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The SNM will periodically define new procedure guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the United States. Existing procedure guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each procedure guideline, representing a policy statement by the Society, has undergone a thorough consensus process in which it has been subjected to extensive review, requiring the approval of the Committee on Guidelines and SNM Board of Directors. The SNM recognizes that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published procedure guideline by those entities not providing these services is not authorized.

THE SNM PRACTICE GUIDELINE FOR THERAPY OF THYROID DISEASE WITH IODINE 131 Draft V2.4

PREAMBLE

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the Society of Nuclear Medicine (SNM) cautions against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician in light of all the circumstances presented. Thus, an approach that differs from the guidelines, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.
I. INTRODUCTION

Oral administration of $^{131}$I has been a commonly accepted procedure for treatment of benign and malignant disorders of the thyroid since the 1940s. Physicians responsible for treating such patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with alternative forms of therapy, and should be able to collaborate closely with other physicians involved in the management of the patient's condition. The treating physician should either see patients in consultation with the physician assuming overall management of the patient's condition or be prepared to assume that role. In the United States, the treating physician should be board certified in Nuclear Medicine, Radiology, or Radiation Oncology or be able to document equivalent training, competency, and experience in the safe use and administration of therapeutic $^{131}$I.

Licensure to possess $^{131}$I and regulations regarding the release of patients treated with radioiodine vary from jurisdiction to jurisdiction. Physicians engaged in therapy with $^{131}$I must be knowledgeable about, and in compliance with, all applicable laws and regulations. The facility in which treatment is performed must have appropriate personnel, radiation safety equipment, and procedures available for waste handling and disposal, monitoring personnel for accidental contamination, and controlling spread of $^{131}$I to conform with the relevant state and federal regulations. All physicians engaged in therapy have a duty to ensure that their knowledge and competencies are up-to-date.

II. GOALS

The purpose of this guideline is to assist appropriately trained practitioners in evaluating patients for therapy with $^{131}$I (sodium iodide) for benign or malignant diseases of the thyroid gland, performing this treatment in a safe and appropriate manner, understanding and evaluating the sequelae of therapy, and reporting the results of therapy.

III. DEFINITIONS

See also SNM Procedure Guideline for General Imaging

A. $^{131}$Iodine is a $\beta$-emitting radionuclide with a physical half-life of 8.1 days; a principal $\gamma$-ray of 364 keV; and a principal $\beta$-particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a mean range in tissue of 0.4 mm. ($I$)

B. Therapy means the oral administration of $^{131}$I as sodium iodide to treat papillary and follicular thyroid cancer, hyperthyroidism, or non-toxic nodular goiter, in contrast to the diagnostic use of radioiodine to detect functioning thyroid tissue.

C. Benign diseases include Graves' disease (toxic diffuse goiter), and toxic or nontoxic nodular goiter.

D. Malignant diseases in this Guideline indicate papillary and follicular types of thyroid cancer that are sufficiently differentiated to be able to synthesize thyroglobulin and, in most cases, accumulate radioiodine.
E. Ablation refers to the use of $^{131}$I to eliminate residual normal thyroid tissue detected after thyroidectomy.

F. Risks to the thyroid cancer patient for recurrence and death vary from very low to high. (2,3) Classifying the prognosis for risks of recurrence and dying from thyroid cancer has also been performed by the American Joint Committee on Cancer (AJCC), in detailed Stages I-IV. (4) The following systems of risk evaluation are very close to each other but not identical:

1. Very low risk: this category excludes cancers with high risk histopathology, e.g. tall cell, insular, columnar, poorly differentiated papillary carcinoma and Hurthle cell variant of follicular carcinoma; also cancers with vascular invasion (2).
   a. Under age 45: microcarcinoma (<1.0 cm), unifocal or multicentric; tumor <4 cm (2) (others see tumor >1.5 cm as more risky (5)) confined to the thyroid; Stage I variation from AJCC (2): (T1-2, N0, M0); MACIS score <6 (6). The MACIS scoring system adds scores for metastases, age, completeness of resection, invasiveness, and size (6).
   b. over age 45: microcarcinomas, unifocal or multicentric; Stage I variation from AJCC (2): (T1-2, N0, M0; MACIS<6 (6).

2. Low risk (two definitions,2,3):
   a. low: under age 45: tumor < 4 cm with/without microscopic central compartment lymph node metastases but no distant metastases (2); Stage I variation from AJCC (2): (T1-T2, N0-N1a, M0); AJCC Stage I (any T, any N, M0) (4); MACIS<6 (6).
   b. low: over age 45: tumor < 4 cm confined to the thyroid with no node involvement (2), i.e. AJCC Stage II (T2, N0, M0)(4); MACIS<6 (6).
   c. low: no local or distant metastases post thyroidectomy and remnant ablation; all macroscopic tumor resected; no tumor invasion of locoregional tissues or structures; no aggressive histology (e.g. Hurthle cell, insular, diffuse sclerosing, tall cell, insular, columnar cell, trabecular, solid, poorly differentiated carcinoma, etc.); no vascular invasion; if $^{131}$I is given, no $^{131}$I uptake outside the thyroid bed on the post-treatment whole body scan (3).

3. Moderate risk (two definitions,2,3):
   a. moderate, under age 45: tumor > 4cm, macroscopic (>1 cm) central compartment or lateral lymph node metastases; aggressive histologic type (Hurthle cell, insular, diffuse sclerosing, tall cell, columnar cell, trabecular, solid, poorly differentiated); minimal extrathyroidal extension (i.e. sternothyroid muscle or perithyroid soft tissue); minimally invasive (i.e. microscopic capsular, but not vascular, invasion) follicular carcinoma <4 cm (some investigators consider minimally invasive follicular carcinoma as low risk)(2); Stage I variation from AJCC (2):(T1-3, N1b, M0); MACIS>6 (6).
SNM Procedure Guideline for Therapy of Thyroid Disease with $^{131}$I  

DRAFT V2.3

b. moderate, over age 45: aggressive histologic type (as listed above);
   minimally (i.e. microscopic) invasive follicular carcinoma <4 cm (2); AJCC
   Stage III (T3,N0,M0 or T1-T3, N1a, M0) (4); MACIS > 6 (6).

c. intermediate risk: microscopic invasion of tumor into the perithyroidal soft
   tissues at initial surgery or tumor with aggressive histology or vascular
   invasion. (3)

4. High risk (2)

a. under age 45: distant metastases; extension to muscle, invasion of
   prevertebral fascia, subcutaneous soft tissues, larynx, trachea, esophagus, or
   recurrent laryngeal nerve; encasement of carotid artery or mediastinal
   vessels; stage I variation from AJCC (2): (T4a,T4b, any N, M0; AJCC
   Stage II.(any T, any N, M1) (4); MACIS > 6 (6).

b. over age 45: tumor extension to muscle, invasion of subcutaneous soft
   tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; invasion of
   prevertebral fascia or encasement of carotid artery or mediastinal vessels;
   central or lateral compartment lymph node metastases; distant metastases;
   macroscopic invasive follicular carcinoma or > 4 cm (2); AJCC Stage IVA
   (T4a , any N, M0 or T1-T3,N1b,M0; AJCC Stage IVB (T4b, any N, M0);
   AJCC Stage IVC (any T, any N, M1) (4); MACIS > 6 (6).

IV. EXAMPLES OF COMMON CLINICAL INDICATIONS

Common indications for therapy of thyroid diseases with $^{131}$I include, but are not limited to, the
following:

A. Benign Diseases

1. Hyperthyroidism.

$^{131}$I may be indicated for the treatment of Graves’ disease and toxic nodular
   disease. (7)

2. Nontoxic nodular goiter.

$^{131}$I therapy may be used successfully to diminish the size of nontoxic nodular
   goiter, especially when surgery is contraindicated or refused. (8, 9)

B. Differentiated Papillary and Follicular Thyroid Cancer

1. $^{131}$I therapy is the principal treatment of residual thyroid tissue post-
   thyroidectomy (thyroid remnant ablation), residual or recurrent thyroid cancer,
   and/or metastatic disease, after near-total thyroidectomy.

