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Chapter 2

# Radioiodine Therapy of Malignant Thyroid Diseases

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**Abstract**

Radioiodine-131 (I-131) is used in the treatment of thyroid diseases: hyperthyroidism and differentiated thyroid cancer (DTC: papillary, follicular, Hurthle cell cancer). Treatment success depends on several factors. The most fundamental factor affecting the success of treatment is the susceptibility to target tissue I-131. In patients with differentiated thyroid cancers following total thyroidectomy, I-131 is given for ablation of residual thyroid tissue and treatment of metastatic disease. Physical and biological characteristics of I-131, uptake and effect mechanisms of the iodine in the thyroid follicular cells, indications and contraindications for I-131 therapy, patient preparation and administration of I-131, follow-up and precautions on possible side effects, and an overview on the clinical studies about I-131 therapy are presented.

**Keywords:** iodine, thyroid diseases, therapeutics, radiation, neoplasms

## 1. Introduction

Radioiodine-131 (I-131) is successfully used in treatment of thyroid diseases: hyperthyroidism and differentiated thyroid cancer for several years. I-131 is available as sodium iodine in gelatine capsules and drinking solution for oral application and intravenous injections. Advantages of this therapy are good tolerability, easy application, safety, and efficacy of treatment. The critical organ for I-131 is the thyroid gland. I-131 is taken up by follicular cells. Retention of I-131 in the cells depends on the metabolic activity of the cells. I-131 simultaneously emits two types of radiation: beta minus ($\beta^-$) radiation used for the therapy and gamma ($\gamma$) used for diagnosis. Due to the penetration of beta particles in the tissue, damaging effect of $\beta^-$ radiation is limited to thyroid cells. The physical and biological characteristics of I-131, uptake and effect mechanisms of the iodine in the thyroid follicular cells, indications and contraindications for I-131 therapy, patient preparation and administration of I-131, follow-up

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and precautions on possible side effects, and an overview on the clinical studies about I-131 therapy are presented under this title.

## 2. Epidemiology

Thyroid cancer constitutes 1.4% of all cancers and 15% of all endocrinologic malignancies. Thyroid cancer is responsible from 0.2 to 0.5% of cancer-related death. About 90–95% of thyroid cancers are differentiated thyroid cancers of follicular cell origin. Annual incidence is 1.2–2.6/100,000 in men and 2.0–3.8/100,000 in women. Mortality rates have been reported as 0.2–1.2/100,000 in men and 0.4–2.8/100,000 in women [1].

## 3. Treatment options: role of radioiodine

Front-line therapy of differentiated thyroid cancer (DTC) is surgery. Because multifocality and multicentricity is frequent, total or near-total thyroidectomy is the treatment of choice. Samaan et al. have reported that recurrence rates were lower and survival rates were higher in total thyroidectomized patients [2]. Following total thyroidectomy, I-131 is given for ablation of residual thyroid tissue and treatment of metastatic disease. To achieve a successful ablation and treatment, I-131 should be taken up by residual thyroid and metastatic tumors. The function of cancerous follicular cells is poorer than normal follicular cells. While normal thyroid tissue concentrates 0.5–1.0% of the administered I-131 dose, cancerous cells concentrate 0.01–0.02%.

Papillary cancer (the largest histopathologic group of thyroid cancers), follicular cancer, less than 10% of Hurthle cell variant papillary cancer, and mixed variant medullary cancer show I-131 uptake [3]. Ablation is defined as the radioiodine therapy given for destruction of functional residual thyroid tissue in or out of the thyroid bed. Therapy is the term used for sterilization of residual functional tumoral cells. As the volume of residual thyroid decreases, success of ablation increases. If residual thyroid tissue weighed <2 grams (gr), ablation efficiency was reported as 94%, while this rate may fall as low as 64% in larger residues [4].

The European Association of Nuclear Medicine (EANM) recommends I-131 ablation for all differentiated thyroid cancer patients who have a tumor size >1 cm [5]. For patients with tumor size smaller than <1 cm with no other risk factors like capsular invasion, lymphovascular invasion, lymph node (LN) or distant metastasis, history of radiation exposure, and diffuse sclerosing subtypes, radioiodine ablation is debatable. The American Thyroid Association (ATA) does not recommend radioiodine in low-risk disease [6].

