Radioiodine Therapy for Thyroid Cancer 6

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6.1 Introduction

Therapy with radioiodine (^{131}I) has been used for over 50 years in the treatment of patients with papillary and follicular thyroid carcinoma, both to ablate any remaining normal thyroid tissue and to treat the carcinoma. Patients treated with surgery and radioiodine have a survival rate that exceeds the rate for most other cancers. Recurrence rates are high in patients treated by surgery alone. However, no treatment protocols have been evaluated in a randomized controlled manner, nor is a prospective study likely in the near future, since the case rate is low, the presentation too variable, and the necessary observation period too long given the low mortality rate. The improvement of survival rates and decrease in rates of recurrence after radioiodine ablation has been documented by retrospective, long-term studies: Samaan et al. [72] followed 1,599 patients with well-differentiated thyroid carcinoma for up to 43 years. Treatment with radioiodine was the single most powerful prognostic indicator for a disease-free interval and increased survival. Those patients categorized as low risk also had significantly lower recurrence and death rates if they received ^{131}I. In the study by Mazzaferri and Jhiang [48], 1,355 patients with papillary and follicular cancer had a median follow-up of 15.7 years; 42% of the patients were followed for 20 years and 14% for 30 years. When patients with stage II or III tumors (WHO classification, Hedinger et al. [29]) were considered, those treated with ^{131}I had lower 30-year recurrence rates (16% compared with 38%) and cancer-specific mortality rates (3% compared with 9%) than those not treated with ^{131}I.

However, management varied widely for the recommendation of radioiodine ablation and for the ablative dose of ^{131}I. Clinical members of the American Thyroid Association were surveyed in regard to their treatment and long-term assessment of differentiated papillary thyroid carcinoma [86]. For a 39-year-old female with a well-encapsulated, 2-cm solitary carcinoma and no history of radiation (index patient), only a small majority of clinicians (61%) would recommend radioiodine administration after surgery. Solomon et al. [86] concluded the need for more formal practice guidelines for patients with thyroid cancer.

6.2 Radioiodine Ablation and Radioiodine Therapy

Radioiodine ablation and therapy is dependent upon uptake of ^{131}I in residual thyroid tissue or metastatic lesions. The beta-particles emitted by ^{131}I penetrate and destroy tissue only within 2 mm, making destruction of large deposits difficult. In addition, the uptake of iodine in malignant thyroidal tissue has been estimated to be 0.04 – 0.6% of the dose/gram of tumor tissue, considerably less than normal thyroid uptake. Therefore, the first step to treat differentiated thyroid cancer is surgery. Near-total or total thyroidectomy improves the ability of ^{131}I to ablate the remaining gland and to concentrate in regional and distant metastases. ^{131}I therapy for thyroid cancer has frequently been divided into radioiodine ablation and radioiodine therapy, the latter term being used to indicate the treatment of residual or recurrent thyroid cancer at the thyroid bed or of metastatic lesions elsewhere [90]. The possible presence of microscopic multifocal thyroid cancer that may be undetected limits the assumption of a disease-free thyroid remnant.

6.2.1 Ablation of Residual Thyroid Tissue

Routine thyroid remnant ablation is widely used and has appeal for several reasons:

1. Thyroid cancer is frequently multifocal, multicentric, and microscopic. Mazzaferri and Jhiang [48] found more than one thyroid tumor in 319 of 1,355 patients (24%). Total thyroidectomy is rarely achievable in practice. Radioiodine may destroy occult microscopic carcinoma within the thyroid remnant because the carcinoma cells receive radiation from ^{131}I taken up by adjacent normal thyroid cells.
2. Residual thyroid tissue may prevent the visualization of distant or local metastatic disease on follow-up ^{131}I scanning. ^{131}I uptake in normal thyroid tissue is far greater than the uptake in thyroid cancer. In the case of large amounts of thyroid tissue, the scan usually shows a starburst effect of high ^{131}I uptake in the remnant that makes visualizing uptake nearby impossible (Fig. 6.1).
3. Residual thyroid tissue may synthesize significant amounts of thyroid hormone, which suppresses thyroid-stimulating hormone (TSH) and further impedes diagnostic imaging. A high level of TSH stimulation (>30 mU/l) is necessary for proper scanning.
4. Follow-up care of patients with thyroid cancer has improved with the utilization of serum thyroglobulin levels. Thyroid ablation allows for greater specificity of testing for serum thyroglobulin by eliminating the endogenous production of thyroglobulin by normal or recovering tissue [54].

