The Benefits and Risks of I-131 Therapy in Patients with Well-Differentiated Thyroid Cancer

Douglas Van Nostrand¹,²

Background: I-131 has been used in the therapy of well-differentiated thyroid cancer for over 50 years. Although the benefits and risks of I-131 remain issues of controversy and research, our understanding of them continues to improve. This review presents an overview of the benefits of I-131 therapy for ablation, adjuvant treatment, and treatment of locoregional and/or metastasis of well-differentiated thyroid cancer and considers the risks of complications of I-131 therapy.

Summary: The benefits of I-131 remnant ablation include: [1] facilitating the interpretation of subsequent serum thyroglobulin levels, [2] increasing the sensitivity of detection of locoregional and/or metastatic disease on subsequent follow-up radioactive iodine whole-body scans, [3] maximizing the therapeutic effect of subsequent treatments, and [4] allowing a postablation scan to help identify additional sites of disease that were not identified on the preablation scan or when a preablation scan was not performed. The potential benefits of I-131 adjuvant treatment include decreasing recurrence and disease-specific mortality for unknown microscopic, locoregional, and/or distant metastatic disease. The potential benefits of I-131 treatment of known locoregional and/or distant metastases are [1] decreasing recurrence, and [2] decreasing disease-specific mortality and/or palliation. The more significant risks and side effects involve organ systems including eye/nasolacrimal, salivary, pulmonary, gastrointestinal, hematopoietic, and gonads as well as secondary primary malignancies.

Conclusions: Although there are never-ending controversies regarding I-131 therapy in well-differentiated thyroid cancer, the benefits and risks are becoming better understood. This in turn helps the treating physician and patient in making decisions regarding therapy.

Introduction

The first use of I-131 in a patient was in 1942 for the treatment of Graves’ disease (1). This intriguing beginning was eloquently described by Sawin and Becker (2). Subsequently, in 1946, radioactive iodine (RAI) was used to treat well-differentiated thyroid cancer (3) and has been an important component in the management of well-differentiated thyroid cancer since. However, the benefits and risks of I-131 have been a subject of continuing controversy. The objective of this report was to review the benefits and risks (i.e. side effects) of I-131 therapy in patients with well-differentiated thyroid cancer. Staging of thyroid cancer will not be discussed as it is beyond the scope of this review.

Ablation Versus Treatment

Frequently, the terms “ablation” and “treatment” for I-131 therapy have been used in various ways. The variable use of these terms and sometimes interchange of these terms is one of the factors that have made issues involving I-131 ablation and treatment confusing. For example, a discussion of the effectiveness of I-131 or the selection of prescribed activity of I-131 is problematic if the participants have a different objective for what ablation and/or treatment should constitute. It is important to define and understand the definitions of and objectives for ablation and treatment. To reduce confusion, the following definitions will be used.

Remnant ablation

This is the use of I-131 to destroy normal residual functioning thyroid tissue with the objectives of [1] facilitating the interpretation of subsequent serum thyroglobulin levels, [2] increasing the sensitivity of detection of locoregional and/or metastatic disease on subsequent follow-up RAI whole-body scans, [3] maximizing the therapeutic effect of any subsequent I-131 treatments, and [4] facilitating a postablation scan that
may identify additional sites of disease that were not identified on the preablation scan or suspected if a preablation scan was not performed. Although remnant ablation is typically the first I-131 therapy, this may be done a second time.

Adjuvant treatment

This is the use of I-131 to destroy unknown microscopic thyroid cancer and/or suspected but unproven residual thyroid cancer to potentially decrease recurrence and mortality from thyroid cancer.

Treatment

This is the use of I-131 to destroy known locoregional and/or distant metastasis with the objectives of potential cure, reduced recurrence and mortality from thyroid cancer, and/or palliation. Although treatment would typically be performed after ablation, it is possible with the above definitions that one is both ablating and treating on the first I-131 therapy.