Ablation provides higher thyroglobulin (Tg) sensitivity, treatment of undetectable micrometastatic disease, and a higher survival. Increase in thyroid-stimulating hormone (TSH) levels for ablation helps detection of metastatic disease on the postablative scan. In a prospective study of 25 years of follow-up, it was reported that none of the patients who were totally ablated died of thyroid cancer, but in seven patients in whom ablation failed, the reason of death was thyroid

cancer [7]. Thyroid hormone replacement may not be started after surgery to achieve high TSH levels before I-131 therapy performed 4–6 weeks later [8, 9]. However, because euthyroidism augments tissue repair and prevents from postsurgical complications, tetraiodothyronine (T4) replacement therapy is generally started after total thyroidectomy [10].

## 4. Patient preparation for radioiodine therapy

T4 is stopped before radioiodine therapy and triiodothyronine (T3) can be started instead (25–75 μg/day), making sure that T3 is also withdrawn 2 weeks before I-131 administration [10]. The reason why T3 is given is that T3 has a shorter half-life than T4 (0.8 days versus 7 days) and yields a faster TSH elevation after withdrawal compared to T4. Thus, hypothyroid period is shortened, and potential tumor growth rate stimulated by TSH is decreased.

Low-iodine diet is recommended for 3 weeks before radioiodine treatment, and drugs with stable iodine content should be ceased (**Tables 1** and **2**).

In cases of inadequate TSH elevation (pituitary disease, pituitary insufficiency of the elderly, extensive functioning thyroid cancer metastasis), recombinant human TSH (rhTSH: thyrotropin alpha, Thyrogen®) can be used. 0.9 mg rhTSH is intramuscularly injected for two consecutive days. Twenty-four hours later than the second dose of rhTSH administration, I-131 is given orally. Its safety and efficacy have been found noninferior to endogenous hypothyroidism [11, 12]. There are a few publications mentioned in the use of rhTSH after redifferentiation therapy with retionic acid (13-cis-retinoic acid, isotretinoin) in undifferentiated thyroid cancer to increase radioiodine uptake [13, 14].

Preablative TSH and Tg levels are measured. If TSH is >30 μU/ml, then I-131 can be given [10]. Thyroglobulin is a glycoprotein produced by functioning follicular cells. Detectable Tg after total thyroidectomy is a marker of persistent or recurrent diseases. In subtotal thyroidectomized patients, Tg measurement is not reliable. Thyroglobulin levels should not be used as a single criterion for determining necessity of radioiodine treatment. However, Tg levels

| |
|---|
| Iodized salt |
| Milk and derivatives (cheese, yoghurt, ice-cream, etc.) |
| Seafood |
| Processed meat products (salami, sausage, etc.) |
| Packed food (chips, cookies, biscuits, etc.) |
| Canned vegetables and fruits |
| Green vegetables (spinach, lettuce, etc.) |
| Red pepper |
| Red food dye |

**Table 1.** Avoided food.

| Drug or molecule | Recommended withdrawal time |
|---|---|
| Propylthiouracil, perchlorate, sulfonamides, tapazole, thiocyanate, penicillin, nitrates, antihistamines, and anticoagulants | 1 week |
| Iodine-containing solutions (Lugol's solution, Betadine), antitussives, and vitamin preparates<br>Triiodothyronine (T3) | 2 weeks |
| Tetraiodothyronine (T4) | 4–6 weeks |
| Amiodarone | 4–12 weeks |
| Intravenous contrast agents | 1–3 weeks |
| Oral cholecystographic agents | 2–3 weeks |

**Table 2.** Drugs decreasing radioiodine uptake in thyroid cells and recommended withdrawal time.

>5–10 mg/dL point out that there exists an amount of functioning thyroid tissue to be ablated. Conversely, Tg < 1 ng/dL does not exclude radioiodine avid disease either [6].

Patients should be fasting for 2–4 hours before I-131 administration. The aim of fasting is to increase I-131 absorption and decrease risk of vomiting.

## 5. Radioiodine for ablation

Ablation doses are still a matter of debate. Beierwaltes et al. have reported that 3.7 GBq (100 mCi) I-131 ablates 85% of thyroid remnants [15]. Lower doses of 1.11 GBq (30 mCi) have been shown to be noninferior; however, there are conflicting results [16–19]. There are three approaches for determination of I-131 dose: low dose, fixed high dose, and optimal dose. Low dose refers to 1.11 GBq (30 mCi). If ablation could not be maintained by a single dose, repeated doses can be given by 3–6 months of intervals. Although it depends on local radiation protection rules, hospitalization can be avoided in some regions in the world by dose administration. Lower whole-body and gonadal radiation doses and lower risk of side effects of radioiodine are other advantages. However, if ablation failed, repeated therapies cause long span of hypothyroidism. Stunning is another important disadvantage in secondary ablation doses. Stunning is defined as decrease of radioiodine uptake due to previous I-131 administrations for diagnostic or treatment purposes. Park et al. have reported that diagnostic doses between 111 and 370 MBq (3–10 mCi) I-131 caused stunning in a dose-dependent manner and this effect was overcome by the use of I-123 [20]. I-123 is a good alternative for scanning before I-131 treatment if preablative whole-body scan is necessary, as it gives a lower absorbed dose and provides better image quality and high accuracy [21]. Fixed high doses for ablation are given as 277.5–555 MBq (75–150 mCi). This is an effective and easy method to achieve ablation at a single step, and hypothyroid state is shorter. Nemec et al. have reported that over 85% of the patients ablation was maintained eradicating the need for a second dose [22].