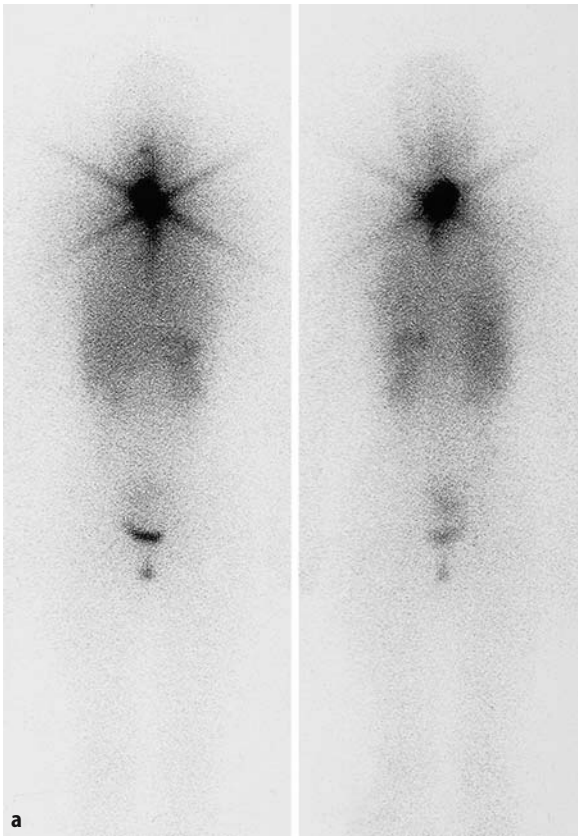

Fig. 6.1 a–d. Twenty-year-old patient with papillary thyroid cancer pT4N1M1 (pulmonary). **a** The first ^{131}I whole-body scintigraphy (1.85 GBq ^{131}I) showed a starburst effect of high uptake in the thyroid remnant. The lung metastases were not visible. **b** ^{123}I whole-body scintigraphy (185 MBq ^{123}I) 3 months later could not demonstrate the pulmonary metastases. **c** Subsequent ^{131}I whole-body scintigraphy (7.4 GBq ^{131}I) and **d** SPECT showed iodine-avid lung metastases

6.2.2 Ablative Dose

An absorbed dose of 300–500 Gy seems to be appropriate with the administered activity calculated as follows:

$$\text{Activity (MBq)} = \frac{\text{Dose (Gy)} \times \text{remnant weight (g)} \times 24.8}{\text{Effective T 1/2 (days)} \times {}^{131}\text{I uptake (24 h)}}$$

With two variables that are difficult to measure (weight of thyroid remnants and effective half-life of ^{131}I), this method is neither attractive or suitable for most hospital departments. A fixed activity of ^{131}I is the easier alternative, but what should this activity be?

The answer requires a clear definition as to what constitutes a 'successful ablation.' Chopra et al. [15] showed that visual assessment of ^{131}I scans overestimated thyroid bed uptake in 22% of cases. They argued in favor of quantitation of uptake of an administered activity and recommended that anything below

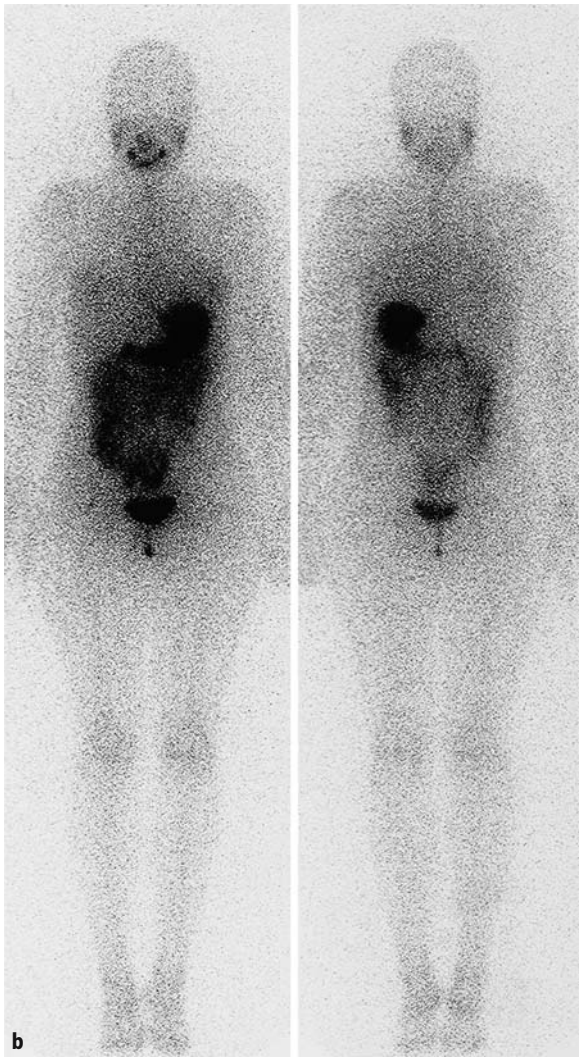

Fig. 6.1 b. ^{123}I whole-body scintigraphy (185 MBq ^{123}I) 3 months later could not demonstrate the pulmonary metastases

1% was indicative of successful ablation. Application of more stringent criteria for ablation, such as the absence of uptake or uptake less than twice the background, could be the reason for reports of failed ablation [2]. It is essential that the presence of uptake in the postablation scan is not a reliable predictor for future treatment and that time should be allowed for the combined effects of ^{131}I and suppressive thyroxine treatment to exert their effect [65].

Proponents of higher-dose ablations suggest that a 3.7- to 5.5-GBq ablative dose may actually be considered adjuvant radiation therapy for occult metastases not detected by ^{131}I imaging [5, 7]. Administering ^{131}I to small remnants