V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL (in the United States)

See also SNM Procedure Guideline for General Imaging
The SNM believes that the ACGME program requirements for graduate medical education in nuclear medicine (10) are appropriate for training physicians to be competent in safe and effective therapy with unsealed radiopharmaceuticals, particularly in those patients who are being treated for cancer, and that training and experience that do not fulfill ACGME nuclear medicine program requirements are inadequate to assure adequate safety and effectiveness in the use of radionuclide therapy. The minimum requirements for supervision and administration of radiopharmaceuticals (11) include the supervised, independent evaluation and treatment with $^{131}$I of a minimum of ten patients for hyperthyroidism, and a minimum of five patients for thyroid carcinoma.

VI. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

See also SNM Procedure Guideline for General Imaging

A. Therapy of Graves’ Disease, Toxic Nodule(s), and Nontoxic Nodular Goiter

1. Goals.

   a. The goal of therapy of hyperthyroidism is to achieve in the patient a nonhyperthyroid status which can be euthyroid or iatrogenic hypothyroidism but completely compensated to the euthyroid state with oral levothyroxine.

   b. The goal of therapy of a nontoxic nodular goiter is to relieve symptoms caused by compression of the goiter on structures in the neck.

2. Patient Preparation

   a. Patients must discontinue for a sufficient time before contemplated therapy (Appendix, Table 1) use of iodide-containing medications and preparations that could potentially affect the ability of thyroid tissue to accumulate iodide.

   b. The treating physician must explain the procedure, treatment, complications, side effects, therapeutic alternatives, and expected outcome to the patient. Written information must be provided to the patient.

   c. The treating physician should obtain signed, written informed consent before therapy. The consent form should include the following items specific to the therapy of hyperthyroidism:

      (1) More than one $^{131}$I treatment may be necessary.

      (2) The likelihood of eventual hypothyroidism is high. It can occur within the first few months following therapy or even decades later, with small, ongoing annual incidence. Lifelong thyroid hormone supplementation would then become necessary.

      (3) Long-term follow-up is necessary.
(4) Ophthalmopathy may worsen or develop after $^{131}$I therapy for Graves’
disease, especially in smokers. High levels of pretreatment serum
triiodothyronine, post-therapy hypothyroidism, and high levels of TSH-
receptor antibody are also associated with an increased risk of the
development or progression of ophthalmopathy. (12)

(5) There is a small (1-5%) chance of a mildly painful radiation thyroiditis
after treatment, for which NSAID analgesics could theoretically lead to a
small risk of hemorrhage (by extrapolation from the cited references)
(13,14), but the Committee did not achieve agreement that this is a
significant risk to the patient. Acetaminophen or other non-narcotic
analgesic therapy usually suffices; rarely corticosteroids may be
required.

(6) On occasion, patients with severe hyperthyroidism may experience
exacerbation of symptoms within the first 2 weeks following $^{131}$I therapy.
These symptoms usually respond to short term beta blocker therapy, but
rarely may progress to frank thyroid storm. Patients should be instructed
to contact their physician or seek immediate medical care should such
symptoms occur.

(7) Based on previous multicenter trials, there is no evidence of increased
risk of thyroid carcinoma or other malignancy, infertility, or increased
incidence of birth defects caused by $^{131}$I therapy for hyperthyroidism.
There does exist a small risk of coexisting thyroid cancer prior
to/without therapy in patients with toxic nodular goiter and Graves’
disease. (15,16)

(8) Other considerations for informed consent.
(a) There are no scientific data on the subject but most experts
recommend waiting 6-12 months after $^{131}$I therapy before trying to
conceive a child to allow for retreatment if necessary.
(b) The patient’s ability to comply with the prescribed radiation
precautions should be ascertained.
(c) Travel precautions should be reviewed and a card or letter
documenting the therapy should be provided.
(d) Pretreatment of selected patients with thionamides (methimazole,
[Tapazole$^{TM}$], or propylthiouracil, [PTU]) to deplete thyroid hormone stores
may be helpful. $^{131}$I therapy can cause radiation-induced thyroiditis with
release of stored thyroid hormone into the circulation, resulting in
occasional transient worsening of hyperthyroidism and, rarely, precipitation
of thyroid storm. This is more likely to occur in patients with large, iodine-
avid multinodular glands who are given higher activities of $^{131}$I.
Accordingly, elderly patients and patients with significant preexisting heart
disease, severe systemic illness, or debility may benefit from pretreatment
with thionamides. The thionamide should be discontinued for 3 to 5 days
before the radiiodine therapy is given. The thionamide can be resumed 2 to
3 days after treatment with $^{131}$I. Some experts recommend administering a
higher activity of $^{131}$I in patients who have been pretreated with a thionamide. While some studies suggest that radioresistance is more likely with propylthiouracil than methimazole, the issue remains unsettled (17,18). A randomized study found no effect of pretreatment of Graves’ disease with methimazole on outcome (19). In another study thionamides had no effect in outcome of Graves’ disease, but here the outcome of radioiodine therapy for toxic nodular goiter was adversely affected. Large goiters and severe hyperthyroidism may also be associated with radioresistance and require a higher $^{131}$I administered activity (18). Other groups of patients for whom a higher activity (uCi/gm) has been recommended include pediatric patients and patients with rapid turnover, e.g. where the radioiodine uptake at 4 hours exceeds that at 24 hours.

e. Treatment with beta-blockers can be helpful for symptomatic control. Beta-blockers need not be discontinued before treatment with $^{131}$I.

f. Recombinant human TSH (rhTSH, Thyrogen™) has been employed (in an off label use) in patients with nontoxic or toxic nodular goiter with low iodine uptake to maximize thyroid gland uptake and minimize the radiation dose to the rest of the body. The optimum dosage to stimulate uptake and not increase circulating thyroid hormone has been reported as 0.03 mg (20), but not yet confirmed or refuted by other studies, as of autumn, 2011.

g. Radiation safety precautions for the patient are of sufficient importance that these appear in a separate section of this Guideline, V.1.C. (following the section on therapy of thyroid cancer).

3. Information Required by the Physician Performing the Procedure

a. The treating physician should obtain the patient’s thyroid-related medical history and perform a directed physical examination. The cumulative administered activity of $^{131}$I should be reviewed and recorded in the patient’s record.

b. The results from recent measurements of thyroid hormone levels (free T4, total or free T3) and thyroid stimulating hormone (TSH) should be available and reviewed. The avidity of the thyroid gland for iodide must be established. This should be accomplished quantitatively using a recent radioiodine uptake measurement (RAIU) with $^{123}$I or $^{131}$I, combined with a thyroid scan, which usually can distinguish between Graves’ disease, a toxic multinodular goiter, and uninnodular adenoma. These procedures will also differentiate silent thyroiditis and thyrotoxicosis factitia from other forms of hyperthyroidism.

(1) If radioiodine is unavailable for scintigraphy, $^{99m}$Tc-pertechnetate is an option and quantitative $^{99m}$Tc uptake can be determined (21, 22).

(2) In the presence of an elevated level of anti-TSH receptor antibody, orbitopathy and pretibial myxedema, a thyroid scan may be unnecessary, and an uptake measurement with 5-10 uCi of $^{131}$I may suffice.
(3) Ultrasonography generally does not contribute to the differential diagnosis of thyrotoxicosis (23).

c. Female patients who have the potential to be pregnant must always be tested for pregnancy using a urine or serum beta-HCG, ideally within 24 hours of treatment, as the pregnancy test may remain negative for up to 7-10 days after fertilization (24). Caution is therefore advised in treating patients who have had unprotected intercourse in the 10 days before treatment and the treating physician should consider discussing the limitation of the pregnancy test with the patient, which could include consideration of delaying the therapy until the beginning of the next cycle.

d. Before omitting a pregnancy test in women of childbearing age, some institutions may require written historical confirmation of hysterectomy (a pregnancy test is still required in some institutions despite a history of tubal ligation), while others may choose to accept the word of the patient that pregnancy is impossible, documenting this as part of the treatment dictation. Cases of pregnancy have occurred when the patient declared that pregnancy was impossible and the beta-hCG omitted.

e. All potentially breastfeeding/lactating women must be asked if they are lactating. If so, they must be advised to stop breastfeeding, and therapy must be delayed until lactation ceases in order to minimize the radiation dose to the breast (25).

(1) Lactation (and the ability of the breast to concentrate large amounts of iodine) usually ceases 4-6 weeks post partum (with no breastfeeding) or 4-6 weeks after breastfeeding stops. A comment that a female patient of childbearing age denies lactation is suggested to be part of the final treatment report.

