wk. At one time, bovine TSH was used to increase stimulation of functional tissue. This, however, has been largely discontinued secondary to allergic reactions and the observed development of neutralizing antibodies (*13*). The goal is to raise the serum level of TSH to >30–50 μIU/ml.

A low iodine diet for 7–10 days prior to ablation therapy is also advocated. This regime will decrease the extracellular iodine pool and may double the delivered radiation dose per millicurie of ^{131}I administered to the thyroid tissue (*13*).

Lithium carbonate, which has long been used to treat manic depressive disease, is known to significantly decrease thyroid iodine release. When given for 1 wk prior to ^{131}I therapy, the adjunctive use of lithium may result in lengthening the biological half-life of ^{131}I in metastatic lesions, thus increasing the radiation dose delivered (*13*).

Within the week prior to treatment, the following laboratory work should be completed.

- TSH
- Thyroglobulin (a baseline level can be used as a tumor marker)

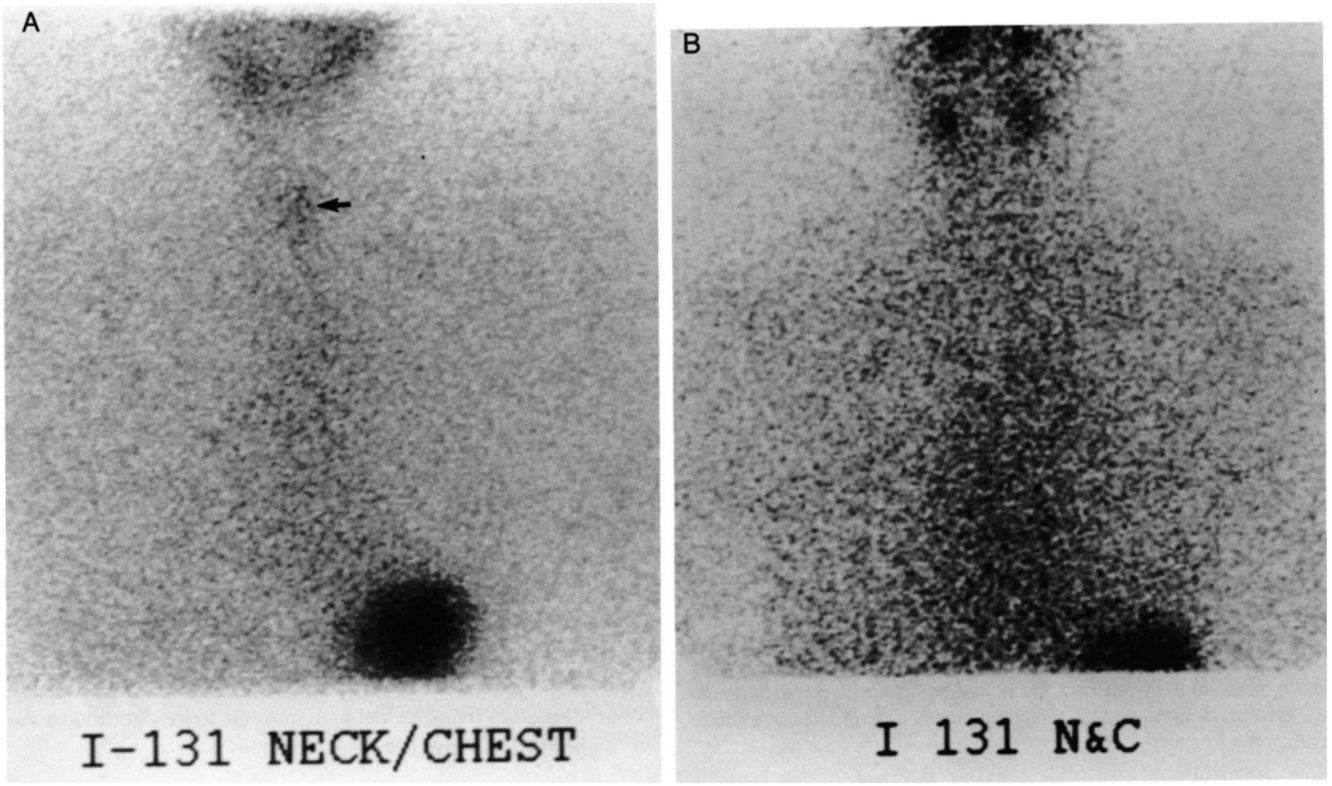

FIG. 2. (A) ^{131}I neck and chest image using 3.1 mCi of ^{131}I-labeled sodium iodide shows one area of increased uptake in the midthyroid bed, which was ablated with 173 mCi of ^{131}I. (B) A ^{131}I neck and chest scan was performed 1 yr later and the previously seen uptake in the midneck was no longer present.

- CBC (baseline hemoglobulin, WBC and platelet levels)
- Serum BUN/creatinine (to check renal function)
- Urinalysis (to screen for occult urinary tract infection)
- Serum calcium (to check parathyroid function)
- BETA HCG (in all women of childbearing age)
- Chest X-ray (to screen for pulmonary mets)

After the patient has been off exogenous thyroid hormone for 6 wk and has a TSH level of >30–50 μIU/ml, a 2–10 mCi dose of ^{131}I is administered. A 24–48-hr ^{131}I uptake and whole-body or neck and chest scans are then performed. The uptake is measured so that the percentage of the administered ^{131}I dose that was taken up by the residual functional thyroid tissue can be determined. The usual values are 0.5%–5% depending on the extent of surgery and residual disease. Images are obtained of the neck and chest and, in some institutions, of the whole body. Pinhole and parallel collimator images over the thyroid bed should be done. It is the gamma rays of ^{131}I that allow images to be obtained. The greatest abundance of these (82%) are at 364 keV, so a high energy collimator with a large field of view is necessary.