I-131 therapy

This is any generic use of I-131, including I-131 remnant ablation, I-131 adjuvant treatment, or I-131 treatment. Although the American Thyroid Association (ATA) guidelines for patients with thyroid nodules and differentiated thyroid cancer reverses the definition of the terms “treatment” and “therapy” as defined above (4), this author believes that the above usages are more consistent with other usage of the terms in oncology. For example, one might use either therapy or treatment to say that the patient received her treatment or therapy with rituxan, adjuvant treatment or therapy with tamoxifen, and/or radiation treatment or therapy. However, one would use therapy and not treatment when speaking generically. For example, one would not say the patient is receiving her chemotreatment. Instead, most individuals would say chemotherapy. Accordingly and for this review, the term therapy is used here for generic purposes to refer to all I-131 therapies, and treatment is used here for specific purposes.

In regard to the usage of terms, it is important to distinguish risk from objectives, even though they are intimately related. Not infrequently when two discussants advocate different management for a patient, this is based on differences in each one’s assessment of risks and/or objectives. For example, two discussants may agree on the risk but disagree on the objective for an I-131 therapy for that patient. Alternatively, they may agree on the objective required to deal with a certain risk, but disagree on what the degree of risk is. Distinguishing risk from objective will help discussants clarify the nature of their practice differences. This will help patients who are often confused by what seems to be two completely different recommendations from experts. If physicians can help the patient understand the different perceptions of risks as well as the different objectives, the patient will not only understand the discordance between their physicians but also be better able to make their own decision. Even if physicians agree on the risk as well as the objectives, some patients will accept much higher risks for a lower likelihood of benefit, whereas some will give up significant potential benefit to minimize risks. Of course, this is not an issue of right or wrong; it is an issue of patient preference.

Benefits of I-131

Ablation

As used in this review, I-131 ablation has four objectives, each with its attendant benefits. The first was to facilitate the interpretation of subsequent serum thyroglobulin determinations. I-131 ablation is widely accepted as being successful in destroying all or almost all of any normal residual thyroid tissue, which in turn facilitates the use of subsequent serum thyroglobulin levels as a tumor marker for follow-up for recurrence (5–10).

The second objective of I-131 ablation was to increase the sensitivity of subsequent follow-up RAI whole-body scans for the detection of locoregional and/or metastatic disease. By ablating normal residual thyroid tissue, subsequent RAI scans may be able to detect locoregional and/or metastatic disease better than if ablation had not been performed for three reasons. The eliminated normal residual thyroid tissue will no longer be competing to take up a portion of the administered RAI and this will allow more RAI to be taken up by the locoregional disease and/or distant metastases. Further, by eliminating any significant residual thyroid tissue in the thyroid bed, this intense uptake is no longer present to obscure other foci of adjacent uptake. Intense uptake in residual thyroid tissue has a star-burst, blossoming, or blooming effect that often obscures less intense adjacent foci of RAI activity and which may be outside the thyroid bed. Finally, for patients prepared by thyroid hormone withdrawal, elimination of normal residual thyroid tissue will reduce endogenous sites of normal tissue-producing thyroid hormone, which in turn may help increase blood levels of thyroid-stimulating hormone (TSH) and allow greater uptake of RAI and a better chance to view locoregional disease or metastatic foci on the whole-body scan (5,7, 8, 11).

The third objective of I-131 ablation was to maximize the therapeutic effect of subsequent I-131 treatments. If a subsequent I-131 treatment is needed, ablation of the normal residual thyroid tissue may increase the therapeutic effect of that treatment for the same reasons that I-131 ablation can improve the sensitivity of subsequent RAI whole-body scans. Again, elimination of normal residual thyroid tissue allows more RAI to be available to go to the tumor, and, if the patient is prepared with thyroid hormone withdrawal, the patient may have potentially higher blood levels of TSH. The latter may increase RAI uptake and radiation-absorbed dose to the tumor.

The fourth objective of I-131 ablation was to allow a postablation scan to help identify additional sites of disease that were not identified on the preablation RAI whole-body scan or when a preablation whole-body scan was not performed. Postablation scans can identify additional sites of disease that are not identified on preablation scans or when preablation scans are not routinely performed, and thus, postablation scans may alter staging, subsequent management, and/or follow-up in as many as 9–15% of patients (12–18). Although I-131 can be very successful in achieving all of the above objectives, many factors may affect the degree of success of I-131 ablation in achieving these objectives. These include but are not limited to the extent of surgery, percent uptake of RAI in normal residual thyroid tissue, volume of normal residual thyroid tissue, prescribed activity of I-131, geometrical shape of normal residual thyroid tissue, effective half-life of I-131 in...
the normal residual thyroid tissue, patient’s compliance with low iodine diet, blood level of TSH, use of diagnostic I-131 with possible stunning, and definition of successful I-131 ablation.