(a) If there is uncertainty as to whether the previously lactating breasts still concentrate iodine, this may be assessed by noting the absence of iodine uptake on pre-therapy scintigraphy (26, 27) or with 99mTc-pertechnetate.

(b) Several approaches are available to speed the cessation of lactation but these are beyond the scope of this Guideline.

(2) The patient may not resume breastfeeding for that child.

(3) Nursing may resume with the birth of another child.

f. The treating physician should confirm that the patient is continent of urine or that arrangements are made to prevent contamination caused by incontinence.

g. The patient’s identity must be confirmed in accordance with institutional policy before administration of $^{131}$I.
If the patient’s mental status prevents the signing of an informed consent form, a guardian, or close family member can do so and should be present during $^{131}$I therapy.

(1) Some patients with cognitive impairment may not be able to tolerate admission and isolation in a hospital or to follow instructions necessary to allow the patient to be treated at home with $^{131}$I.

(2) Treatment in these cases must be carefully individualized. Diapering the patient and bagging the contaminated material may be necessary, but waste disposal must be done in cooperation with relevant local authorities so as not to set off alarms at waste facilities.

(3) With a history of renal disease or diabetes, renal function should be assessed. Peritoneal or hemodialysis is not a contraindication to $^{131}$I therapy (28).

4. Selection of Administered Activity

a. A variety of methods have been used to select the amount of administered activity (29, 30). The thyroid radiation dose depends on the RAIU, gland size, as well as the biological half-life of the radioiodine in the thyroid gland, which can vary widely. While it is reasonable to base $^{131}$I activity on the radiation dose delivered to the thyroid gland rather than administered activity, there are few publications documenting this unequivocally (30,31). Dosimetry for the $^{131}$I treatment of thyrotoxicosis has not been standardized.

(1) One nondosimetric method is to use the estimated thyroid gland size and employ the results of a 24 hour radioiodine uptake measurement (RAIU) to calculate the therapeutic activity of $^{131}$I in order to achieve a desired concentration of $^{131}$I in the thyroid gland. Delivered activity of 3–8 MBq (80–220 uCi) per gram of thyroid tissue has been employed (18, 19, 32, 33), although the great majority of Committee members felt that 3 MBq per gram was rather low to have an acceptable cure rate if hypothyroidism is the goal. While some treating physicians choose to aim for a euthyroid state using a lower activity, decreasing the administered therapeutic activity in an effort to achieve a euthyroid state can lead to prolongation of hyperthyroidism with adverse clinical sequelae.

(2) Administered $^{131}$I activity toward the upper end of this range or even higher are especially suitable for patients with nodular goiters, very large toxic diffuse goiters, and repeat therapies (7), as well as for pediatric patients and those patients with rapid iodine turnover, e.g. with 4 hours iodine uptake exceeding 24 hour uptake.

(3) Empiric rather than calculated dosage strategies are also used for Graves’ disease, toxic multinodular goiter, and solitary toxic nodules. For example, 550 MBq (15 mCi or 7.4 MBq/gm (200 uCi/gm) may be used for the usual size solitary nodule (approximately 1.5-3 cm diameter) and higher doses for larger nodules (32, 33).
5. Follow-up

a. The treated thyrotoxic patient must be closely followed, as $^{131}$I-induced hypothyroidism may occur within 2-3 months of therapy. L-thyroxine replacement therapy should be started when TSH elevation is detected and should have as its goal a euthyroid, symptom-free state. Many experts consider hypothyroidism after a single dose of $^{131}$I a desired outcome of $^{131}$I therapy because it avoids repeated, frequent office visits and laboratory testing to detect the late onset of hypothyroidism as well as decreasing the possibility of untreated, persistent or recurrent hyperthyroidism. These patients should be followed for many years to maintain the euthyroid state.

b. The patient treated for compressive symptoms for an enlarged nontoxic goiter should be followed very closely as swelling of the gland could worsen symptoms and signs.

B. $^{131}$I Therapy of Thyroid Cancer (to ablate post-thyroidectomy remnants, destroy residual or recurrent tumor)

1. Indications for Treatment with $^{131}$I; Relationship to Staging

a. $^{131}$I ablative and/or, tumoricidal treatment of differentiated thyroid cancer with radioiodine should be considered in the post surgical management of patients with any of the following features listed under a.(1) and a.(2):

(1) Maximum tumor diameter > 1.0 to 1.5 cm

(2) Maximum tumor diameter <1.0 cm in the presence of high risk features such as:

   (a) Aggressive histology (Hurthle cell, insular, diffuse sclerosing, tall cell, columnar cell, trabecular, solid, and poorly differentiated subtypes of papillary carcinoma);

   (b) Lymphatic or vascular invasion;

   (c) Lymph node or distant metastases;

   (d) Multifocal disease;

   (e) Capsular invasion or penetration

   (f) Peri-thyroidal soft tissue involvement. (34-37)

   (g) Anti-thyroglobulin antibody level elevation, post-thyroidectomy so that scintigraphic evaluation can be employed for surveillance.

(3) The treatment of very low and low risk thyroid cancers, as suggested by a group from Cedars-Sinai Medical Center is controversial, as the majority of data (but not all) suggest no statistically significant improvements in disease specific survival, although the recurrence rates may decrease. (2)
(4) Since treatment choices depend, among other factors, on the pathology, location, and size of thyroid cancer, perioperative staging should evaluate the presence of metastases. These staging studies should be employed depending on the level of risk of the cancer, as defined above, e.g. low risk cancers may simply need a baseline ultrasound examination of the neck post-operatively.

(a) Preablation thyroid scintigraphy is a controversial issue and is examined in the section entitled “Data Required by the Treating Physician” in B.3.h. (1)-(3) below.

(b) Cervical lymph nodes:

(i) Ultrasound (for staging and biopsy) is less expensive and more widely employed, but operator dependent, as compared to MRI or CT; there do not appear to be documented differences in sensitivity.

(c) Lung metastases:

(i) Computed tomography (without contrast) is far more sensitive than chest x-ray; MRI is not recommended.

(d) Bone metastases, especially in the presence of musculoskeletal symptoms:

(i) Pre-ablative dose $^{99m}$Tc-bisphosphonate (diphosphonate) bone scans and/or bone x-rays (each appears to be about 65-75% sensitive) $^{38,39}$.

(ii) $^{18}$F-fluoride bone PET/CT may be more sensitive than $^{99m}$Tc-bisphosphonate (diphosphonate) skeletal imaging $^{40}$.

(e) PET imaging

(i) $^{18}$F-FDG may be helpful in detecting metastases when used in follow-up imaging if the radioiodine study is negative and the serum thyroglobulin is rising and/or elevated. The presence of $^{18}$F-FDG-avid disease, especially high volume $^{18}$F-FDG-avid disease indicates a relatively poor prognosis compared to patients with no $^{18}$F-FDG uptake in viable tumor. $^{41,42}$

(ii) $^{124}$I PET/CT has higher spatial resolution and image contrast than planar or SPECT imaging with $^{131}$I but has yet to be shown to make a clinical impact $^{43}$, $^{124}$I may have a role in improving lesion dosimetry $^{44}$. However $^{124}$I is not an FDA-approved radiopharmaceutical at this time.

b. Post thyroidectomy $^{131}$I therapy for metastases to lymph nodes, lung, bone, and, less often, brain, liver, and other sites.
Brain and vertebral metastases must be approached with caution as intracerebral bleeding and cerebral edema may occur after $^{131}$I therapy and concurrent corticosteroids may be required (45).

2. Patient Preparation

a. A state of iodine deficiency should be induced to increase $^{131}$I uptake.

1. Patients must discontinue use of iodide-containing preparations and other medications that could potentially affect the ability of the thyroid tissue to accumulate iodide for a sufficient time before contemplated therapy. (Appendix, Table 1)

2. Most experts recommend a low-iodide diet for 7-14 d before administration of therapy to increase radioiodine uptake and improve the ablation rate. (46) Institutions should develop written instructions to assist patients in complying with the low iodine diet (47). Although the 24 hour urinary iodine excretion is not routinely measured in most institutions, this study can be useful when patient compliance with the low iodine diet is uncertain. There is agreement that it should optimally be below 50 mcg/24 hours (46).

   (a) A list of foods containing a significant amount of iodine appears in the Appendix, Table 2 and at http://www.thyca.org/rai.htm.

   (b) There are no studies on whether resuming a normal diet 24, 48, or 72 hours post-$^{131}$I therapy yields any difference in ablation/successful therapy rates, so no recommendation can be unequivocally made in this regard.