Whether residual function of thyroid tissue is imaged depends on its size and depth, the ability of the tissue to concentrate radioiodine, the presence of background activity, the amount of ^{131}I given, and the imaging equipment used (*14*). Since even an extensive thyroidectomy usually leaves at least 2 g of thyroid tissue, there is invariably some residual uptake in the thyroid bed (*15*). The extent of uptake visualized on the scan as well as the calculated percent of uptake help determine the dose of radioiodine that the patient will receive.

TABLE 1. Characteristics of Patients Who Are Candidates for Iodine-131 Ablation Therapy

Ages 5–20, Men >40, and Women >45–50
Follicular cancer
Extracapsular extension
Multifoci of vascular invasion
Primary lesion larger than 2.0 cm
Distant metastases

TREATMENT GUIDELINES

Many institutions follow the guidelines set out by Beierwaltes. This protocol advises that at least 100 mCi be given to treat thyroid bed tissue; 150–175 mCi for uptake in cervical nodes, and 175–200 mCi for distant metastases (*8*). Other centers report that because functional metastases may lose their ability to function and take up ^{131}I, the largest dose of ^{131}I that is both therapeutic and safe should be used (*16*). Benua, and more recently Leeper et al., used blood samples, urine collections, and whole-body counts to determine whole-body retention and rate of clearance in determining the maximum safe dose (*16*). Maxon and his colleagues used

estimated size of the thyroid bed activity derived from the scan and surgical reports, as well as count rates under a calibrated uptake probe, to determine ^{131}I doses (*17*).

The maximum amount of radioiodine that can be administered is that which will deliver no more than 2 Gy (200 rad) to the whole blood, with a whole-body ^{131}I retention at 48 hr of <120 mCi (4440 MBq) or <80 mCi (2960 MBq) with pulmonary metastases (*13,16*).

Once the dose has been determined and informed consent obtained, the patient is ready for treatment. Some physicians treat the thyroid remnant with <30 mCi. In this case, the patient may be treated as an outpatient. For larger doses, the patient is admitted to a private hospital room because the U.S. Nuclear Regulatory Commission (NRC) requires isolation for any dose of ^{131}I that is >30 mCi.

It is the responsibility of the physician and the radiation safety officer (RSO) to insure that the patient's room is properly prepared and that correct isolation procedures are followed during the patient's hospitalization. Prior to administering ^{131}I-Na, appropriate linen and trash containers should be placed in the room, and the patient and staff should be instructed in their use. All food and drink must be delivered in disposable containers. The mattress should be covered with vinyl and the bathroom floor with absorbent paper to decrease the contamination of these surfaces. The phone may also be covered with plastic or vinyl. The patient is reminded to stay in the room at all times and to flush the toilet three times after use to ensure that the ^{131}I excreted in the urine is washed away.

Staff members caring for the patient are given film badges to monitor their radiation exposure and are advised to minimize the time spent in direct patient contact. Preferably, contact time should be kept to 10 min or less. Pregnant personnel are not allowed to care for the patient. The patient may have visitors for limited amounts of time, to be determined by the level of ^{131}I retained.

The patient should be kept NPO (nil per os) prior to, and for 2–4 hr after, receiving ^{131}I-Na to minimize the possibility of nausea and vomiting, and an antiemetic can be ordered if necessary. The patient should also be advised to suck on lemon wedges or sour balls to stimulate salivation and decrease the retention of ^{131}I in the salivary glands.

The physician should be sure that the appropriate dose of ^{131}I-Na is available from the hospital or commercial pharmacy prior to admission. Sodium iodide ^{131}I is available in capsule and liquid preparations. The hard gelatin capsules are available in multiple dose sizes and they contain sodium iodide mixed with semi-solid polyethylene glycol or absorbed on anhydrous sodium phosphate (*11*). Though encapsulated ^{131}I-Na is easier to handle when administered to the patient, there is some concern that poorly dissolved capsules may result in a decrease of the absorption of the drug. The capsule form also decreases the flexibility of the dose, though higher activity capsules can be allowed to decay to lower levels when a lesser amount is desired.

The liquid form of ^{131}I-Na is easily measured and doses can be finely adjusted. Unfortunately, liquid ^{131}I-Na is volatile and can be readily inhaled into the lungs if special precautions are not taken. Solutions are manufactured at an alkaline pH and kept refrigerated and shielded from the light. The vial should be opened only under an exhaust hood to vent the head space above the liquid before use. Two constant concerns with the liquid formulation are the potential for spills resulting in contamination of staff and environment and the potential for inhalation leading to thyroid irradiation.

Prior to administration of ^{131}I-Na, the physician must insert the designated dose into a dose calibrator to ascertain that the actual dose is within 10% of the ordered dose. The ^{131}I-Na is then conveyed to the patient's bedside in a lead pig. The patient's name, hospital number, and other identifying factors, as well as the amount of ^{131}I-Na, are again checked. If the ^{131}I-Na is liquid, the patient is draped with absorbent paper as is the bedside table. If the patient has dentures, they are removed. The patient is then instructed to drink the small amount of ^{131}I-Na solution through a straw. The vial is rinsed several times with water. After each rinse, the patient is asked to drink the residual water to ensure that the entire dose of ^{131}I-Na is ingested.

After oral administration, the ^{131}I-Na is absorbed rapidly from the gastrointestinal tract and is trapped and organified within residual functional thyroid tissue. As it undergoes beta decay to stable xenon-131 (^{131}Xe), it releases beta particles and gamma rays. The radiation dose from the ^{131}I is derived from beta emissions that have a maximum energy of 607 keV; these emissions deposit the majority of their energy within 2.2 mm of their site of origin (*18*). The energy is sufficient to destroy microscopic foci of malignant tumor and produce fibrosis, causing an unfavorable mileau for further neoplastic growth (*5*).