Approach of optimal dose ablation aims to provide ablation of the whole residual thyroid tissue with the lowest radiation burden possible to extrathyroidal tissues [9]. For optimal dose

calculation, formulations considering the weight of residual tissue and radioiodine uptake are used:

$$\text{Administered activity}: \frac{\text{Planned dose} \times \text{Gland weight} \times 6.67}{T_{eff} \times \%\ \text{uptake(24 hour)}} \quad (1)$$

$$\text{Absorbed dose}: \frac{\text{Peak activity of the lesion} \times T_{eff} \times 1.443}{\text{Tissue weight}} \quad (2)$$

$T_{eff}$: effective half-life

Dose calculation approach may be theoretically reasonable, but it is troublesome to calculate biological half-life by collecting samples of urine and gaita from the patients, and interobserver variabilities in the measurement of residual tissue may cause mistakes. Ablation success rates of fixed high-dose and dose calculation methods are similar. So, fixed high-dose administration is the preferred method with regard to dose calculation.

As I-131 is primarily excreted by urine, dose reduction in renal failure and dialysis should be concerned. Kaptein et al. have reported that in patients who undergo continuous abdominal peritoneal dialysis, radioiodine clearance decreased five times and in order to optimize whole-body and bone marrow dose, radioiodine dose should be reduced by 5 [23]. By dialysis, effective half-life is shortened and tumoral dose is decreased. I-131 administration should be postponed after dialysis. Other situations which cause a change in distribution and increase retention are peritoneal ascites, pleural effusion, and extensive functioning metastasis.

Whole-body I-131 scan should be performed on postablative 2–6 days or after whole-body radiation dose is measured below 370 MBq (10 mCi). This study is important in determination of prognosis, as the absence of detectable metastases decreases risk of recurrence.

## 6. Adjuvant radioiodine therapy and treatment of metastasis

Postsurgical administration of I-131 provides a significant decline in recurrence rates. This is attributable to adjuvant usage of radioiodine which aims destruction of unknown micrometastasis rather than ablation of residual thyroid [10, 24, 25]. For apparent metastases detected before surgery or in the follow-up, the primary requirement is radioiodine avidity. Fixed high doses are frequently used for treatment of thyroid cancer metastases (**Table 3**).

Another approach in treatment of metastasis is dose calculation according to the upper limits of blood and whole-body dosimetry and quantitative tumor or lesional dosimetry.

Five hundred fifty-five MBq (150 mCi) treats 95% of metastases in the thyroid bed. Upper limit of radioiodine dose for a single administration is determined as 740 MBq (200 mCi), set for a blood radiation dose below 200 rad (200 cGy) (maximum tolerated dose) [9]. In order to provide enough radiation to the tumor, formulations concerning radioiodine uptake value, tumor volume, and effective half-life are used:

$$D(\text{Gy/mCi}): \frac{\%\ \text{uptake (24 hr)} \times 152 \times T_{eff}}{\text{Tumor mass (gram)}} \quad (3)$$

| Metastatic region | Dose GBq (mCi) |
|---|---|
| Residual thyroid cancer in the thyroid bed | 3.7 (100) |
| Cervical LN metastases | 5.55–6.47 (150–175) |
| Lung metastases | 6.47–7.4 (175–200) |
| Distant metastases | 7.4 (200) |

**Table 3.** Doses used in the treatment of functioning thyroid cancer metastasis.

For lymph node metastases, surgery is the first treatment to try, especially in bulky disease. Small LN metastases with adequate radioiodine uptake can be treated with I-131.

Adjunctive radioiodine therapy after surgery is generally recommended. Published in a retrospective series is that, a delay in radioiodine therapy for 6 months or more caused disease progression, and survival rates were decreased [26].