   (c) It must be emphasized to the patient that this is not a low salt diet but a low iodine diet (approximately 50 mcg per day), and that non-iodized salt is allowed and widely available.

   (d) Red dye number 40 (Food, Drug and Cosmetic Act Dye No. 40, FDAC 40), an “azo” dye, is iodine-free.

   (e) FDA red dyes number 3 and 28 contain up to eight atoms of iodine per molecule and must be excluded from any low iodine diet.

(3) Thyroid hormone contains iodine, and some clinicians stop thyroid hormones for about four days before administration of $^{131}$I therapy if rhTSH is employed. This time period will not induce a hypothyroid state. Outcome studies on this approach are unavailable, and the half-life of thyroxine, about seven days in a euthyroid patient, makes this recommendation of uncertain value.

   (a) The use of a diuretic to reduce body iodine content is no longer advised due to the side effects of hypokalemia and hypotension; and since furosemide causes a decrease in urinary iodide excretion and higher blood concentration. (48)
b. The serum thyroid stimulating hormone, TSH, should exceed about 30 micro-International Units (µIU)/mL to maximize $^{131}$I uptake. The data to support 30 µIU/mL as a number representing the threshold of optimal stimulation is more a matter of consensus than the result of detailed scientific study. (49)

(1) This may be achieved in one of two ways:

(a) Thyroid hormones may be withheld for a time sufficient to permit an adequate rise in TSH (>30 µIU/mL). This is at least 10-14 d for triiodothyronine (T3) and usually 3 weeks for thyroxine (T4) (50).

(i) TSH may not rise to this level if a large volume of functioning tissue remains or if hypopituitarism is present.

(b) Recombinant human thyroid stimulating hormone, rhTSH, may be employed.

(i) The manufacturer’s suggested dosage of rhTSH is 0.9 mg. injected intramuscularly in the buttock on two consecutive days.

(ii) A 4 mCi (148 MBq) $^{131}$I dosage for the whole body scan has been shown by the manufacturer, Genzyme Corp., in data on file with the FDA, to be more effective than lower activities in the diagnostic use of rhTSH post-thyroidectomy.

(iii) Recombinant human TSH (rhTSH) is approved in the United States and Europe for use in diagnostic testing and for ablation of thyroid remnants (51, 52, 53). Randomized double blind prospective studies showing the equivalence of rhTSH and thyroid hormone withdrawal to elevate the serum TSH in treating distant metastatic disease have not been published as of autumn, 2011, but a retrospective study has indicated similar five year survival in thyroid cancer patients with distant metastatic disease prepared for $^{131}$I therapy with either thyroid hormone withdrawal or rhTSH (54). The use of rhTSH requires a larger therapeutic activity of $^{131}$I than thyroid hormone withdrawal and dosimetric studies have been suggested to be helpful here. Whole body radiation exposure is less than that after thyroid hormone withdrawal for an equal administered activity of $^{131}$I due to the preservation of GFR in the euthyroid state.

c. The treating physician must explain the diet, preparatory procedures, treatment, potential side effects, therapeutic alternatives, radiation precautions and the probability of expected outcome to the patient or his/her representative. Written material containing this information should be provided to the patient or patient representative.

d. The treating physician must obtain signed written informed consent before therapy, which should include the following items specific for the therapy of thyroid cancer and also include possible adverse reactions:
(1) The purpose of ablative treatment is to destroy normal thyroid tissue remnant and presumed remaining cancerous thyroid tissue. Other normal tissues may also be affected.

(2) More than one $^{131}$I treatment may be necessary.

(3) Early side effects may include oral mucositis, nausea, occasional vomiting, sialadenitis, loss of taste or unusual, often metallic-like alterations in taste. Painful thyroiditis only occurs if there is a sizeable post-surgical remnant present.

   (a) To address sialadenitis, measures should be taken to maintain a high level of hydration and stimulate salivary flow following therapy by recommending administration of a sialagogue (e.g., sugar free candy) for as long as seven days.

   (i) Since the constant use of candy and gum has been shown to eliminate acute radiation sialadenitis (55), concerns about lemon candy increasing the salivary radiation dose as studied by Nakada et al (56) appear to have been overcome with this regimen of seven days of keeping hard candy or gum in the mouth constantly.

   (b) Nausea and, rarely, vomiting may occur about 2-8 hours after $^{131}$I administration and resolve within 24-72 hours.

   (i) Vomiting can be prevented by prophylactic administration of oral antiemetics, including phenothiazines or selective serotonin 5-HT3 receptor antagonists. Corticosteroids have been successfully used to potentiate the antiemetic effect of these drugs when high dosages of $^{131}$I are employed.

   (c) Neck pain and swelling can occur if a sizeable thyroid remnant remains after surgery, especially when the post-operative, pre-ablative $^{123}$I or $^{131}$I uptake is found to be close to the normal range.

   (i) If this level of uptake is observed, further cytoreductive surgery may be advisable to avoid symptomatic radiation thyroiditis and increase the probability of complete ablation.

   (ii) For lower risk patients with iodine uptake levels in the 8-10% range a decrease in administered activity is often sufficient.

   (iii) Patients whose TSH failed to rise on a withdrawal protocol have been successfully treated with approximately mCi of $^{131}$I and retreated later, at about 90 days when the TSH rose over 30 uIU/mL with a higher activity.

   (d) With $^{131}$I activity in excess of 5.55 to 7.4 GBq (150-200 mCi), transient decreased white blood cell and platelet counts may occur for up to 6-10 weeks that might uncommonly result in increased
susceptibility to infection or bleeding if the marrow dose exceeds about 2 Sv (200 rem) (57).

(i) A normal pretherapy complete blood count (CBC) and renal profile make these side effects unlikely.

(ii) If these blood tests are abnormal, dosimetry is advised to determine the highest safe $^{131}$I activity while delivering less than 2 Sv (200 rem) to the blood/bone marrow.

(e) Oral mucositis with small mouth ulcerations may often be prevented by gentle brushing of the entire oral mucosa with a soft toothbrush about every 3-4 hours for 4-7 days while awake; a few Committee members advise their patients to also do this every three hours at night for the first four days after treatment, and this minority has found that mouth ulcers have been prevented by this practice. Other Committee members see oral mucositis as a less frequent and less clinically important occurrence.

(f) Uncommon side effects can result from rhTSH-induced edema of metastases in bone (pain), brain or spinal cord (neurologic symptoms) or lung (dyspnea).

(4) Late side effects may include:

(a) Fertility issues

(i) Increases in gonadotropins (serum FSH level) and presumably any degree of diminished spermatogenesis is usually transient except in men receiving high therapeutic doses of $^{131}$I, when permanent infertility is possible as administered activities progressively exceed 7.4-11.1 GBq (200-300 mCi) (58). The level of administered activity above which azoospermia occurs is not clear since infertility has been described in a most unusual patient who received 3.33 GBq (90 mCi) of $^{131}$I (59) and an author of this document (E.B.S.) has a patient who fathered a child after receiving a cumulative $^{131}$I activity in excess of 14.8 GBq (400 mCi). Nevertheless, in one the largest prospective studies the radiation dose from a single ablative therapy with $^{131}$I was well below that associated with permanent damage to the germinal epithelium, but patients requiring multiple radiiodine administrations may be at higher risk, although no infertility was found in the group studied. (60)

(ii) The radiation dose to the testes can be reduced by frequent voiding. Sperm storage prior to high dose $^{131}$I therapy may be considered, since the post-therapy sperm count may not return to normal when higher doses of $^{131}$I are administered.

(iii) Impairment of female fertility by $^{131}$I therapy or increased risk of miscarriage has not been described (61, 62). An author of this Guideline (E.B.S.) is caring for a patient who has
given birth to two healthy children after receiving a total $^{131}$I dosage of 46.18 GBq (1248 mCi). The available data are insufficient to suggest a threshold.

(iv) No effect on birth weight or prematurity in subsequent pregnancies following $^{131}$I has been reported (63).

(b) Permanent damage to the salivary glands resulting in xerostomia, sialolithiasis, excessive dental caries, and reduced taste.

(c) $^{131}$I-induced xerophthalmia or epiphora is uncommon.