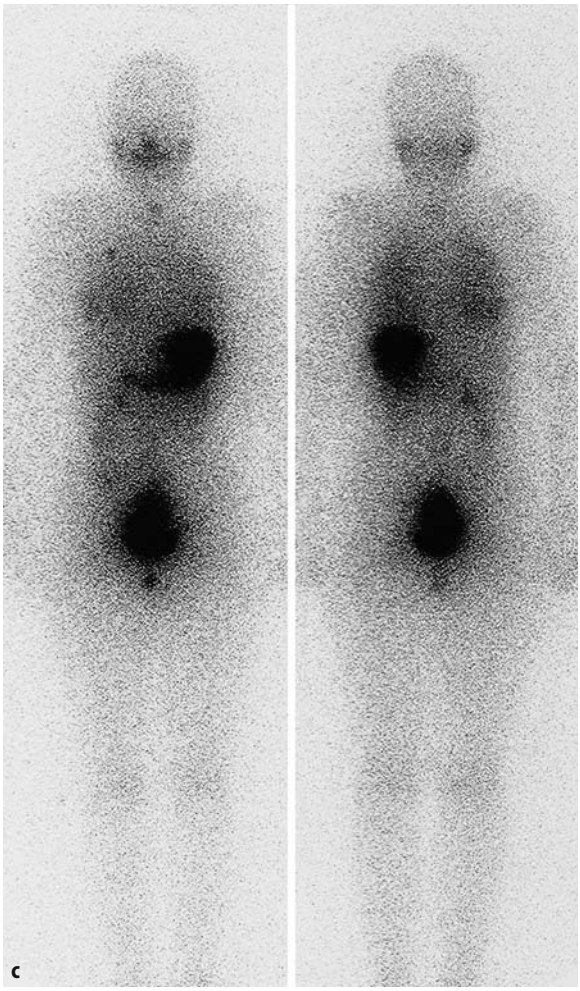

Fig. 6.1 c. Subsequent ^{131}I whole-body scintigraphy (7.4 GBq ^{131}I)

(<5% ^{131}I uptake) can have a tumoricidal rather than an ablative effect by eliminating multiple microscopic foci in 'normal' thyroid tissue that can be alarmingly abundant, thus reducing the possibility of local recurrence.

Comtois et al. [16] compared the efficacy of low (925–1110 MBq), intermediate (≥1,850 MBq) and high activities (≥3.7 GBq) of ^{131}I and observed an ablation rate of 7–83% with a low activity and 60–100% with intermediate or high activities of ^{131}I. Some of the factors that have contributed to the initial high failure rate of low-dose ablation trials can now be identified. Poor success rates were noted following high-dose diagnostic scans using 185 MBq, with higher success rates being achieved after diagnostic scans of 37–74 MBq ^{131}I, indicating a possible stunning effect. Other factors contributing to the poorer success rates were incomplete surgical excision, failure to reduce preablation iodine intake, and very stringent criteria for ablation.

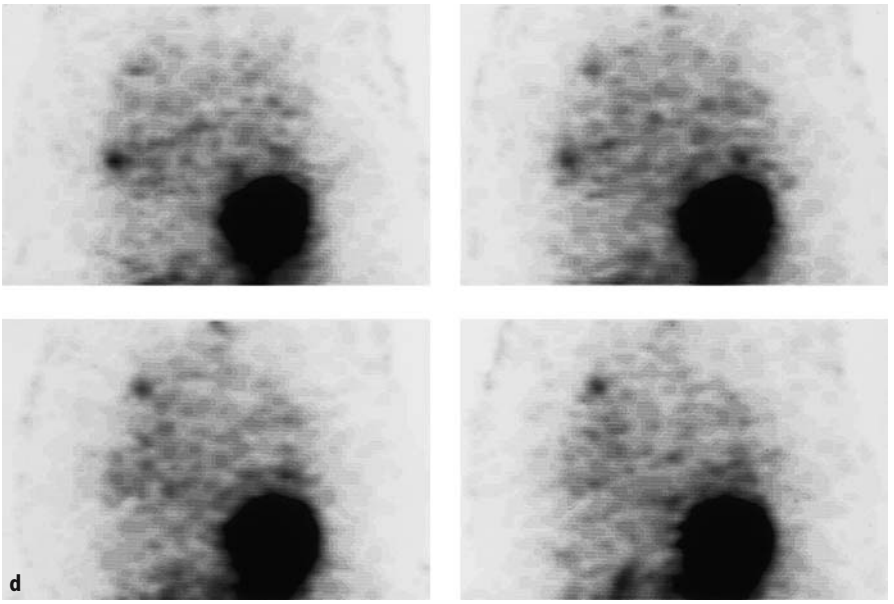

Fig. 6.1 d. SPECT showed iodine-avid lung metastases

There appears to be enough evidence to suggest that, in nonmetastatic well-differentiated thyroid carcinoma, radical surgery followed by an intermediate activity of about 1,850 MBq ^{131}I, preferably without a preceding diagnostic scan using ^{131}I (^{123}I may be used) to avoid stunning, will achieve a reasonable rate of ablation with a reduction in thyroid bed uptake of a tracer ^{131}I dose of less than 1%. Residual uptake should be checked again after 3–6 months with a low-dose ^{131}I scan before embarking on a therapy dose [2].

Lin et al. [35] have devised a 'sliding scale' by which patients with higher uptake receive higher ablation doses. A recommendation of 2–5 GBq ^{131}I for ablation of detectable residual thyroid is given by the German Society of Nuclear Medicine [19].

6.2.3 In Which Patients Is Ablation Unnecessary?

In the study by Mazzaferri and Jhiang [48], low-risk patients, defined as those with tumors smaller than 1.5 cm completely confined to the thyroid, were not found to benefit from thyroid ablation. In contrast, Samaan et al. [72] examined the use of radioactive iodine in 1,156 low-risk patients and found beneficial effects in low-risk patients, with significantly fewer recurrences and deaths. They recommended radioactive iodine therapy for all patients who have a positive scan after surgery.