Immediately after administration of ^{131}I-Na and at least once each following day, the patient's retained ^{131}I level is measured, using an ionization survey meter at skin level and at 1 m. The information is used to calculate the residual patient activity level. The patient is hospitalized until the retained radioactivity is <30 mCi (1110 MBq) or the measured exposure rate from the patient is <5 mR/hour at 1 m (*19*). This level is usually reached in 2–3 days and can be hastened if the patient drinks copious amounts of fluid to promote urinary excretion of ^{131}I.

If the patient has received more than 12 mCi of ^{131}I-Na, it is advisable to instruct the patient, at the time of discharge, on how to maintain radiation safety precautions for the next 2–4 days. These precautions include avoiding prolonged close contact with others, especially infants, children, and pregnant women. Mouth to mouth contact including sharing food or eating utensils should also be avoided. The patient should be encouraged to use disposable dishes and silverware, or to wash utensils in the dishwasher or handwash them separately. Any clothes worn during hospitalization should be laundered separately. The patient should also continue to flush the toilet 2–3 times after each use.

When the patient is discharged from the hospital, the RSO or designee must monitor the room to rule out contamination (a radiation level of >2× that of background constitutes

contamination) before it can be used again. All trash and laundry must be surveyed with a Geiger counter. Any items that have levels above background radiation must be stored in an appropriate storage area until sufficient decay has occurred (usually to 10 half-lives). The pharmacist who prepared the dose and the individual who actually dispensed the dose must undergo a thyroid bioassay.

SIDE EFFECTS OF ^{131}I THERAPY

There are several side effects that can occur after ^{131}I ablation therapy. Those that occur immediately during the first few days of hospitalization include the following.

Nausea and Vomiting. These symptoms occur rarely in the first two days after treatment and tend to resolve by the time of discharge. These symptoms can be treated with antiemetics.

Sialadenitis. This includes complaints of pain, tenderness, and swelling of the salivary glands with dry mouth and bad taste. This occurs more commonly in the parotid then in the submandibular glands and typically starts the day after therapy (*20*). It resolves in three days and may be prevented with the use of lemon drops to stimulate salivation. Reserpine is also advocated (*13*). Aspirin can be used for pain relief. A dry mouth may last for one year.

Diffuse Neck Pain. Severe pain radiates into the ears and may be accompanied by odontophagia. It occurs 3–4 days after the administration of the dose and is most commonly seen in patients with extensive cervical soft tissue invasion. The diffuse neck pain is felt to be the result of tumor radiation necrosis.

Cerebral Edema or Spinal Cord Compression. This is a very rare complication secondary to posttreatment edema of metastatic functional lesions in the brain or spinal cord. Pretreatment prophylactic doses of glycerol or mannitol are advocated in patients with metastatic lesions in these locations. Corticosteroids are not recommended as they may decrease the uptake of ^{131}I in thyroid tissue (*4,13*).

Side effects that occur in the first 3 mo following discharge include the following.

Bone Marrow Suppression. Transient anemia, leukopenia, and thrombocytopenia are seen initially at approximately 4 wk after treatment and peak at 6 wk (*13*). The patient recovers spontaneously.

Vocal Cord Dysfunction. This is seen occasionally in posttherapy patients who have extensive soft tissue invasion near the vocal cords or recurrent laryngeal nerve. Iodine-131 can cause inflammation and edema in these areas.

Transient Hyperthyroidism. This is rarely seen in patients with large amounts of follicular functional thyroid cancer. It occurs 2–10 days after treatment as the tissue is destroyed. The patient should be treated with a beta blocker to minimize this transient hyperthyroid state.

Long-term side effects that occur more than 3 mo after ablation include the following.

Parathyroid Dysfunction. Those who exhibit this problem usually have a preexisting diminished parathyroid reserve secondary to surgery, which was unmasked by the ^{131}I therapy. The condition is due to the radiation exposure and the parathyroid's close proximity to functional thyroid tissue. It appears to have the greatest effect on premenopausal women (*13,21*).

Radiation Pneumonitis. This can cause pulmonary fibrosis if the patient has extensive pulmonary metastases and the whole-body retained activity was greater than 80 mCi at 48 hr (*13,16*).

Carcinogenic Effect. Internal exposure to ^{131}I beta particles is significantly less carcinogenic than is exposure to external photon radiation at a high dose rate (*22*).

Leukemia. There is an apparent increased incidence of leukemia in patients in Europe receiving a total dose of ^{131}I that is >1100 mCi. Cases of leukemia occurring in the U.S. after ablation do not strongly correlate with the total dose of ^{131}I and may be coincidental. It is also possible that patients with thyroid disorder have an increased predisposition to develop leukemia (*13,23,24*).

Bladder Cancer. This is seen in patients receiving very large doses of ^{131}I and is felt to be secondary to the radiation dose received by the bladder while excreting ^{131}I. There is a latency period of 15–20 years (*23*).

Breast Cancer. Some studies show an increased incidence, but not an increase in mortality. This may be due to a genetic disposition for both breast and thyroid cancer and may be unrelated to the ^{131}I treatment (*23*).

Anaplastic Thyroid Cancer. Prior ^{131}I therapy does not appear to cause well differentiated thyroid cancer to undergo anaplastic transformation (*13*).