**Adjuvant treatment**

Additional unknown sites of microscopic disease or local or distant metastases may be present, and an additional potential benefit of I-131 is adjuvant treatment of these sites with the objective of their elimination. This in turn may reduce the likelihood of recurrence and increase the likelihood of cure. Whether or not I-131 adjuvant treatment achieves these objectives, and the amount of I-131 administered to achieve these objectives are two of the more controversial areas. The former is discussed below, and the latter has been reviewed previously (5).

Although many studies support a significant reduction in the rate of recurrence (19–22) and mortality using I-131 adjuvant treatment (20–24), others have found no significant benefit (24,25–30). Of note, many of the above reports included known residual locoregional disease. Nevertheless the trend appears to be that the lower the risk, the lower the benefit. However, frequently the difficulty is determining the risk. The ATA Guidelines Taskforce has published a table (see Table 1) discussing the expected benefit of I-131, and this can be used to help decide whether or not I-131 adjuvant treatment should be used (4).

**Treatment of locoregional disease**

The benefit of I-131 treatment of known locoregional disease after surgery is also controversial. If the histopathology shows tumor extending to the margins, local invasion, and/or lymph node involvement, the benefit of I-131 treatment may be greater (31). More surgery before I-131 treatment provides an additional option that makes management decisions even more complex. In short, the higher the risk, the greater the potential benefit of I-131 treatment (refer to Table 1 from the ATA Guidelines Taskforce).

**Treatment of distant metastatic disease**

The benefit of I-131 in the treatment of distant metastases has been extensively reviewed (31). The following represents a distillation of that review and an update. The objectives of I-131 treatment of distant metastases are cure, control of recurrence, or palliation. Unfortunately, the literature on the effectiveness of I-131 to achieve these objectives is problematic for two reasons. First, there are no prospective studies that prove that RAI treatment for organ-specific distant metastases increases survival, reduces recurrence, or has significant palliative effect. This is unfortunate but is due to many reasons, including low volume of patients, difficulty in controlling the many prognostic factors (e.g., variable patterns of pulmonary metastases of single lesion to diffuse uptake to multiple bone metastases), and the long time required to follow these patients. Second, although many good retrospective studies are available (32–59), these studies have many limiting factors (see Table 2) and are frequently contradictory. For example Ruegemer et al. (39), Dinneen et al. (46), and Sisson et al. (51) report little to no evidence to suggest a therapeutic benefit of I-131 treatment in patients with pulmonary metastases whereas Casara et al. (44), Schlumberger et al. (38), Samaan et al. (37), Pacini et al. (45), and Ronga et al. (59) do report benefit. For a more detailed discussion of each of the major studies by location of distant metastases in 2006, please see an earlier review (31). Several trends concerning benefits or lack

---

**Table 1. Major Factors Impacting Decision Making in Radioactive Iodine Therapy**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Decrease risk of death</th>
<th>Decrease risk of recurrence</th>
<th>May facilitate initial staging and follow-up</th>
<th>RAI ablation usually recommended</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 cm or less, intrathyroidal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>1–2 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data b</td>
<td>Yes</td>
<td>Selective use b</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2–4 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data b</td>
<td>Yes</td>
<td>Selective use b</td>
<td>C</td>
</tr>
<tr>
<td>T3</td>
<td>&lt;45 years old</td>
<td>No</td>
<td>Conflicting data b</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>≥45 years old</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Any size, any age, minimal</td>
<td>No</td>
<td>Inadequate data b</td>
<td>Yes</td>
<td>Selective use b</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>extrathyroidal extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>extrathyroidal extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nx, N0</td>
<td>No metastatic nodes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>documented</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>&lt;45 years old</td>
<td>No</td>
<td>Conflicting data b</td>
<td>Yes</td>
<td>Selective use b</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>&gt;45 years old</td>
<td>No</td>
<td>Conflicting data b</td>
<td>Yes</td>
<td>Selective use b</td>
<td>C</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
</tr>
</tbody>
</table>

Evidence of benefit is graded based on the following scale: A, strongly recommends based on good evidence; B, recommends based on fair evidence; C, recommends based on expert opinion; D, recommends against based on expert opinion; E, recommends against on fair evidence; F, recommends against based on good evidence; I, recommends neither for nor against.

Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (See original guidelines (4)).

Reproduced with permission from David Cooper, M.D., and Mary Ann Liebert, Inc. Publishers.

RAI, radioactive iodine.
The method, detail, and thoroughness of review
Small patient populations
Variable histopathology
Variability of control of prognostic factors (e.g., age)
Extent of initial surgery
Use or lack of use of I-131 for ablation
Prescribed activity of I-131 used for ablation
Location of metastasis
Number of metastases
Pattern of metastases
Combining different locations of distant metastases
Variability of patterns of distant metastases located in the same organ
Use of I-131 for treatment
Prescribed activity of I-131 used for treatment
Method of determination of prescribed activity of I-131
Inability to accurately determine radiation-absorbed dose delivered to metastases
Length of time and frequency of follow-up
The definition of clinical, partial, and no remission
t restoration are emerging, but further studies are warranted to confirm the concepts noted below.

Pulmonary. Selected literature suggests several characteristics of pulmonary metastases that may predict benefits of I-131 when there is metastatic pulmonary disease (see Table 3). The most prominent characteristics are as follows: presence or absence of RAI uptake of I-131, pattern on RAI uptake on whole-body scan (e.g., micronodular, macronodular, diffuse, and/or focal), size of metastases on computed tomography (CT) and chest X-ray (CXR), and uptake on 18-F fluoro-deoxy-glucose (FDG) positron emission tomography (PET).

Many authors report that the benefit of I-131 is greater if the pulmonary metastases are RAI avid than if they are not RAI avid. However, it is difficult to determine if observed benefits are due to I-131, simply because patients with iodine avid pulmonary metastases have a better prognosis even without I-131 treatment. It is known, for example, that age is an important prognostic factor, and pediatric patients with RAI-avid pulmonary metastases have an excellent prognosis, even without I-131 treatment (36, 58-62).

The pattern and size of RAI uptake may be important in regard to response to I-131. If there is a fine, diffuse pattern on RAI whole-body scan, there may be a greater benefit from I-131 administration than if the pattern is focal or coarse (33, 36, 38, 59). As discussed later, this may be related, at least in part, to size. Again, the difference in outcome between the two types of pulmonary metastasis may be related to their inherent prognosis, not to their response to RAI.

Considerations relating to the concept that smaller metastases have a better response to I-131 than larger metastases are complicated by the various methods to determine size and definitions relating to size. Size has been determined by RAI whole-body scans, noncontrast CTS, chest X-rays, and even FDG PET scans. Schlumberger et al. (38) used <1 cm as the threshold for micronodular and >1 cm for macronodular disease. Casara et al. (44) used <0.5 cm as the threshold for micronodular and >0.5 cm for macronodular disease, the former having a better prognosis. Others have proposed as an approximate categorization of size by whether or not pulmonary metastases are or are not viewed by CT and/or CXR. There are a number of reports that those seen on both CXR and CT respond less to I-131 than smaller lesions seen only on CT or CXR but not on both (33, 37, 38, 44, 45, 58, 59). Zhuang et al. (63) proposed a volume of 125 mL as determined on 18-FDG PET scan as a useful cutoff between micronodular and macronodular as a guide to determine response to I-131 and prognosis. A better concept is probably that the smaller the size of metastatic pulmonary lesions, the greater the benefit of I-131, but the lack of non–I-131-treated controls makes it difficult to determine to what degree the better outcome in the I-131-treated group is due to I-131 treatment rather than to a possible inherently better prognosis of smaller pulmonary metastases. In fact, Sisson et al. (64) have questioned whether RAI can deliver a meaningful radiation absorbed dose to pulmonary metastases <1 mm in diameter. They make the case that as a tumor becomes smaller and smaller, the energy deposited within the tumor decreases per unit activity administered. Thus, <40% of the energy of RAI is deposited within a 0.5 mm diameter sphere of the source. This may be most germane to small 100–500 µm papillary projections that would receive less radiation than the 1-mm focus of pulmonary metastases and therefore, unlike the former, not be destroyed.