Regarding the biological behavior of the papillary microcarcinomas and the frequency in autopsy studies, most authors do not generally recommend radioiodine administration for patients with solitary papillary microcarcinoma, diameter up to 1.0 cm, a subgroup of the pT1NOMO stage [18, 74, 94]. If a patient with papillary microcarcinoma wishes to undergo this therapy, radioiodine ablation can be selectively performed.

6.2.4 Radioiodine Therapy for Thyroid Cancer

For those patients with proven or assumed residual or recurrent thyroid cancer, the term 'radioiodine therapy' is usually used.

However, there are differing theories regarding the activity of ^{131}I needed for proper therapy. Of the dosimetry methods available, the most widely used and simplest is to administer a large fixed dose. Most clinics use this method regardless of the percentage uptake of ^{131}I in the remnant or metastatic lesion. Patients with distant metastases are treated with 3.7 – 11 GBq ^{131}I. There is no convincing evidence that treatment is improved by quantitative methods of measurement of retention, uptake, and effective half-times necessary for dosimetric studies [24].

A second approach is to use quantitative dosimetry methods. If the calculated dose to be delivered is less than 35 Gy, it is unlikely that the cancer will respond to ^{131}I therapy. These patients should be considered for surgery, external radiation, or medical therapy. Doses that deliver more than 85 Gy to metastatic foci are likely to be effective [45].

A third approach is to administer a dose calculated to deliver a maximum of 2 Gy to the bone marrow, keeping the whole-body retention less than 4.5 GBq at 48 h and the amount in the lungs less than 3 GBq when there is diffuse pulmonary uptake. The maximum dose is kept at 11 GBq ^{131}I [47].

6.2.5 Radioiodine Therapy with Negative Radioiodine Scan

A distinct group of patients who warrant special consideration are those with differentiated thyroid cancer with positive or rising serum thyroglobulin levels and negative radioiodine scans. Although definitions vary, a positive thyroglobulin level means a value greater than 2 ng/ml in a patient who has undergone total thyroidectomy and ^{131}I ablation. This special case of elevated serum thyroglobulin levels and absent radioactive iodine uptake poses a clinical dilemma. The following explanations should be considered:

- Diffuse metastases that are too small for detection
- Thyroid cancer that produces thyroglobulin but does not take up enough iodine for detection
- High levels of 'cold' iodine blocking the uptake of radioiodine
- Normal thyroid tissue that hinders the imaging of metastatic disease
- A falsely positive elevation of thyroglobulin level

Table 6.1. Studies reporting documented disease in thyroglobulin-positive patients with negative radioiodine scans (from Sweeney and Johnston [90])

Study	No. of patients	Elevated thyroglobulin levels	Negative diagnostic ^{131}I scan	Evidence of disease
Pacini et al. [58]	17	17/17 (15–976 ng/ml)	17/17 (185 MBq ^{131}I)	16/17 had positive post-therapy scan
Robbins [67]	10	10/10 (>10 ng/ml)	10/10 (370 MBq ^{131}I)	9/10 had positive post-therapy scan
Pineda et al. [63]	17	17/17 (8–480 ng/ml)	17/17 (55–185 MBq ^{131}I)	16/17 had positive post-therapy scan 13/16 had decreased thyroglobulin levels post ^{131}I
Ronga et al. [69]	10	10/10	10/10	7/10 had positive post-therapy scan
Schlumberger et al. [79]	25	25/25	25/25 (74–185 MBq ^{131}I)	18/25 had positive post-therapy scan
Total	79	79/79	79/79	66/79 had positive post-therapy scan

Table 6.1 lists reports of thyroglobulin-positive patients with negative diagnostic scans who had documented metastatic or persistent thyroid cancer. These results highlight the failure of small diagnostic doses of ^{131}I to visualize recurrent or metastatic disease. Therapeutic doses of ^{131}I may be warranted in thyroglobulin-positive patients with negative radioiodine diagnostic imaging. The decrease in thyroglobulin-levels after the administration of 3.7 GBq ^{131}I despite the absence of clear ^{131}I uptake [63] suggested a possible benefit of such an ^{131}I dose. Furthermore, these patients should have urinary iodine measured to ensure that the values are less than 200 μg/day per gram creatinine, thus excluding artifactual suppression of ^{131}I uptake.

6.2.6 Radioiodine Therapy in Patients on Maintenance Hemodialysis

The behavior of radioiodine in hemodialyzed patients with thyroid carcinoma was described by Daumerie et al. [17]. Over six treatments, blood activity decreased with a half-life of 3.4±0.5 h (1 SD) during hemodialysis. Taking the physical half-life of 8.06 days between dialyses and carrying out the first dialysis 24 h after radioiodine administration, the total body irradiation was 3.9 times greater in hemodialyzed patients than in nondialysis subjects. Daumerie et al. [17] recommended delivering 25% of the currently prescribed activity and performing the first dialysis session after 24 h to reduce total body irradiation.

6.3 Prognostic Factors and Therapeutic Strategies in Metastatic Thyroid Cancer

The study by Schlumberger et al. [77] highlighted the prognostic significance of the early discovery of distant metastases by the combined use of thyroglobulin-measurement and ^{131}I whole-body scanning. Of 394 patients with lung and/or bone metastases, two-thirds of the patients had ^{131}I uptake in their metastases, but only 46% achieved a complete response. Prognostic factors for complete response were: younger age, presence of ^{131}I uptake in the metastases and small extent of disease. Patients who achieved a complete response following treatment of distant metastases had a 15-year survival rate of 89%, while those who did not achieve complete response had a survival rate of only 8%.