Gonadal Damage. This can occur in patients who receive a high dose of ^{131}I or have ^{131}I-concentrating metastases in the pelvis (*13*). Decreasing the amount of retained ^{131}I in the bladder or bowel can decrease the exposure. There are reports of elevated follicle-stimulating hormone (FSH) and azoospermia after ^{131}I treatment (*25*). Iodine-131 may cause ovarian failure but the incidence is not known (*13*). There is no increase in the risk of major congenital abnormalities in children born to mothers who had received ^{131}I several years earlier (*13*).

FETAL AND CHILDHOOD ^{131}I EXPOSURE

Pregnancy is an absolute contraindication for ^{131}I ablation therapy. In the first week of life prior to implantation, a fetus can receive significant radiation from the adjacent bladder and blood similar to the amount that the ovaries receive (*13*). Once the placenta develops, ^{131}I can cross into the fetal circulation. The fetal thyroid does not concentrate iodine during the first 12 wk of gestation and receives the same whole-body radiation dose as does the mother (0.1 mGy/MBq). After 13 wk, the iodine uptake increases progressively until term; thus even small doses of radioiodine can deliver significant radiation to the fetal thyroid. Ablation of the fetal thyroid (which results in cretinism) has been reported in cases where the mother received a therapeutic dose during the latter part of pregnancy.

The child exposed as a fetus is theoretically at risk for radiation-induced thyroid neoplasm in later life and should be monitored indefinitely (*3*). To avoid this problem, it is mandatory that any woman of childbearing age receive a sensitive pregnancy test prior to ^{131}I therapy. Females should be cautioned to abstain from sexual intercourse from the time of the test until 6 to 12 mo after treatment (*26*).

Thyroid cancer traditionally accounts for 3%–4% of malignancies in children (*3*). During the 1940s through the 1970s, there was a marked increase in the incidence of this neoplasm secondary to the use of head, neck, and chest irradiation for benign disease in the preceding three decades.

When seen in the pediatric population, thyroid cancer tends to present as a well-differentiated thyroid cancer with a high incidence of multicentricity, and it usually spreads to lymph nodes. Pulmonary metastases are not uncommon, although bony metastases are rare (*27*).

After diagnosis, the initial treatment is usually total, as opposed to partial, thyroidectomy and resection of involved cervical lymph nodes. Ablation therapy with ^{131}I-Na is especially important in order to destroy any other foci of cancer and to irradiate existing metastatic disease in the lymph nodes or lungs. Doses of radioiodine are similar to those used in adults. The dose is usually sufficient to deliver 50,000 rad to functioning thyroid remnants. Despite the initial aggressive appearance of their symptoms, there is a favorable prognosis for pediatric thyroid cancer patients, with a 15–20-yr survival rate of 90%–95% (*27*).

FOLLOW-UP OF TREATED PATIENTS

The efficacy of radioiodine ablation therapy on the course of well-differentiated thyroid cancer is still a controversial topic. Multiple studies have shown that ^{131}I-Na significantly decreases the rate of recurrent tumor and the development of metastatic disease in patients who have local residual ^{131}I uptake. Results vary with the patient's age, tumor histology, and extent of the disease. Patients under 40 who undergo a total thyroidectomy for a well-differentiated papillary carcinoma have the best prognosis. Unfortunately, ^{131}I-Na is not as effective in ablation of metastases. Though treatment can result in palliation and prolonged life, only one-third of patients with pulmonary metastases, and virtually none with bone metastases, are cured. Thus, it is important to monitor annually all patients with a history of thyroid cancer for evidence of recurrent or metastatic disease.

Following ^{131}I ablation therapy, patients are placed on exogenous thyroxine with a dose large enough to suppress secretion of TSH and small enough to avoid thyrotoxicosis. The usual adult dose is 0.15–0.20 mg of levothyroxine sodium daily, but individual requirements vary. Synthetic thyroxine is the optimum replacement since it duplicates the normal secretory hormone and gives the body some control in the delivery of hormone by regulating deiodination (*28*). Failure to adequately suppress TSH increases the risk of reoccurrence by allowing stimulation of residual functional thyroid cancer remnants.

TABLE 2. Normal Areas of Iodine-131 Uptake Seen in Whole-Body Scan

Nasopharynx
Salivary glands
Gastric mucosa
Urinary bladder
Cardiac and pulmonary blood pool (in the first 24 hr)
Bowel activity (seen in later films after salivary and nasal secretions have been swallowed and passed through the intestines)

Most patients are reimaged ~1 yr after their ablative therapy. In order to maximize ^{131}I uptake, these patients must be withdrawn from exogenous T4 for 6 wk (2–3 wk for T3) to allow elevation of endogenous TSH. Ten days prior to imaging, the patients are placed on a low iodine diet. The patient is dosed with anywhere from 2–10 mCi of ^{131}I and neck uptake and images are obtained at 24–48 hr. If these scans show no abnormal ^{131}I accumulation, some centers will choose not to obtain further images in patients with good prognostic factors, unless clinical symptoms or other radiological or laboratory tests indicate a suspicious lesion. Other groups believe that all patients need to have follow-up radioiodine scans every 2–5 yr for the remainder of their lives.

It is imperative that the physician who reads the initial work-up and the follow-up ^{131}I scans have a complete knowledge of which normal anatomical structures are routinely seen on ^{131}I scans (see Table 2).

A large number of artifacts can cause a false-positive uptake on whole-body ^{131}I scans. These include retained activity in the following areas.

- Esophagus secondary to achalasia or colonic bypass graft
- Saliva or sputum on patient's skin or on handkerchief in patient's pocket
- pericardial effusions
- bilateral breast uptake during lactation
- Meckel's diverticulum or duplication cysts with gastric mucosa
- certain inflammatory lung diseases
- lung tumors
- severe burns

It is also important to realize that thyroid cancer treated with ^{131}I can dedifferentiate and lose its ability to concentrate ^{131}I. Thus, a patient can have metastatic disease in spite of a negative whole-body scan. For this reason, many physicians elect to follow thyroid cancer patients with both ^{131}I scans and serum thyroglobulin (Tg) levels.