Cervical lymph node involvement doesn't increase mortality but morbidity. The lymph node is common especially in papillary carcinoma, and its incidence has been reported 48 and 17% below and over age 40 [27]. Recurrence rates are twice as much in nodal metastatic disease [10]. It has been proved that recurrent metastases decrease by treatment of metastatic lymph nodes by I-131 [28].

Distant metastasis significantly reduces survival rates. Mortality rates are higher in brain and skeletal metastasis. In a series, distant metastasis was detected in 19% of the patients who received radioiodine treatment. Of these, 44% were to lungs, 31% to mediastinum, and 23% to the skeletal system [29]. Pulmonary metastasis is seen in 2–12% of the cases, and its frequency is less in patients who had undergone total thyroidectomy and radioiodine therapy [28, 30].

Pulmonary metastasis occurs by lymphogen, whereas skeletal metastasis occurs by microinvasion and hematogen way. The fact that there is a correlation between cervical lymph node and pulmonary metastasis and a reverse correlation between nodal and skeletal metastasis supports this opinion. Skeletal metastasis has a worse prognosis than lung metastasis. Skeletal metastasis is seen five times more frequent in follicular carcinoma patients than in papillary carcinoma patients and in the elderly. The cranium, vertebral column, and costae are generally involved [22].

3.7–7.4 GBq (100–200 mCi) I-131 is recommended to be administered by 6–12 months of intervals. Therapy should be continued till all radioiodine avid lesions are ablated or an intolerable complication is likely to arise. For iodine avid disease, there is no upper limit for cumulative dose. However, due to high complication risks, doses over 22.2 GBq (600 mCi) should be evaluated on a patient basis. If complete response can't be achieved but disease stays stable, then intervals between doses can be extended, or therapy can be stopped with close monitoring [5].

## 7. Differentiated thyroid carcinoma derived from ectopic tissue

Sublingual area is the most common place for ectopic thyroid development. Insufficient T4 production in ectopic tissue may cause TSH elevation and thus hyperplasia by stimulation. Long-term and intense TSH stimulation is blamed for carcinoma development in these cases. Thyroglossal canal originated papillary carcinoma may have an invasive character in 10% of the cases [31]. In 3% of the cases, ectopic thyroid tissue is found in ovarian teratoma (struma ovarii). Low-grade malignant tumor may arise from struma ovarii (5–20%), and some may metastasize [32]. Although management approaches are still uncertain, treatment of cancer of an aberrant thyroid tissue is the excision of the tumor followed by radioiodine therapy.

## 8. Contraindications

Absolute contraindications are pregnancy and nursing. If I-131 administration is essential, then nursing should be stopped [33, 34]. I-131 passes through the placenta and concentrates in fetal thyroid (<12 weeks). This causes serious hypothyroidism. Maternal bladder activity also causes fetal irradiation. Pregnancy should be avoided for 6–12 weeks after radioiodine therapy. Other relative contraindications for I-131 are bone marrow depression, pulmonary, salivary gland and renal function interruption, possibility of severe edema, and compression symptoms in brain metastasis [5].

## 9. Complications

There are acute (first 3 months) and chronic (later than 3 months) complications of radioiodine therapy. Acute complications are sialadenitis (most frequent), radiation parotitis and thyroiditis, metallic taste, gastrointestinal symptoms like nausea and vomiting due to radiation gastritis, transient bone marrow depression (anemia in 36% of the patients, leukopenia 10%, thrombocytopenia 3%), radiation pneumonitis and pulmonary fibrosis, radiation cystitis, transient amenorrhea (secondary to pituitary-gonadal hormonal axis), decreased testicular function or fertilization, cerebral edema or spinal compression in metastatic cases, keratoconjunctivitis, and decreased lacrimal function [35]. Chronic complications include secondary malignancies most frequently leukemia, myeloid leukemia, less frequently bladder cancer, salivary gland neoplasia, hypo- and hyperparathyroidism, and hypothyroidism [36–38].

## 10. Radioiodine therapy of pediatric differentiated thyroid cancer

Prognostic factors in differentiated thyroid cancer of the thyroid are not very well known because it is a relatively rare entity (3–4%) compared to thyroid cancer of the adults. In

long-term follow-up, survival rates are found to be high despite increased rates of local recurrences and distant metastasis. Neck and pulmonary metastases concentrate and respond to radioiodine well [10]. Aggressive surgery followed by radioiodine is generally the preferred treatment option [39]. Radioiodine decreases recurrence in patients with known residual disease [40]. Disease-free survival rates are shown to be improved by radioiodine ablation without any significant increase in the risk of secondary malignancies [41]. I-131 treatment is recommended in radioiodine avid unresectable locoregional or distant metastasis [42].

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