Finally, in addition to size as a factor that determines the response to I-131 there is the finding of whether the metastasis concentrates 18-FDG on PET. Thus it has been noted that uptake of 18-FDG within metastases on PET is associated with a worse prognosis and reduced response to I-131 (65, 66).

In summary, the response and benefit of I-131 treatment of pulmonary metastases is variable and at least partially
determined by the size of the metastases and their pattern of uptake on RAI PET scans.
pendent on the degree of RAI uptake in metastases and the pattern of metastases as determined by RAI whole-body scan, size on CXR and CT, and also on the degree of uptake on 18-FDG PET scan. In addition, patients with pulmonary metastases should not be viewed as a homogeneous group but rather can probably be grouped into several categories. For example, one group could be those with focal areas of I-131 uptake and a negative CXR and CT. A second group could be those with diffuse I-131 uptake and a negative CXR and CT. The third and other groups could be those having the following characteristics: [1] focal nodules on CT but not on CXR with I-131 uptake, [2] focal nodules on CT and CXR with I-131 uptake, [3] focal masses on CT and/or CXR with no I-131 uptake, and [4] focal nodules or masses on CT and/or CXR with I-131 uptake and no I-131 uptake. I would submit that the variable prognosis of these having different patterns of pulmonary metastases is probably a major reason why it is so difficult to perform good controlled prospective— or even retrospective—studies regarding the benefits of I-131 treatment in patients with pulmonary metastases from differentiated thyroid cancer.

**Bone.** I-131 therapy can benefit selected patients with bone metastases. The benefit of I-131 treatment appears to be better if the bone metastases are RAI positive, fewer in number, smaller in size, and negative on X-ray. However, for a patient with a single bone metastasis, other therapies such as surgical excision, external radiotherapy, radiofrequency ablation, cryotherapy, and/or arterial embolization should be considered (31). Little data are available comparing the benefit of I-131 treatment with standard empiric prescribed activity (e.g., 100–300 mCi [3.7–111 GBq]) as compared with the potentially higher dosimetrically determined prescribed activity of I-131. If there are multiple, extensive, RAI-negative bone metastases, I-131 treatment is not beneficial for survival or palliation (31).

**Brain.** Although I-131 treatment of a brain metastasis may have benefit as adjuvant or palliative treatment, the probability of any significant effect is very low (67, 68), and surgical excision or external radiotherapy such as γ-knife should be considered first (67, 68).

**Rare distant metastatic sites**

No significant data are available regarding the benefit or lack of benefit of I-131 therapy in patients with less frequent sites of distant metastases such as kidney, skin, muscle, liver, pancreas, and/or ovary.

**Risks of I-131**

The side effects of RAI therapy may occur in many areas and organ systems. These can be categorized by their time of occurrence after therapy. Here I have used the categories “early or immediate” (Table 4), “intermediate” (Table 5), and “late” (Table 6). Although some use the categories early or later, the above periods are closer to the major clinical periods in which patients are observed. This is immediately after therapy to ~10 days after therapy, the remainder of the first year after therapy, and the long-term follow-up period.

A discussion of the side effects of I-131 is complicated because so many factors affect the frequency and severity of side effects (see Table 7). Thus when the team of treating physicians and the patient are weighing the benefits and risks of I-131, it is frequently very difficult. This has lead to many approaches by experts.

**Loss of hair**

Hair loss secondary to I-131 therapy is very rare. When a hair loss is noted in patients who have received I-131 therapy, it is more likely secondary to the development of hypothyroidism (69).

**Brain**

Patients with RAI-avid brain metastases and treated with I-131 may develop cerebral edema with abrupt and even marked deterioration or death (70–72). If a patient is to be treated with I-131, pretreatment with manitol, glycerol, and/or glucocorticoids should be considered (67).