Tg is a protein released by follicular thyroid cells and serves as a biochemical marker for residual functioning thyroid tissue. Normal Tg levels are ≤25 ng/ml and should be undetectable in a thyroid cancer patient who has had a total thyroidectomy and has been successfully ablated. A rise in the Tg level is almost always an indicator of recurrent or

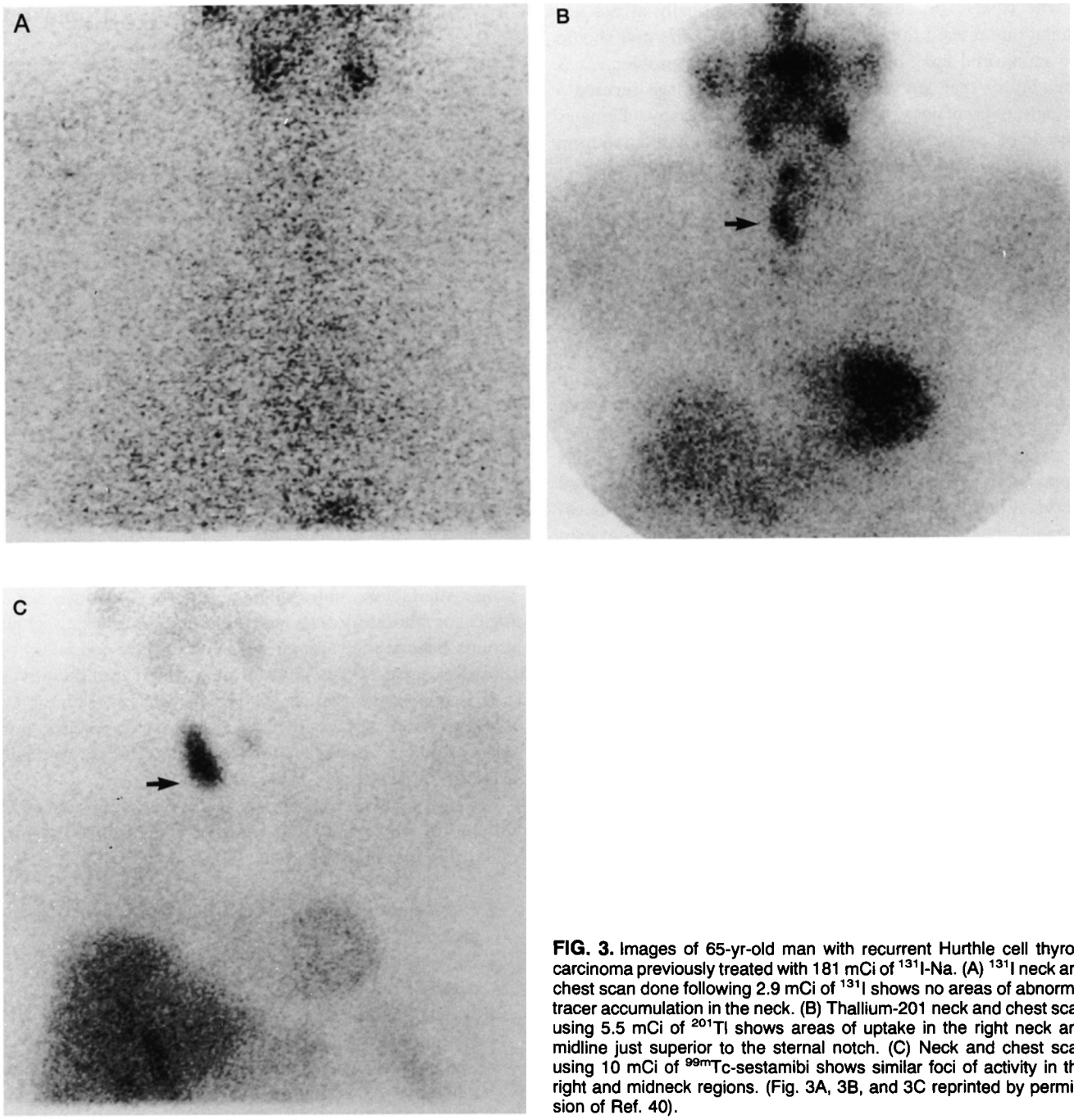

FIG. 3. Images of 65-yr-old man with recurrent Hurthle cell thyroid carcinoma previously treated with 181 mCi of ^{131}I-Na. (A) ^{131}I neck and chest scan done following 2.9 mCi of ^{131}I shows no areas of abnormal tracer accumulation in the neck. (B) Thallium-201 neck and chest scan using 5.5 mCi of ^{201}Tl shows areas of uptake in the right neck and midline just superior to the sternal notch. (C) Neck and chest scan using 10 mCi of ^{99m}Tc-sestamibi shows similar foci of activity in the right and midneck regions. (Fig. 3A, 3B, and 3C reprinted by permission of Ref. 40).

metastatic disease. A Tg level drawn while the patient is on thyroid hormone replacement may be falsely depressed and should preferably be measured after the patient has been withdrawn from thyroid replacement (*29*). Antithyroglobulin antibodies are seen in 10%–23% of the population and will cause false-negative or false-positive results (*30*).

A recent study has shown that Tg and radioiodine scans are both positive in a majority of patients with recurrent or metastatic disease. In a small percentage (13%) of patients, the scan will be normal and the serum Tg levels will be abnormally elevated, suggesting nonfunctioning metastases. In a smaller percentage (4%) of patients, the scan will show abnormal uptake and the Tg will be normal (*31*).