6.3.1 Lymph Node Metastases

At the time of initial therapy, cervical or mediastinal lymph node metastases were found in 32% of 535 patients [28] and in 42% of 1355 patients [48] with papillary and follicular cancer. Radioiodine therapy reduced both the recurrence rate and death rate in these patients [7, 48]. Because ^{131}I uptake may vary from one tumor deposit to another, the complete dissection of involved lymph node areas is highly recommended. When surgery is performed, a complete dissection of the affected lymph node area is preferred to lymph node sampling.

Travagli et al. [91] described the combination of radioiodine and probe-guided surgery for the treatment of patients with functioning lymph node metastases. Fifty-four patients had already undergone total thyroidectomy (51 patients) or lobectomy with isthmusectomy (3 patients), with lymph node dissection in 33 patients. Surgical excision of neoplastic foci might have been difficult in these patients and was facilitated by accurate localization on the preoperative ^{131}I scan and the use of an intraoperative probe. The following protocol was used at the Institute Gustave Roussy:

Day 0: Administration of 3.7 GBq ^{131}I
Day 4: Whole-body scan
Day 5: Surgery using an intraoperative probe
Day 7: Control whole-body scan

The probe made a major contribution to the operative procedure in 86% of patients (in 22% for unusual sites, in 20% for neoplastic foci embedded in sclerosis, and in 44% for easy localization of neoplastic foci). Finally, it confirmed the completeness of surgical excision. Further studies are required for a more general recommendation.

6.3.2 Pulmonary Metastases

In the study by Schlumberger et al. [79], the four independent variables that adversely affected survival were extensive metastases, older age at discovery of the metastases, absence of ^{131}I uptake, and moderately differentiated follicular cell type. Nemec et al. [55] achieved a 10-year survival rate of 80% in young patients with papillary carcinoma whose chest X-rays showed fine pulmonary metastases. The best prognosis is with lung metastases seen only on ^{131}I imaging and not by X-ray or computed tomography (Table 6.2). Schlumberger et al. [75] observed 23 patients treated with ^{131}I for diffuse pulmonary metastases detected only by ^{131}I imaging, and 87% of these patients had no lung uptake on subsequent scans and thyroglobulin became undetectable (Fig. 6.2).

In contrast, the experience of Sisson et al. [84] with patients manifesting pulmonary micronodular lung metastases demonstrated that radioiodine therapy uncommonly produced complete remissions. The authors asked whether the tumors might be too small for effective irradiation from radioiodine. Less than 40% of the beta and electron emission energy is deposited within a spherical

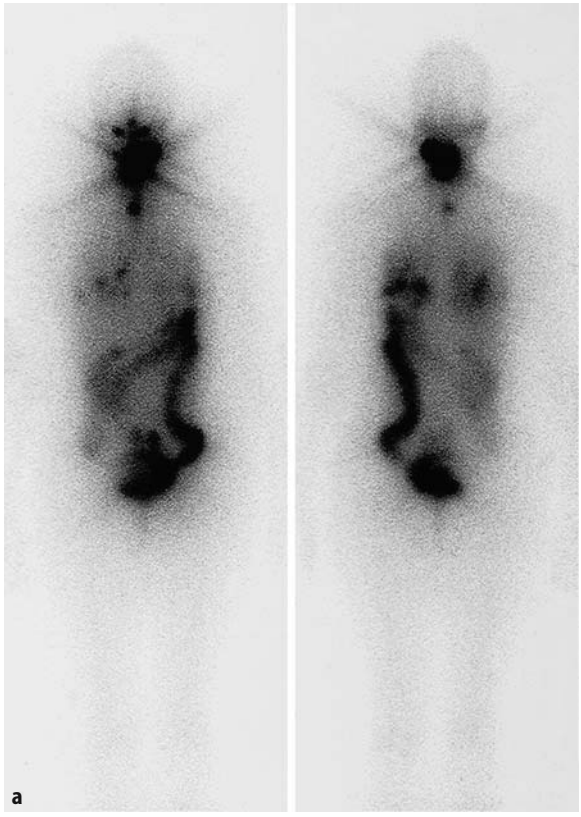

Fig. 6.2 a, b. Thirty-seven-year-old patient with papillary thyroid cancer pT2N1aM1 (pulmonary). **a** The first ^{131}I whole-body scintigraphy (3.7 GBq ^{131}I) showed lung metastases that concentrated radioiodine.

Table 6.2. Survival rates for patients with thyroid cancer with pulmonary and/or bone metastases

Study	No. of patients	1-year survival (%)	5-year survival (%)	10-year survival (%)	Remission (%)
Lung metastases					
Brown et al. [10]	20	–	63	54	–
Massin et al. [42]	58	68	44	28 (8 years)	–
Casara et al. [12]					
Normal X-rays, ^{131}I positive	42	100	100	95	–
Visible on X-rays, ^{131}I positive	54	92	59	40	–
Visible on X-rays, ^{131}I negative	38	90	18	8	–
Schlumberger et al. [79]					
Normal X-rays	73	–	–	91	83
Micronodules	64	–	–	63	53
Macronodules	77	–	–	11	14