**Table 4. Early Side Effects of I-131 Therapy (Day of Therapy to ~10 Days After Therapy)**

| Salivary | Acute sialadenitis |
| Xerostomia | |
| Nasal | Abnormalities in smell |
| Epistaxis | |
| Thyroid | Thyroiditis |
| Gastroenteritis | Ageusia |
| Ageusia | Nausea |
| Vomiting | |
| Stomatitis and/or ulcers | |

**Table 5. Intermediate Side Effects of I-131 Therapy (~10 Days After Therapy to 1 Year)**

| Salivary | Chronic sialadenitis |
| Xerostomia | |
| Salivary duct obstruction | |
| Eye | Xerophthalmia |
| Epiphoria | Conjunctivitis |
| Vocal cords | Recurrent laryngeal nerve injury (very rare) |
| Parathyroid | Hypoparathyroidism (very rare) |
| Gastrointestinal | Ageusia |
| Ageusia | Abnormalities in smell |
| Pulmonary | Acute radiation pneumonitis (very rare when guidelines followed) |
| Pulmonary fibrosis (very rare when guidelines followed) | |
| Genital | Transient decreased ovarian or testicular function |
| Hematopoietic | Anemia |
| Neutropenia | Low platelet count |
| Low platelet count | |

**Table 6. Late Side Effects of I-131 Therapy (1 Year After Therapy to Life)**

| Salivary | Acute sialadenitis |
| Xerostomia | |
| Nasal | Abnormalities in smell |
| Epistaxis | |
| Thyroid | Thyroiditis |
| Gastroenteritis | Ageusia |
| Ageusia | Nausea |
| Vomiting | |
| Stomatitis and/or ulcers | |

**Table 7. Summary of Side Effects**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Brain</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Ocular</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Oral</td>
<td>Hair loss</td>
</tr>
</tbody>
</table>

**Table 8. Summary of Side Effects**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Brain</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Ocular</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Oral</td>
<td>Hair loss</td>
</tr>
</tbody>
</table>
### Table 6. Late Side Effects of I-131 Therapy
(≥1 Year After Therapy)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary</td>
<td>Chronic sialoadenitis</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
</tr>
<tr>
<td></td>
<td>Salivary duct obstruction</td>
</tr>
<tr>
<td>Eye/nasolacrimal</td>
<td>Xerophthalmia</td>
</tr>
<tr>
<td></td>
<td>Epiphoria</td>
</tr>
<tr>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>Genital</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
</tr>
<tr>
<td></td>
<td>Aplasia</td>
</tr>
<tr>
<td>Second primary malignancies</td>
<td></td>
</tr>
</tbody>
</table>

### Spinal cord

Murakami et al. (73) have reported radiation myelopathy secondary to I-131 treatment of a spine metastasis from a well-differentiated thyroid cancer.

### Eye/nasolacrimal

The risks of I-131 treatment to the eye include inflammation of the lacrimal gland with resulting xerophthalmia, obstruction of the lacrimal duct with resulting epiphoria, and conjunctivitis. No specific data regarding the frequency of inflammation of the lacrimal glands are present, but Zettinig et al. (74) have reported xerophthalmia in 16% of patients and evidence of reducing tearing using the Schirmer tear test in as many as 92% of patients. Solans et al. (75) reported xerophthalmia in as many as 33% of patients which lasted for at least 2 years in 17% of patients. As evidence of lacrimal duct obstruction, Zettinig et al. (74) and Kloos et al. (76) reported an incidence of epiphoria in 11% and 2.6% of patients, respectively. Alexander (69) reported a frequency of chronic or recurrent conjunctivitis in 23% of patients.

### Nose

Pain in the tip of the nose has been reported in 2 of the 15 patients receiving >7.4 GBq (200 mCi) of dosimetrically determined amounts of I-131 for the treatment of metastatic disease (77). This is attributed to the accumulation of I-131 in mucous cells in the tip of the nose. Some patients may have epistaxis.

### Salivary glands

The risks of I-131 therapy to the salivary glands include sialoadenitis of the salivary glands and obstruction of Stenson’s and/or Warthon’s duct with resulting pain and/or swelling. The incidence of sialoadenitis ranges from 10% to 67% (78), and the variability of frequency and severity is again multifactorial. Sialoadenitis may result in xerostomia, the incidence being 2–55%, and xerostomia may result in significant problems with oral hygiene, resulting in increased incidence of dental caries and candidiasis. Obstruction of Stenson’s and/or Warthon’s duct may occur from inflammation of the duct with resulting fibrosis and narrowing, which may become obstructed by thickened saliva. This can present with sudden swelling and/or severe pain.

### Taste and smell

Altered taste (ageusia) and smell may be experienced in 2–58% of patients after therapy with I-131 (78), and this may occur as early as 24 hours after therapy (79). Although typically the ageusia is transient, it may last from 4 weeks to 1 year in as many as 37% of patients (69).