Some centers are investigating new protocols for thyroid cancer follow-up that do not require thyroid hormone withdrawal. There is encouraging research currently being conducted on the use of technetium-99m sestamibi as a radiopharmaceutical for whole-body imaging. Scans have been done both before and after withdrawal of thyroxine and then correlated with ^{131}I scans (Fig. 3).

Follow-up care is especially important in thyroid cancer patients as it can be a very indolent disease with an unanticipated accelerated phase. Approximately 60%–70% of deaths from well-differentiated cancer will occur within 10 yr of diagnosis, but 20% of papillary and 37% of follicular deaths do not occur until two decades after diagnosis (*13*). In

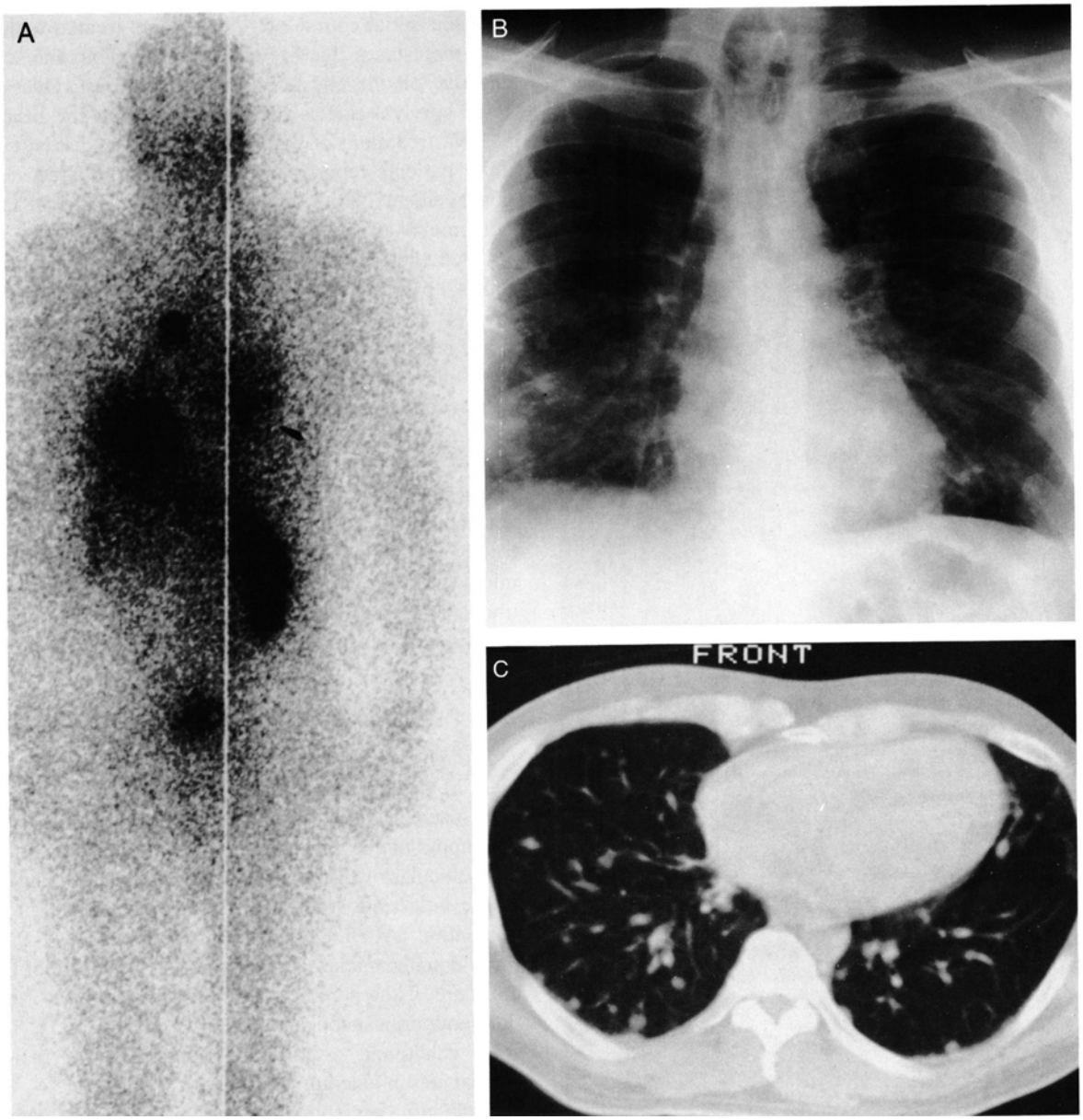

FIG. 4. (A) ^{131}I uptake, posterior, whole-body image, obtained 48 hr after ablation therapy with 250 mCi of ^{131}I-Na, shows focal areas of increased uptake in the right neck, left hilar region of the chest, and right lung base. (B) A chest X-ray reveals multiple pulmonary nodules. (C) The CT scan of the chest also reveals multiple small pulmonary nodules.

one study, there was a delay of 12 yr between the initial diagnosis and the appearance of pulmonary metastases (*32*).

In patients considered disease free following treatment for papillary and follicular cancer: 8.8% developed nodal metastases, 6.0% developed local recurrence, and 5.8% developed distant metastases (*13*).

The most common distant metastatic site for cancer is the lung. One study showed the highest incidence of pulmonary metastases in Hurthle cell tumor (25%) when compared to follicular (13%) and papillary cancer (9%) (*33*). Only ~50%–60% of metastatic pulmonary lesions will concentrate ^{131}I. Another 30%–40% will not concentrate ^{131}I but will show up on chest X-rays as tiny miliary densities (micronodules) or as nodules that are 0.5–3.0 cm in diameter (macronodules) (*3*). The prognosis is best for patients with a positive scan and a negative chest X-ray and worst for those with a negative scan and a positive chest X-ray. Men have a greater incidence of pulmonary metastases (*33*) (Fig. 4).