(d) No threshold for radiation-induced carcinogenesis has been firmly established (64). Following high doses of $^{131}$I therapy the uncommon development of other malignancies has been reported, including carcinoma of the stomach, bladder, colon, and salivary glands, melanoma and leukemia (65, 66). Reported neoplasms usually occur after more than one dosage, but one author of the Guideline has a patient who developed chronic myelogenous leukemia three years after receiving only 100 mCi of $^{131}$I therapy. A radiogenic etiology is neither implied nor excluded. A causative role for $^{131}$I in carcinogenesis, other than for thyroid cancer in children at Chernobyl, is difficult to establish since the baseline rate for cancer occurrence in the United States is about one in three for women and one in two for men. (67)

(e) During the informed consent process it is important to emphasize to the patient that these late side effects are rarely seen and should not deter him/her from receiving $^{131}$I for treatment of thyroid cancer when the benefits of ablation or therapy of metastatic or recurrent cancer clearly outweigh the risks.

e. Female patients who have the potential to be pregnant must always be tested for pregnancy using a urine or serum beta-HCG, ideally within 24 hours of treatment, as the pregnancy test may remain negative for up to 7-10 days after fertilization (24). Caution is therefore advised in treating patients who have had unprotected intercourse in the 10 days before treatment and the treating physician should consider discussing the limitation of the pregnancy test with the patient, which could include consideration of delaying the therapy until the beginning of the next cycle.

(1) Before omitting a pregnancy test in women of childbearing age, some institutions may require written historical confirmation of hysterectomy (a pregnancy test is still required in some institutions despite a history of tubal ligation), while others may choose to accept the word of the patient that pregnancy is impossible, documenting this as part of the treatment dictation.

(2) Cases of pregnancy have occurred when the patient has declared that pregnancy was impossible and the beta-hCG omitted (68, 69).
f. All potentially breastfeeding/lactating women must be asked if they are lactating. If so, they must be advised to stop breastfeeding, and therapy must be delayed until lactation ceases in order to minimize the radiation dose to the breast (25).

(1) Lactation (and the ability of the breast to concentrate large amounts of iodine) usually ceases 4-6 weeks post partum (with no breastfeeding) or 4-6 weeks after breastfeeding stops. It is suggested that a comment that a female patient of childbearing age denies lactation be part of the final treatment report.

(a) If there is uncertainty as to whether the previously lactating breasts still concentrate iodine, this may be assessed by noting the absence of iodine uptake on pre-therapy scintigraphy or with $^{99m}$Tc-pertechnetate. (26, 27)

(b) Several approaches available to speed the cessation of lactation are beyond the scope of this Guideline.

(2) The patient may not resume breastfeeding for that child.

(3) Nursing may resume with the birth of another child.

g. The treating physician should confirm that the patient is continent of urine or that arrangements are made to prevent/contain contamination caused by incontinence.

h. Good hydration of the patient (about 3000 mL/day of any liquid except milk) is required with instructions urging frequent (about hourly) urination for several days to a week which will reduce radiation exposure to the bladder and salivary glands.

i. The patient should have at least one bowel movement a day to reduce colon exposure. Laxatives (but not stool softeners which do not stimulate the bowel) may be necessary in constipated patients.

j. The patient’s identity must be confirmed in accordance with institutional policy before administration of $^{131}$I.

k. A mental status assessment should be performed since:

(1) patients with cognitive impairment may not be able to tolerate admission and isolation in a hospital;

(2) in such cases following instructions at home may require special supervision.

l. Renal insufficiency

(1) The rhTSH dose may be reduced by 50% or more (70).

(2) Hemodialysis is not a contraindication to $^{131}$I therapy (71).
Travel precautions should be reviewed and a card indicating the administration of radioactive therapy should be provided to the patient.

Radiation safety precautions for the patient are of sufficient importance that these appear in a separate section of this Guideline, V.1.C.

3. Data Required By the Treating Physician to Perform $^{131}$I Therapy for Thyroid Cancer

a. The treating physician must obtain the patient’s thyroid-related medical history, including all areas where adverse reactions are possible, and perform a directed physical examination.

1. The cumulative administered activity of $^{131}$I up to this point in time should be reviewed and entered in the patient’s record.

2. The operative and especially the pathology reports should be reviewed, as well as prior images.

3. The patient must not be lactating.

4. The patient must be able to read, or hear someone reading to him, the consent form, and give written informed consent per institutional standards.

b. The treating physician must confirm that appropriate laboratory testing has been performed and must review the results of these tests, including:

1. TSH level should be elevated to about 30 uIU/mL before the diagnostic scan pre-therapy for those medical centers performing this study or when a pretreatment scan is not performed.

2. Serum thyroglobulin (Tg) obtained, if possible, under TSH suppression and again at the time of maximal TSH stimulation;

   a. For rhTSH this occurs three days after the last rhTSH injection.

3. A post-thyroidectomy serum calcium, to exclude hypoparathyroidism, if not already available;

4. CBC within about a month of therapy;

5. Renal profile within a few weeks of therapy;

6. In women of child bearing age, a pregnancy test (urine or serum beta-hCG) must be obtained within 24 hours of treatment (these tests may remain negative for 7-10 days after fertilization);

   a. Therapy with $^{131}$I is always contraindicated in the pregnant patient.
(b) Merely questioning the patient, or having her sign a form as to the possibility of pregnancy is an inadequate precaution.

(c) Signage in those languages in common use in the community is recommended, advising patients to inform their physician if they are pregnant or breast feeding.

(d) The fetus is very radiosensitive. The fetal thyroid begins to concentrate iodine at 10-13 weeks (72) and can be severely affected by uptake of $^{131}\text{I}$.

(i) Unfortunately, this inadvertent administration of $^{131}\text{I}$ has occurred multiple times, since the beta-hCG serum pregnancy test may remain negative for 7-10 days after fertilization.

(ii) If inadvertent administration to a pregnant patient does occur, information on counseling patients about the significance of accidental administrations of $^{131}\text{I}$ is available from the patient’s obstetrician and the reference provided by this Guideline (73).

c. The physician must reconfirm that the patient is not lactating/nursing.

d. The patient’s identity must be reconfirmed before treatment.

e. The physician should reconfirm that the patient is continent of urine and feces.

f. The physician should confirm that the patient has not received iodinated contrast media within the previous two months. Any uncertainty may be reduced by measuring urinary iodine excretion.

g. The physician must reconfirm that the patient can understand and fulfill all requirements of home or hospital care post-therapy.

h. The presence or absence of iodine-accumulating thyroid tissue preablation may be documented by uptake measurement and imaging (see SNM Procedure Guideline for Scintigraphy for Differentiated Thyroid Cancer).

(1) A small minority of patients will either need no $^{131}\text{I}$ ablative therapy (since there is no remnant left) or have too much residual tissue to give $^{131}\text{I}$ safely, as the risk of symptomatic radiation thyroiditis becomes significant (cf. VI.B.2.d.(3),(c) above). A completion thyroidectomy may be required in such cases.
(2) The preablation scan may sometimes also reveal metastases in the lung, bone or brain causing a reevaluation of the use of $^{131}$I, change in $^{131}$I dosage, corticosteroid administration, or some combination of these (74,75).

(3) There are experts who believe this happens too infrequently to justify the time and cost required for pre-ablation scanning, and the issue remains somewhat controversial (76).

(a) Those centers which do not perform pre-ablation scans also raise concerns about the diagnostic administered activity of $^{131}$I possibly stunning the thyroid remnant, so that a therapeutic dosage of $^{131}$I would have less uptake in subsequent ablative therapy.

(a) The likelihood and clinical relevance of stunning with low activity (37-111 MBq [1-3 mCi]) diagnostic imaging is controversial. Some investigators feel that the therapeutic $^{131}$I activity given within three days after the the diagnostic activity reduces the probability of stunning. Others see the reported decrease in $^{131}$I uptake of the therapeutic activity after the administration of a low diagnostic activity of this radiopharmaceutical as caused by the cytocidal effect of the latter.

(i) A randomized study of $14.8$ MBq (0.4 mCi) of $^{123}$I showed no difference in the ablation rate vs $74$ MBq (2 mCi) of $^{131}$I (81% v.74%, p>0.05) (77).

(ii) Since $^{123}$I produces Auger electrons and at least one report of $^{123}$I stunning exists (albeit to a lesser degree than with $^{131}$I) (78), it is possible that both activities of these radiopharmaceuticals cause stunning, but the ablation rates from both are comparable to those in the literature.