### Facial nerve

Rarely, facial nerve paralysis has been attributed to I-131 therapy (80). The proposed mechanism is a radiation sialoadenitis with swelling of the gland around the facial nerve that passes through the parotid gland.

### Vocal cord

Recurrent laryngeal nerve injury secondary to I-131 therapy has been reported by Lee et al. (81, 82). The proposed mechanism is swelling of the thyroid tissue surrounding the recurrent laryngeal nerve. This is rare.

### Thyroid

The objective of I-131 ablation is to destroy normal residual thyroid tissue. Thus, radiation thyroiditis, which occurs in some patients, might not be considered a true side effect but rather related to the objective. The signs and symptoms of radiation thyroiditis include swelling, tenderness, and pain of the normal residual thyroid tissue as well as neck and ear pain, dysphagia, and painful swallowing. In patients who had I-131 for ablation of a lobectomy, Burmeister et al. report that 60% had neck pain or tenderness (83). When more extensive surgery, such as a total or near-total thyroidectomy, is performed, radiation thyroiditis is less frequent.

### Parathyroid

Permanent hypoparathyroidism secondary to I-131 therapy has been reported but is rare (84, 85). Glazebrook et al. (85) postulated that patients treated with I-131 may have reduced parathyroid reserve. In the absence of symptoms, however, routine monitoring of serum calcium does not appear appropriate. Guven et al. (86) demonstrated a transient decline in parathyroid hormone levels at the sixth month after I-131 therapy. However, this was not associated with symptoms of hypocalcemia.

### Table 7. Factors Causing Variability in Characterizations of Side Effects of I-131

- Criteria for the presence of a side effect
- Thoroughness in the search for signs and symptoms of a side effect
- Grading of side effects
- Length of follow-up
- Prescribed activities of I-131 therapies
- Total cumulative prescribed activities of radioiodine
- Time between therapies
- Methods implemented or not implemented to prevent the various side effects
In patients with pulmonary metastases, acute radiation pneumonitis with subsequent radiation fibrosis may be severe and even fatal after I-131 treatment. In different series (78), less than 2% (6/305) of patients developed acute radiation pneumonitis and the prevalence of pulmonary fibrosis or impairment was less than 3% (12/426). To minimize the frequency and severity of acute radiation pneumonitis and pulmonary fibrosis, Rall et al. (87) and Benua et al. (88) have recommended dosimetry and a limit of 80 mCi (2.96 GBq) whole-body retention of I-131 at 48 hours. This has been discussed elsewhere (89). As an alternative to full dosimetry, Sisson et al. proposed (90) and Van Nostrand et al. further developed (91) the single-point measurement of the percent whole-body retention at 48 hours. This helps ensure that the whole-body retention of 80 mCi (2.96 GBq) is not exceeded.

**Gastrointestinal system**

Nausea may occur in as many as 67% of patients after I-131 therapy (77), but usually the frequency is substantially less (78). Vomiting is infrequent. When antiemetics are administered before, during, and after therapeutic I-131, the frequency and severity of nausea and vomiting is reduced or less severe and therefore reasonably well tolerated (78). Occasionally, stomatitis may occur after I-131 therapy (78).

**Urinary bladder**

Several cases of cystitis secondary to I-131 therapy have been reported by Balan et al. (92) and Dobyns et al. (93). However, with adequate hydration and frequent urination during the first day and night after I-131 therapy, radiation cystitis should be very rare.

**Hematopoietic**

A major risk of I-131 therapy is bone marrow suppression and even aplastic anemia, which have been reported in 1.1–100% and 0–3.7% of patients, respectively (78). There are many factors that affect the frequency and severity of bone marrow suppression and aplastic anemia. These include the prescribed activity of I-131, the patient’s clearance rate of I-131, the frequency of therapies, the interval between therapies, the total cumulative prescribed activity of I-131, the patient’s bone marrow reserve, and degree to which bone metastases are present. To minimize bone marrow suppression, Benua et al. (88) performed dosimetry and established the guideline of not exceeding 200 cGy (rad) to the blood, which was the surrogate for the bone marrow. Subsequently, however, Leeper (94), Tuttle et al. (95), and Kulkarni et al. (96) demonstrated that empiric prescribed activity of 11.1 GBq (300 mCi), 7.4 GBq (200 mCi), and even 3.7 GBq (100 mCi) may exceed 200 cGy (rad) to the blood, thereby potentially increasing the frequency and degree of bone marrow suppression.