Bony metastases occur with the next greatest frequency and most are seen after the appearance of lung metastases. They can be seen as single lesions 29% of the time and multiple lesions 71% of the time (*13*). The most common sites are, in order of frequency: spine, skull, ribs, pelvis, sternum, long bones, and scapula-clavicle (Fig. 5).

Sites of soft-tissue metastases include: mediastinal nodes (often seen with pulmonary metastases), brain, liver, and other organs.

If follow-up imaging reveals metastases, retreatment with ^{131}I-Na is advocated. Second doses are usually greater than the original doses. None-the-less, the best chance for cure is

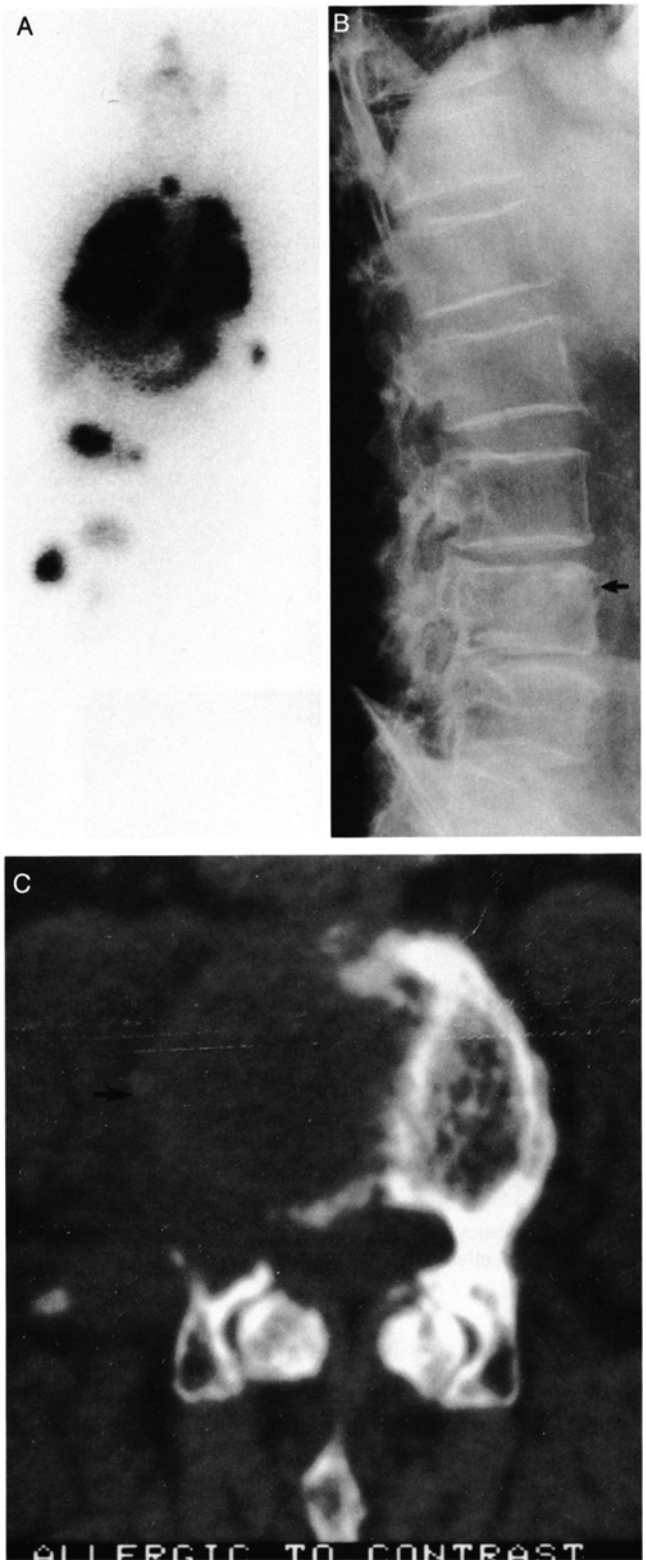

FIG. 5. (A) ^{131}I anterior whole-body scan obtained 5 days after ablative therapy with 264 mCi of ^{131}I-Na shows marked uptake in the lung fields bilaterally, the lower neck, soft tissues of the left upper quadrant, right psoas, and right hip. (B) A lateral view of the LS spine demonstrates compression deformity with increased bone trabeculation of L4. (C) Subsequent CT of the LS spine shows an osteolytic lesion involving the right vertebral body, pedicle and transverse process of L4 with an associated soft tissue mass.

with the initial course of ^{131}I. Patients treated with pulmonary metastases that are positive on radioiodine scans and negative on the chest X-ray fared the best; Overall, their 10-yr survival rate is high (90%) (*4*). On the other hand, ^{131}I-Na treatment of bony metastases is a palliative procedure; patients report pain relief, but there is no significant improvement of the lesions. The 10-yr survival rate with bone metastases is 44% (*4*).

Other therapy modalities can be considered for initial or follow-up treatment of thyroid cancer. External radiation therapy is useful when the tumor exhibits invasion of soft tissue adjacent to the thyroid that is unresectable, ^{131}I scans show no uptake, or the patient complains of severe bone pain secondary to metastases. Doses from 40–65 Gy (4,000–6,500 rad) over a period of 15–35 treatments, are advocated (*34*). This therapy can result in tumor regression and also offers substantial pain palliation for skeletal metastases.

Chemotherapeutic drugs that have been used to treat thyroid cancer include adriamycin, bleomyocin, cyclophosphamide, cis-platinum, methotrexate, 6-mercaptopurine, thiouracil, and vincristine (*32*). These agents are not curative and are used when more traditional methods are ineffective.