(iii) Studies of patients receiving $111-185$ MBq (3-5 mCi) dosages of $^{131}$I, vs. no $^{131}$I preablation diagnostic scintigraphy also show no differences in percent ablation, 65% for scanned patients, 67% for unscanned patients. (79)

4. Selection of Activity: In general, the greater the risk of metastases or recurrent tumor and the more extensive the invasiveness or dissemination of the cancer at the time of therapy, the higher the $^{131}$I activity required.

a. A variety of approaches have been used to select the administered activity which relate to the risk (see Definitions, III F) of cancer recurrence or death (2,3).

(1) For postoperative ablation of thyroid bed remnants, activity in the range of 1.11–3.7 GBq (30 to 100mCi) is typically prescribed, depending on the RAIU and amount of residual functioning tissue present. (80,81)
(2) For treatment of thyroid cancer in the cervical or mediastinal lymph nodes, activity in the range of 5.55–7.4 GBq (150–200 mCi) is typically administered.

(a) Patients with advanced local/regional disease may be treated first with surgical debulking, then with $^{131}\text{I}$, and, if clinically indicated, external beam radiation. (82)

(3) For treatment of distant metastases, activity of 7.4 GBq (200 mCi) or more is often given.

(a) The radiation dose to the bone marrow is typically the limiting factor. Most experts recommend that the estimated radiation dose to the bone marrow be less than 2 Sv (200 rem) (57).

(b) Blood and whole body dosimetry may be indicated when a high activity of $^{131}\text{I}$ is planned to treat metastatic disease. Dosimetry will determine the maximum safe activity of $^{131}\text{I}$ and is recommended for all such patients over 50-55 years of age, especially in the presence of a reduced GFR and where lung metastases may concentrate a large amount of $^{131}\text{I}$ (83,84).

(c) Retention of radioiodine in the body at 48 h should be <4.44 GBq (120 mCi), or <2.96 GBq (80 mCi) if diffuse lung metastases are present, to reduce the risk of radiation pneumonitis and clinically significant myelosuppression.

(4) In the absence of anti-thyroglobulin antibodies, an elevated or rising serum thyroglobulin is a useful indicator of residual or recurrent thyroid cancer and may be an indication for empiric radioiodine therapy, using 150-200 mCi with marrow dosimetry if indicated, even in the absence of discernible activity on the diagnostic radioiodine scan (85).

(a) An elevated serum thyroglobulin does not imply iodine avidity of the tumor. If the thyroglobulin is elevated but no discernible activity is seen on the diagnostic $^{123}\text{I}$ or $^{131}\text{I}$ scan, there may still be visualization of thyroid tissue on a post therapy scan, and, the serum thyroglobulin may fall following empiric $^{131}\text{I}$ therapy. However, with continuous TSH suppression the serum thyroglobulin may fall without $^{131}\text{I}$ therapy in some patients. There are no double blinded studies demonstrating that recurrence rates and prognosis are altered by such a course of empiric $^{131}\text{I}$ therapy, so this remains a controversial issue (86). Risks from radioiodine administration must be weighed against uncertain benefits in this situation, although such empiric $^{131}\text{I}$ therapy often causes a decrease in thyroglobulin levels, presumably reflecting a cytocidal effect. (86) Besides empiric $^{131}\text{I}$ therapy, surgery is a consideration if focal resectable tumor can be located. Both $^{18}\text{F-FDG}$ PET imaging (more sensitive after TSH stimulation) and thyroid ultrasound may be helpful in identifying thyroid cancer metastases when the $^{131}\text{I}$ scan is negative but the stimulated serum thyroglobulin is elevated. Older data indicate that
when $^{18}$F FDG is unavailable, $^{99m}$Tc-sestamibi and $^{201}$Tl scintigraphy may detect metastatic thyroid cancer with reasonable sensitivity. (38,87)

(5) In general $^{131}$I therapy is less effective in bulky disease with diameter greater than 1-2 cm, where surgical excision prior to radioiodine may yield better results.

b. A short intra-thyroidal and/or body effective $^{131}$I half-life can be a source of failure of $^{131}$I therapy in metastatic lesions. Oral administration of lithium carbonate inhibits the liberation of thyroidal thyroxine and thus prolongs the intrathyroidal biological half-life of administered $^{131}$I and occasionally may be useful in patients who have a rapid turnover of radioactive iodine. Serum lithium levels should be monitored to avoid toxicity. There are no double blind outcome studies on lithium, and its use adds another layer of complexity to the therapeutic procedure. It is infrequently employed at this time. (88,89)

c. The side effects of $^{131}$I therapy are generally dose related and are listed above in the consent form outline summarized in VI.B.2.d. above.

5. Follow up

a. For staging purposes patients should have whole body scintigraphy approximately three to seven days after treatment.

b. A serum TSH should be checked about six to eight weeks after treatment to confirm the level is within the desired therapeutic limits.

c. Since the overall recurrence rate for thyroid cancer approaches 20%, and up to 10% of recurrences occur after twenty years, long term follow-up of the patient is required, both to maintain appropriate serum TSH levels and to detect recurrences of disease. The serum TSH may be allowed to rise to low normal levels if two consecutive assays of stimulated serum thyroglobulin performed in different years, are negative (with negative anti-thyroglobulin assays) along with negative $^{131}$I scans, since the risk of recurrence by then, under these circumstances, is very low (3).

C. Radiation Safety Issues

1. Therapy with $^{131}$I is always contraindicated in the pregnant patient. Even the use of low activities of $^{131}$I for the diagnosis of a thyroid disorder is not encouraged in women of childbearing age without first performing a pregnancy test. A pregnancy test (urine or serum beta-hCG) must be administered to all women in the childbearing years prior to receiving therapeutic dosages of $^{131}$I, and such therapy must not be administered if pregnancy is confirmed. The fetus is very radiosensitive and the fetal thyroid concentrates iodine after 10-13 weeks and can be severely affected by diagnostic or therapeutic dosages of $^{131}$I.
Unfortunately, administration of $^{131}$I can still occur since the serum beta-hCG pregnancy test remains negative for 7-10 days after fertilization. Information on counseling patients about the significance of accidental administration of $^{131}$I can be obtained from the obstetrician and also is found in reference 73 of this Guideline.

2. Breast feeding must be completely discontinued for about 4-6 weeks prior to $^{131}$I therapy. Radioiodine is secreted in breast milk and both the breast and the infant can receive a significant radiation dose from administration of $^{131}$I during lactation.

3. Regulatory requirements for hospitalization and other radiation protection vary among the states and from country to country, with many guidelines more stringent than those of the U.S. Nuclear Regulatory Commission (NRC).

4. Relevant NRC Regulations

   a. The NRC has three alternate criteria allowing patient release from the hospital after $^{131}$I therapy:

      (1) When no individual member of the public is likely to exceed a radiation dose of 5 mSv (500 mrem) from that patient, assuming all other regulatory requirements for patient instructions and record keeping are met.

         (a) NUREG-1556, Vol 9, “Consolidated Guidance about Materials Licenses: Program-Specific Guidance about Medical Use Licenses,” describes methods for calculating doses to other individuals and contains tables of activities not likely to cause doses exceeding 5 mSv (500 mrem).

         (b) This “guidance” is not a regulation, and scientifically valid, less conservative calculations on patient release have been published (90, 91, 92).

      (2) When the survey meter reading is less than 0.07 mSv/h (7.0 mrem/h) at one meter. Some radiation meters measure exposure rates in milliroentgens/hour (mR/h), but for low linear energy-transfer-rate radiation (including beta particles and most x-rays and gamma rays) the exposure rate at 7 mR/h will be equivalent to the dose rate at 0.07 mSv/h (7 mrem/h). (93)

      (3) When the administered activity is 1.22 GBq (33 mCi) or less.

   b. If the patient is to be treated as an inpatient:
(1) Nursing personnel must be instructed in all relevant radiation safety procedures.

(2) Selected nursing personnel should be provided appropriate radiation monitors (film badge, direct-reading dosimeters, etc.). Nurses who are or who may be pregnant are excluded from direct patient care.

(3) Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency, as concern about radiation exposure should not interfere with prompt, appropriate medical treatment of the patient should an acute medical problem develop.

c. Written instructions describing methods to limit the dose to others must be given to the patient if:

(1) an individual member of the public is likely to exceed a radiation dose of 1 mSv (100 mrem) from that patient;

(2) if the administered dosage is greater than 0.26 GBq (7 mCi) (94)

d. Individual Agreement States may have specific rules and regulations regarding release of patients with significant residual activity.

e. Details on the relevant federal regulations can be obtained at the NRC web site, www.nrc.gov, or by telephone (301-415-7000).