**Fertility**

Temporary amenorrhea/oligomenorrhea may occur in as many as 20–27% of woman. However, long-term rates for infertility, miscarriages, and fetal malformations do not appear to be increased in woman after I-131 therapy (97–100). In men, a transient reduction in sperm count and elevated serum follicle-stimulating hormone (FSH) levels has been reported by Wichers et al. (101) and Hyers et al. (102). Higher cumulative activities of I-131 may be associated with persistent elevation of serum FSH levels (103, 104). Sperm banking may be recommended in males who have a history of infertility problems and will or have received higher cumulative activities of I-131 (104, 102).

**Secondary primary malignancies**

Long-term follow-up studies have indicated an increased incidence of second primary malignancies after I-131 therapy (105). Of the two major recent reports, Rubio et al. (106) reported an increased risk of solid tumors and leukemia with increasing cumulative activity of I-131 administered with an excess absolute risk of 14.4 solid cancers and 0.8 leukemias per GBq of I-131 and 10⁵ person-years of follow-up, as well as a relationship between I-131 and bone and soft tissue, colorectal, and salivary gland cancers. Brown et al. (107) reported an overall increased risk of second primary malignancies. The review by Sawka et al. of the above two articles reported a significant but small increased relative risk of a second primary malignancy in patients treated with I-131 with a 2.5 relative increased risk of leukemia. No significant increased risk of the following cancers was observed: bladder, breast, central nervous system, colon/rectum, digestive tract, stomach, pancreas, kidney, lung, or melanoma of the skin (108).

**Weighing Benefits and Risks**

Despite all the data in the literature and published guidelines, weighing the benefits and risks of I-131 therapy is often very complex. When this is the case, the treating team and the patient should know the priorities that need to be considered. These include the following: [1] considering the patient’s desires, [2] working within the local logistics for the patient and treating team, [3] minimizing side effects, [4] maximizing the radiation-absorbed dose to the tumor, and [5] understanding the objectives of the I-131 therapy. With a better understanding of the treating teams’ priorities as well as the objectives of I-131 therapy, weighing the benefits and risks will be easier.

**Summary**

This review discussed the benefits of I-131 therapy in patients with well-differentiated thyroid cancer and the risks (e.g., side effects) of I-131 therapy. The benefits of I-131 include the following: [1] facilitating the interpretation of subsequent serum thyroglobulin levels, [2] increasing the sensitivity of metastatic disease detection on subsequent RAI whole-body scans, [3] maximizing therapeutic effect of subsequent therapies, [4] decreasing recurrence and disease-specific mortality for unknown and known locoregional and distant metastatic disease, and [5] palliating complications of metastatic disease. The more significant and frequent side effects were discussed.

**Acknowledgments**

The author would like to acknowledge the support of those who have financially contributed to the research efforts in the Division of Nuclear Medicine at the Washington Hospital Center, which include but not limited to the Robert Woods Center, which include but not limited to the Robert Woods...
Johnson Foundation, the Latham Fund, the Genzyme Corporation, Abbott Corporation, IBA Molecular Imaging, Nancy and Carl Gewirz, Mitchell Schar, and Leonard Wartofsky. The author would also like to thank all of the staff of the Division of Nuclear Medicine, Endocrinology, and Cytopathology for their support of this research. It has been a team effort.

Disclosure Statement

The authors declare that no competing financial interests exist.

References

29. Sugitani I, Fujimoto Y 1999 Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective


64. Sisson JC, Jamadar DDA, Kazerouni EA, Giordano TJ, Carey JE, Spaulding SA 1998 Treatment of micronodular lung metastases of papillary thyroid cancer: are the tumors too small for effective irradiation from radioiodine? Thyroid 8:215–221.


Address correspondence to:
Douglas Van Nostrand, M.D.
Division of Nuclear Medicine
110 Irving Street, N.W.
Suite BB43
Washington Hospital Center
Washington, DC 20010

E-mail: douglas.van.nostrand@medstar.net