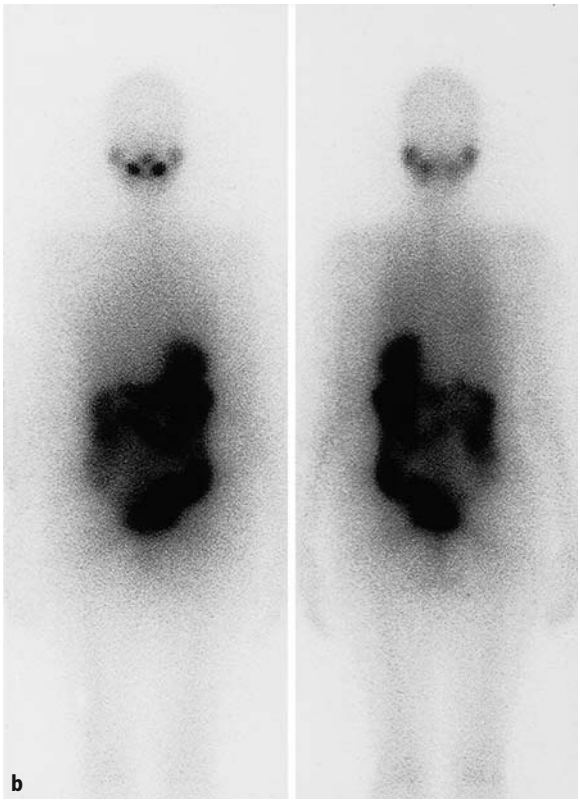

Fig. 6.2 b. The second ^{131}I whole-body scintigraphy (7.4 GBq ^{131}I) demonstrated complete remission 3 months later

Table 6.2. *Continued.*

Study	No. of patients	1-year survival (%)	5-year survival (%)	10-year survival (%)	Remission (%)
Bone metastases					
Brown et al. [10]	21	–	7	0	–
Schlumberger et al. [79]					
Single	37	–	–	total 21	22
Multiple	71	–	–		3
Lung and bone metastases					
Schlumberger et al. [79]	72	–	–	13	7

target with a diameter of 0.5 mm and much less if the target is smaller. Sisson et al. [84] did not mean that treatments with ^{131}I were not useful because the measured tumor volumes might have underestimated the total tumor volumes and the actual absorbed dose of ^{131}I might be higher than the calculated dose.

Mazzaferri [47] recommended a dose of 7.4 GBq ^{131}I when the metastases concentrate ^{131}I. Scanning and treatment with ^{131}I are repeated at 6- to 12-month intervals until the tumor no longer concentrates ^{131}I, large cumulative doses are reached, or adverse effects appear. Total cumulative doses of 37 GBq or more can be given to patients with serious distant metastases, but the frequency of complications rises.

6.3.3 Bone Metastases

Schlumberger et al. [79] treated 142 patients with bone metastases. A total of 92 patients had radioactive iodine therapy in association with external radiotherapy, 18 patients received only external radiotherapy, 45 patients underwent surgery, and 35 patients were given chemotherapy. Fourteen patients had a complete response to therapy, and each of the 14 had been treated with ^{131}I in association with external radiotherapy. No patients responded to chemotherapy. The poor prognosis of patients with bone metastases is linked to the bulkiness of the lesions (Table 6.2) [75].

Sweeney and Johnston [90], Mazzaferri [47], and Schlumberger [75] gave the recommendation that surgical resection to decrease the bulk of disease, to resect solitary metastases, or for neurologic or orthopedic palliation is important. The large volume of tumor in bone metastases makes ^{131}I therapy alone difficult. Radioactive iodine therapy is worthwhile; it may not cure but does offer palliation, particularly if used over time in high doses (Figs. 6.3 and 6.4). External radiotherapy may offer some benefits when used in conjunction with ^{131}I therapy. External radiotherapy should be given to all patients who have bone metastases visible on conventional radiographs.