5. Post-release precautions

a. The licensee (ideally the treating physician) should instruct the patient on how to reduce unnecessary radiation exposure to family members and members of the public. Written instructions must be provided both to reduce the radiation dose to the patient and to members of the public and may be required in some jurisdictions.

b. With simple precautions, the radiation dose to family members is low (considerably less than the NRC upper limit of 5 mSv [500 mrem]) even when patients are not admitted to a hospital. In a study where the patients were to sleep alone and avoid prolonged personal contact for two days post-therapy, 65 household members received a mean dose of 0.24 mSv (24 mrem) (range 0.01-1.09 mSv [1-109 mrem]). (95)

(1) The patient must sleep alone and abstain from intercourse for approximately one week post-therapy unless patient specific calculations, employing several assumptions, indicate that this period can be shortened. Children and pets should not sleep in/on the bed of the patient for this week.

(2) There are no other restrictions on the patient being with other adults.
(3) Allowing ten minutes per day of zero distance ("hug time") for children, with a distance limit of three feet for all other activities, it would be extremely unlikely to receive a dose >1mSv (100 rem) and the Committee is unaware of the documentation of such an occurrence when these guidelines have been followed.

(4) Infants and small children requiring feeding, changes of clothing, etc. from the treated parent require another caregiver for up to a week, although there is never a reason for the treated parent to move out of the home.

(5) There is no hazard to any member of the family arising from sites where the patient sits, what the patient has touched, or what the patient cooks. Internal exposure of family members from items contaminated by patient saliva or urine must be prevented.

(a) Disposable plates and utensils are not only unnecessary, but if employed, can trigger overly sensitive waste facility alarms. Dishes and utensils should not be shared.

(b) It is unnecessary to wash the patient’s laundry separately.

(6) Patients should flush the toilet twice after use and wash their hands for 20 seconds. Men should urinate sitting down to avoid small levels of floor contamination in front of the toilet.

(7) Although certain proprietary products are advertised for specifically decontaminating $^{131}$I in the home, such products are not necessary in the typical home situation.

(8) Use of public transportation is discouraged for the first 24 hours after $^{131}$I therapy.

(9) Although 10 CFR 35.75 does not expressly prohibit the release of a radioactive patient to a location other than a private residence, such as a hotel, the NRC strongly discourages this practice, because it can result in radiation exposures to members of the public for which the licensee may not be able to assess full compliance with 10 CFR 35.75(a) and may result in doses which are not ALARA (as low as reasonably achievable) (96).

(10) Most experts recommend that both men and women wait 6-12 months after $^{131}$I therapy before trying to conceive a child, although there are no reliable data on the validity of these suggested intervals. The 12-month interval also allows for follow-up imaging to evaluate the effectiveness of the treatment (97) and for retreatment if deemed appropriate.

   c. Patient specific calculations of radiation exposure to others can be performed, employing several assumptions, and specific recommendations given to each patient about the time and distance to stay away from others.
6. Radiation surveys of the thyroid gland on personnel administering $^{131}$I are performed periodically, depending on local regulations and institutional policy.

7. Patients must be provided with a written document stating they have been given a radioactive substance for documentation of the source of radiation in the event it is detected by monitoring devices during travel.

D. Interactions of $^{131}$I with other forms of treatment

1. Patients with advanced local/regional recurrent disease or distant metastases, especially those with involvement of the aerodigestive tract, brain, or spinal cord may be treated with both $^{131}$I and external beam radiation postoperatively. Corticosteroids to prevent swelling may be required if central nervous system metastases are to be irradiated. The use of external beam radiation prior to, or alternating with $^{131}$I treatment, has not been documented to be associated with a subsequent reduction in tumor uptake of radioactive iodine. Therefore external beam radiation, if clinically and emergently indicated, need not be delayed. The toxicity, acute and late, is likely to be additive within the field of irradiation. Dosimetry calculations are especially important if $^{131}$I therapy and external beam radiotherapy are both being considered, or have previously been performed in patients with spinal metastases, to avoid potential radiation-induced spinal cord damage.

2. Skeletal metastases that are painful or are a threat to life or function may be treated, in addition to $^{131}$I, with bone-seeking beta-emitting radiopharmaceuticals (e.g. $^{89}$Sr or $^{153}$Sm-lexidronam) if the bone scan is positive at the painful site, although these carry a greater risk of myelosuppression than $^{131}$I, external radiotherapy, or surgery.

E. Radiopharmaceuticals

1. See Sections VI.A.3 and VI.B.3 for guidance on selection of the administered activity for the treatment of hyperthyroidism and thyroid cancer, respectively.

2. Therapeutic $^{131}$I can be administered in liquid or capsule form.

a. If a capsule or a liquid form is used, strategies for minimizing volatilization and/or inhalation of volatilized iodine during dosage preparation and administration should be used, for example, venting the dose into a filtering system, such as a fume hood, maintaining alkaline pH, and administering the dose to the patient shortly thereafter. Stabilized forms of radioactive iodine, in wide use in the United States, should not require these precautions but remain a condition of many licenses.

3. The prescribed activity of $^{131}$I must be verified, ideally by two observers, in a dose calibrator before administration.

F. Issues Requiring Further Clarification
1. The utility of $^{123}$I or $^{131}$I whole-body imaging in patients following total thyroidectomy but before initial $^{131}$I ablative therapy for thyroid cancer.

2. The pathophysiological and prognostic significance of “stunning” of the thyroid remnant and metastatic deposits.

3. The diagnostic role of alternative imaging agents for thyroid cancer, such as $^{123}$I, $^{124}$I, and $^{99m}$Tc.

4. The necessity of $^{131}$I therapy for low risk papillary cancers with diameter <1.0 cm if there is favorable molecular assessment, e.g. absence of BRAF (a proto-oncogene encoding a serine/threonine protein kinase called B-Raf) expression, favorable histology, and no evidence of distant metastatic involvement.

5. The equivalence of recombinant human TSH as an adjunct to $^{131}$I therapy of metastatic thyroid carcinoma to $^{131}$I therapy after endogenous TSH elevation from thyroid hormone withdrawal.

6. The frequency and length of long term follow up after $^{131}$I therapy for thyroid cancer in a variety of clinical situations.

7. Predicting the length of time required for the TSH to rise sufficiently in individual patients after thyroid hormone withdrawal before $^{131}$I therapy.

8. The need to attain a serum TSH level of $\geq 30$ µU/mL before therapy vs. lower or higher degrees of elevation.

9. Standardization of $^{131}$I dosimetry to deliver:
   a. a therapeutic dose to hyperfunctioning thyroid glands;
   b. ablative radiation doses to thyroid remnants post-thyroidectomy.

10. The role of $^{124}$I in thyroid dosimetry, and the efficacy of lesion dosimetric planning. (98)

11. The actual benefits and risks of empiric high dose $^{131}$I therapy (e.g. $> 11.1$ GBq [300 mCi]) for patients with serum thyroglobulin elevation but negative iodine scintigraphy.

12. The therapeutic benefit of administered activities in excess of 300 mCi in iodine-avid metastatic disease, relative to lower activities of $^{131}$I.

13. Determination of whether external beam radiotherapy delivered to regional neck metastases before therapeutic $^{131}$I decreases the subsequent $^{131}$I therapeutic effect.

VII. DOCUMENTATION/REPORTING

A. Goals of a Nuclear Medicine Report

See SNM Procedure Guideline for General Imaging
B. Direct Communication

See also SNM Procedure Guideline for General Imaging and ACR Practice Guideline for Communication: Diagnostic Radiology

C. Written Communication

The report to the referring physician should include: the indication for therapy; \(^{131}\text{I}\) administered activity; indication that informed consent (including mention of all possible side effects) was obtained; the results of a urine or serum pregnancy test; a statement that the patient was informed in writing of home radiation safety precautions; notation that travel precautions were discussed and a relevant card or letter provided

See SNM Procedure Guideline for General Imaging

D. Contents of a Nuclear Medicine Report

See Section VII. of SNM Procedure Guideline for General Imaging for content of each section.