OTHER THYROID CANCERS

Though the principal oncologic use of ^{131}I is in the treatment of papillary and follicular thyroid carcinomas, it has been used in trials as a therapeutic agent for medullary carcinoma of the thyroid. This neoplasm derives from the parafollicular or C cells of the thyroid and is considered one of the neuroendocrine amine precursor uptake and decarboxylation (APUD) tumors. It accounts for 2%–9% of all thyroid malignancies. Approximately one-fourth of these tumors are of the hereditary variety, that is, part of the multiple endocrine neoplasia (MEN) syndrome (*35*). They secrete calcitonin, a hormone responsible for maintaining normal serum calcium levels.

Medullary carcinoma of the thyroid is a more aggressive tumor than the papillary or follicular forms of thyroid cancer. Multiple foci are often found especially in the MEN variety. Local nodal invasion is seen in 70%–80% of patients (*34*). Distant metastases to lung, liver, and bone are not uncommon and occur with greater frequency in older adults.

These tumors usually present as an enlargement or palpable nodule in the thyroid. Often, there is associated cervical adenopathy. Thyroid scans done with technetium or ^{131}I typically demonstrate a "cold" lesion in the lateral aspect of the midlobe and an elevated serum calcitonin level.

Approximately one-third of these patients will have diarrhea, flushing, and other symptoms associated with a carcinoid syndrome.

The definitive treatment is total thyroidectomy with dissection and removal of involved lymph nodes. Follow-up care includes careful monitoring for elevated calcitonin levels. If these levels are high, extensive testing is often required to locate residual or metastatic lesions. Routine radiographs and computed tomography (CT) scans may be

helpful in locating metastases to lung, liver, or bone. Alternately, several radiopharmaceuticals including ^{131}I-Na, ^{131}I m-iodo-benzyl-guanidine (MIBG), technetium-99m (^{99m}Tc) MDP, and pentavalent ^{99m}Tc-DMSA have been used in an effort to image medullary thyroid cancer (*3,36*).

If tumor foci are identified, several treatment options are available. One of the methods which has been tried is ^{131}I-Na. Medullary thyroid cancer may have two tumor components (C cells and follicular cells), and it is thought that ^{131}I can be trapped in the follicular element and the resultant beta emission will destroy the adjacent C cells (*37*). Studies in the past decades show that ^{131}I-Na therapy does not significantly effect the prognosis of patients with disease outside of the thyroid bed, but may be helpful in preventing reoccurrence in patients who have residual foci in the thyroid bed.

THERAPEUTIC TRIALS WITH ^{131}I-MIBG

Another form of ^{131}I that has been used in trials is ^{131}I-MIBG. This agent is an analog of norepinephrine, which was originally developed as an imaging agent for pheochromocytoma. It localizes within intracellular neuroendocrine storage granules, but its exact method of uptake in medullary thyroid cancer is not known. Its uptake is sporadic and may depend on tumor volume and calcitonin level (*38*).

In one study, two patients each received 100 mCi of ^{131}I-MIBG, followed by 150 mCi of ^{131}I-MIBG 3–4 mo later. Both patients experienced pain relief and a decrease in diarrhea as well as a transient fall in calcitonin, which lasted 2 mo. The patients' symptoms reoccurred, even after two treatments, and a cure resulting from ^{131}I-MIBG has not been documented.

Unfortunately, medullary thyroid cancer is not very sensitive to external radiation therapy or chemotherapy. Radiation is used to treat cervical and mediastinal nodes if the calcitonin level is elevated and metastases cannot be detected. The best prognosis is seen in patients whose tumor is detected early, before it has metastasized.

Pheochromocytoma

Clinically, patients with pheochromocytoma present with headache, palpitations, hypertension, and excessive perspiration. Their symptoms are the result of excessive catecholamines released by the tumor and can be detected as excessive catecholamines and associated metabolites in the plasma and urine.

Patients initially undergo CT or MRI to look for obvious tumor. If these imaging modalities fail, then ^{131}I-MIBG may be given intravenously, and images of the anterior and posterior neck, chest, abdomen, and pelvis are obtained, using a high energy parallel-hole collimator and a gamma camera at 24, 48, and 72 hr. Five drops of Lugol's solution are given prior to the administration of MIBG and for ten days after. Lugol's solution blocks iodine uptake in the thyroid.

MIBG has been studied as an oncological agent in several centers in the U.S. and Europe. The therapeutic dose of MIBG is calculated by using dosimetry parameters of estimated tumor volume, functional dose uptake at 24-hr, and biological half-life. The optimal dose is in the range of 200 mCi, which is administered intravenously over 90 min using pump infusion. ECG, heart rate, and blood pressure are carefully monitored to detect a catecholamine crisis. Certain drugs such as cocaine, reserpine, tricyclic antidepressives, and phenopropanolmine can interfere with the uptake of MIBG and should be discontinued prior to the use of MIBG. A study at University of Michigan in 12 patients showed that 40% of treated patients had a decrease in catecholamines and a small percentage of patients had a decrease in the size of their tumors (*39*).

At this point, MIBG is looked upon as a promising oncologic drug for treatment since the tumor is resistant to chemo- or radiation therapy. MIBG has, on rare occasions, been used as an oncological agent for neuroblastoma, carcinoid, and paraganglioma.

CONCLUSION

In summary, ^{131}I-sodium iodide is the principal oncologic agent used in the treatment of papillary and thyroid cancers. Its use in the treatment of medullary carcinoma of the thyroid, pheochromocytoma, and several other tumors is currently being investigated and shows potential for having at least a palliative, if not curative, effect.

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