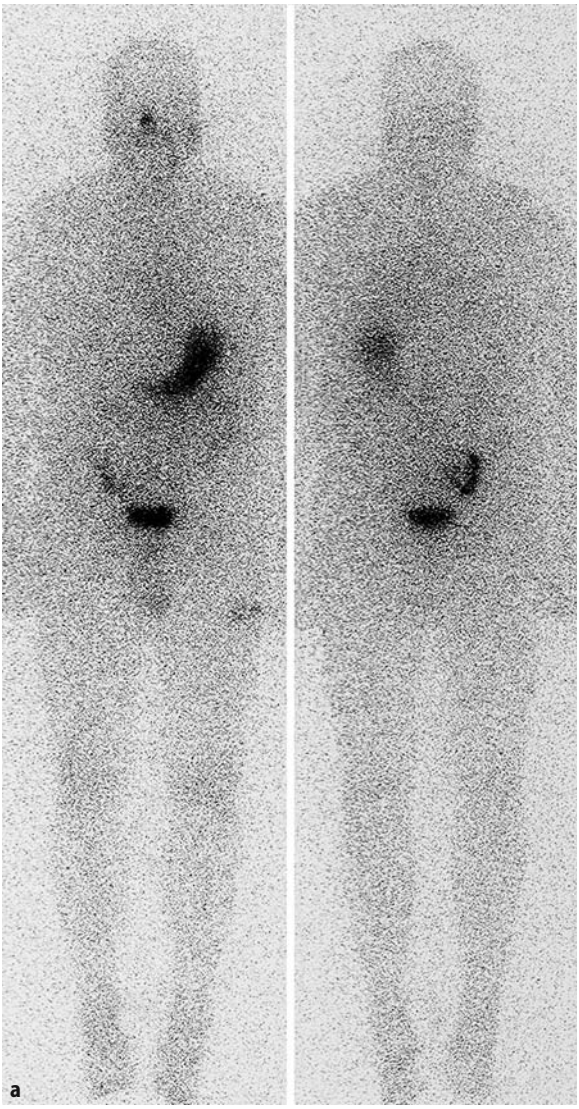

Fig. 6.3 a, b. Sixty-two-year-old patient with follicular thyroid cancer pT2N0M1 (right os ilium). The first radioiodine therapy (3.7 GBq ^{131}I) and subtotal resection of the osseous metastasis had already been performed. **a** ^{123}I whole-body scintigraphy (185 MBq ^{123}I) 3 months later, and **b** ^{131}I whole-body scintigraphy (7.4 GBq ^{131}I) demonstrated the osseous metastasis in the right pelvis and thyroid remnant on the right side. Misinterpretation as residual activity in the large bowel must be avoided. Subsequently, the patient underwent external radiation therapy

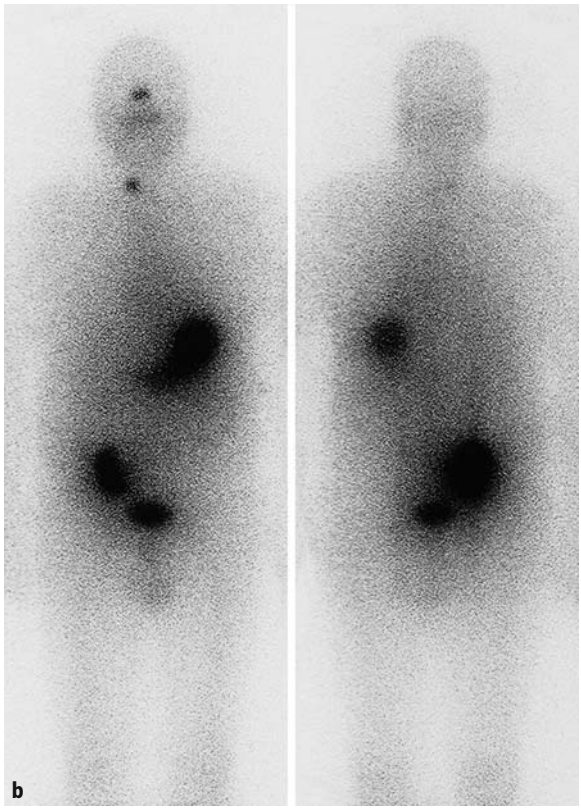

Fig. 6.3 b. ^{131}I whole-body scintigraphy (7.4 GBq ^{131}I) demonstrated the osseous metastasis in the right pelvis and thyroid remnant on the right side. Misinterpretation as residual activity in the large bowel must be avoided. Subsequently, the patient underwent external radiation therapy

6.3.4 Brain Metastases

Brain metastases are rare in thyroid cancer and were found in 1 of 325 patients by Maheshwari et al. [40] and in 2 of 571 patients with papillary cancer by Mazzaferri and Young [50].

Chiu et al. [14] analyzed 47 cases of brain metastases from thyroid cancer seen at one institution over five decades. Brain metastases from thyroid carcinoma are a poor prognostic sign. Although selection bias and other unidentified factors inherent to retrospective analysis limit their conclusion, surgical resection of brain metastases may be associated with prolonged survival. However, no evidence of survival benefit was found from radioiodine therapy, external beam radiotherapy, or chemotherapy.

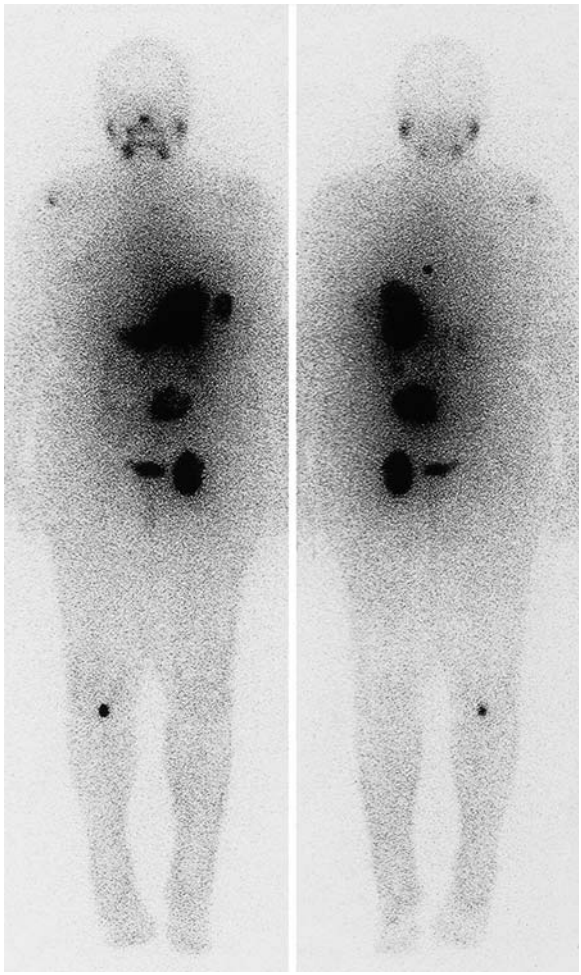

Fig. 6.4. Seventy-four-year-old patient with follicular thyroid cancer pT2N0M1 (os sacrum, left acetabulum, thoracic spine, right humerus, right tibia, left adrenal gland). ^{123}I whole-body scintigraphy demonstrated iodine avid metastasis following two radioiodine therapies (14.8 GBq ^{131}I)

6.3.5 Locally Invasive Thyroid Cancer

Locally invasive, surgically unresectable thyroid cancer is associated with a high cancer mortality and recurrence rate. Radioiodine is useful in these patients if uptake is proven. Some investigators report the use of radiosensitizers such as adriamycin, along with ^{131}I to increase the tumoricidal effect [67], but this approach has not yet been incorporated into clinical practice.