1. Study identification
2. Patient demographics
3. Clinical information
4. Procedure description
5. Description of therapeutic administration including premedication details, mention of absence of pregnancy and lactation in women of childbearing age
6. Recommendations for follow-up
7. Comments.

VIII. EQUIPMENT SPECIFICATION

See SNM Procedure Guideline for General Imaging.

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION CONCERNS

See SNM Procedure Guideline for General Imaging.

X. RADIATION DOSIMETRY

See also SNM Procedure Guideline for General Imaging.

A. It is the position of SNM that patient exposure to ionizing radiation should be at the minimum level consistent with obtaining a diagnostic examination or performing effective therapeutic procedures. Reduction in patient radiation exposure may be
accomplished by administering a lower dosage of radiopharmaceutical when the clinical situation and technique or equipment used for imaging can support such an action. Each patient procedure is unique and the methodology to achieve minimum exposure while maintaining diagnostic accuracy and therapeutic efficacy needs to be viewed in this light. Radiopharmaceutical dosage ranges outlined in this document should be considered as a guide. Dose reduction techniques should be utilized when appropriate. The same principles should be applied when CT is used in a hybrid imaging procedure. CT acquisition protocols should be optimized to provide the information needed while minimizing patient radiation exposure. Minimizing radiation dose is especially important in children. (Cf.VI.B.6.)

**B. Exposure to the public is always a consideration (95).**

**C.** The following dosimetry tables are somewhat different from those in some other SNM Guideline documents. The organ receiving the highest dose (usually thyroid) is given, along with the dose to red marrow. In situations involving radiation therapy, it is inappropriate to use the quantity 'effective dose', as this quantity relates to the risk of stochastic effects from a low dose procedure. In this application, dose to red marrow is of more clinical interest, as clinically significant pancytopenia could occur with $^{131}$I therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximum Thyroid Uptake (%)</th>
<th>Organ Receiving the Largest Radiation Dose mGy/MBq (rad/mCi)</th>
<th>Red Marrow Dose mGy/MBq (rad/mCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>0</td>
<td>0.61 Bladder (2.3)</td>
<td>0.035 (0.13)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>72 Thyroid (270)</td>
<td>0.038 (0.14)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>210 Thyroid (780)</td>
<td>0.054 (0.20)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>360 Thyroid (1300)</td>
<td>0.070 (0.26)</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>500 Thyroid (1850)</td>
<td>0.086 (0.32)</td>
</tr>
<tr>
<td>Stage of Gestation</td>
<td>Fetal Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child (5 y old)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>640 Thyroid (2400)</td>
<td>0.10 (0.37)</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>790 Thyroid (2900)</td>
<td>0.12 (0.44)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.8 Bladder (6.7)</td>
<td>0.10 (0.37)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>370 Thyroid (1370)</td>
<td>0.10 (0.37)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1100 Thyroid (4100)</td>
<td>0.14 (0.52)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>1900 Thyroid (7000)</td>
<td>0.18 (0.67)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>2600 Thyroid (9600)</td>
<td>0.22 (0.81)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3300 Thyroid (12000)</td>
<td>0.26 (0.96)</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>4100 Thyroid (15000)</td>
<td>0.29 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

D. Dose estimates to the fetus from $^{131}$I were provided by Russell et al. (99). Information about possible placental crossover of this compound was included in the calculations.
E. Estimated doses to the fetal thyroid (mGy per MBq administered to the mother) were given by Watson (100):

<table>
<thead>
<tr>
<th>Gestational Age (months)</th>
<th>Dose from I-131 mGy to fetal thyroid/MBq administered to the mother, (rad/mCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>230 (850)</td>
</tr>
<tr>
<td>4</td>
<td>260 (960)</td>
</tr>
<tr>
<td>5</td>
<td>580 (2150)</td>
</tr>
<tr>
<td>6</td>
<td>550 (2000)</td>
</tr>
<tr>
<td>7</td>
<td>390 (1400)</td>
</tr>
<tr>
<td>8</td>
<td>350 (1300)</td>
</tr>
<tr>
<td>9</td>
<td>270 (1000)</td>
</tr>
</tbody>
</table>

F. Other special cases of dosimetry for the potentially pregnant patient, including dosimetry for hyperthyroid patients, athyreotic patients, and the unique case in which conception occurs some days or weeks after administration of $^{131}$I, can be found on the RADAR web site http://www.doseinfo-radar.com/RADAR-INT-NM.html, under the heading "The Pregnant Patient".

XI. ACKNOWLEDGEMENTS

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SNM Procedure Guideline for Therapy of Thyroid Disease with $^{131}$I DRAFT V2.3


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94. 10 CFR 35.75


96. NRC Policy on Release of Iodine-131 Therapy Patients Under 10 CFR 35.75 to Locations Other Than Private Residences. 25 January 2011.


XIII. BOARD OF DIRECTORS APPROVAL DATES:

Version 1.0 January 7, 2002

Version 2.0 September 8, 2005

XIV. APPENDIX
Table 1
Pharmaceuticals Blocking Radioiodine Uptake

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Recommended time of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionamide medications (e.g., propylthiouracil, methimazole, carbachol)</td>
<td>3 d for thionamides</td>
</tr>
<tr>
<td>Multivitamins containing iodide</td>
<td>7-10 d for multivitamins*</td>
</tr>
<tr>
<td>Natural or synthetic thyroid hormones</td>
<td>10-14 d for triiodothyronine</td>
</tr>
<tr>
<td>Kelp, agar, carrageenan, Lugol’s solution.</td>
<td>2–3 wk, depending on iodide content*</td>
</tr>
<tr>
<td>Saturated solution of potassium iodide (SSKI)</td>
<td>2-3 wk*</td>
</tr>
<tr>
<td>Topical iodine (e.g., surgical skin preparation)</td>
<td>2–3 wk*</td>
</tr>
<tr>
<td>Intravenous radiographic contrast agents:</td>
<td></td>
</tr>
<tr>
<td>- water soluble</td>
<td>6-8 wk, assuming normal renal function</td>
</tr>
<tr>
<td>- lipophilic agents</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3–6 mo or longer (101)</td>
</tr>
</tbody>
</table>

Table 2
Dietary Sources of Significant Amounts of Iodine

- Iodized salt
- All dairy products: milk, yogurt, cheese, ice cream, etc.
- Egg yolks (not egg whites or egg substitutes)
- All seafood, (crustaceans; fish) except tuna
- Turkey and liver
- Seaweed and kelp products (carrageenan, alginate)
- Commercial bread when made with iodide conditioners
- Milk chocolate
- Iodide-containing multivitamins
- FDC red dyes #3 and #28.
- Grains (may be consumed in small portions, e.g., one-fourth of plate)
- Soy proteins (goitrogens in humans so fortified with iodine) (102)

Table 3
Radiation Absorbed Dose from $^{131}$I (NaI)

<table>
<thead>
<tr>
<th>Organ</th>
<th>mGy/MBq</th>
<th>rad/mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assuming no thyroid uptake (athyrotic)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.610</td>
<td>2.3</td>
</tr>
<tr>
<td>Lower colon wall</td>
<td>0.043</td>
<td>0.16</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.065</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Assuming 55% thyroid uptake and 20-g gland

<table>
<thead>
<tr>
<th>Organ</th>
<th>Radiation Dose (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>790 (2.920)</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.290 (1.1)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.091 (0.34)</td>
</tr>
<tr>
<td>Upper colon wall</td>
<td>0.058 (0.21)</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.041 (0.15)</td>
</tr>
<tr>
<td>Testes</td>
<td>0.026 (0.10)</td>
</tr>
</tbody>
</table>

### Table 4

**Radiation Dose to Red Marrow for 74–7,400 MBq (2–200 mCi) $^{131}$I**

<table>
<thead>
<tr>
<th>Thyroid uptake (%)</th>
<th>MBq (rad/mCi)</th>
<th>Adult mGy/MBq</th>
<th>Child (10 y) mGy/MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.035 (0.13)</td>
<td>0.065 (0.25)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.038 (0.14)</td>
<td>0.070 (0.26)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>0.086 (0.32)</td>
<td>0.160 (0.59)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>0.100 (0.37)</td>
<td>0.190 (0.70)</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>0.120 (0.44)</td>
<td>0.220 (0.81)</td>
<td></td>
</tr>
</tbody>
</table>

*Dose may vary depending on the whole-body effective half-life of $^{131}$I. From ICRP 53, pp. 275–278.