Adjuvant external radiotherapy improves the recurrence-free survival in patients older than 40 years with invasive papillary thyroid cancer pT4 and lymph node involvement [21]. Further details are included in Chap. 7.

6.4 Optimizing the Therapeutic and Diagnostic Capabilities of ^{131}I

6.4.1 Thyroid-Stimulating Hormone Stimulation

Following total or near-total thyroidectomy, TSH elevation reaches a maximum in 3–5 weeks. However, in patients with a large thyroid remnant, elevation of TSH may occur slowly or minimally. In the follow-up care, patients are maintained on suppressive doses of thyroid hormone. Before whole-body imaging or ^{131}I therapy, levothyroxine replacement must be discontinued for approximately 4–5 weeks. Short-term administration of triiodothyronine (40–60 μg) alleviates some of the symptoms of prolonged hypothyroidism and must be stopped 2 weeks before radioiodine administration. There is no significant evidence that rapid tumor growth is stimulated by a brief rise in TSH concentration [47].

6.4.2 Administration of Recombinant Human Thyrotropin

Administration of recombinant human thyrotropin (Thyrogen) stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy. In the study by Ladenson et al. [34], 127 patients with thyroid cancer underwent whole-body radioiodine scanning by two techniques: first after receiving two doses of thyrotropin while thyroid hormone therapy was continued, and second after the withdrawal of thyroid hormone therapy. Sixty-two of the 127 patients had positive whole-body radioiodine scans by at least one technique. The scans obtained after stimulation with thyrotropin were equivalent to the scans obtained after withdrawal of thyroid hormone in 41 of these patients (66%), superior in 3 (5%), and inferior in 18 (29%).

In the study by Haugen et al. [27], ^{131}I whole-body scans were concordant between the recombinant TSH-stimulated and thyroid hormone withdrawal phases in 195 of 220 (89%) patients. Of the discordant scans, 8 (4%) had superior scans after recombinant human TSH administration, and 17 (8%) had superior scans after thyroid hormone withdrawal.

The use of Thyrogen allows for radioiodine imaging while the patients are euthyroid on triiodothyronine and/or thyroxine. Data on ^{131}I kinetics indicate that the clearance of radioiodine is approximately 50% greater in euthyroid patients than in hypothyroid patients, who have decreased renal function. Thus, radioiodine retention is less in euthyroid patients at the time of imaging, and this factor should be considered when selecting the activity of radioiodine for use in radioiodine imaging.

Thyrotropin also stimulates the production of thyroglobulin, which may increase the usefulness of this tumor marker in patients treated with thyroid hormone who have had thyroid tissue ablated. Based on a serum Tg level of 2 ng/ml or more in the study by Haugen et al. [27], thyroid tissue or cancer was de-

tected during thyroid hormone therapy in 22%, after recombinant human TSH stimulation in 52%, and after thyroid hormone withdrawal in 56% of patients with disease or tissue limited to the thyroid bed and in 80%, 100%, and 100% of patients, respectively, with metastatic disease.

The use of recombinant human TSH is recommended in patients who have no evidence of recurrent or metastatic thyroid cancer and whose serum thyroglobulin is undetectable during thyroid hormone suppression of TSH [49, 76]. Special indications for Thyrogen testing concern patients who are unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is medically contraindicated due to comorbidity (e.g., severe cardiovascular or pulmonary diseases, diabetes mellitus, psychotic disorders).

Dosage and administration: Thyrogen 0.9 mg intramuscularly may be administered every 24 h in two doses. For radioiodine imaging, radioiodine administration should be given 24 h following the final Thyrogen injection. Scanning should be performed 48 h after radioiodine administration. For serum thyroglobulin testing, the serum sample should be obtained 72 h after the final injection of Thyrogen.

Recombinant human TSH is also allowed as a preparation for radioiodine thyroid-remnant ablation under thyroid hormone replacement. Robbins et al. [68] retrospectively have reviewed the rate of complete remnant ablation in patients having radioiodine ablation after hormone withdrawal (n = 42 patients, ^{131}I ablation activity 4.77 ± 2.74 GBq) compared with those having radioiodine ablation after recombinant human TSH (n = 45 patients, ^{131}I ablation activity 4.07 ± 2.41 GBq). A successful ablation was defined as no visible radioiodine uptake on the follow-up diagnostic scans, performed with 185 MBq ^{131}I. Robbins et al. [68] have found that 84% of those prepared by recombinant human TSH and 81% of those prepared by hormone withdrawal have complete resolution of visible thyroid bed uptake after radioiodine ablation. The likelihood of a complete ablation appears to be similar for these two methods of preparation. Pacini et al. [59] have used, for postsurgical ablation of thyroid remnants, a 1.1-GBq (30 mCi) standard dose of ^{131}I and prospectively compared three treatment arms: in the first arm, patients (n = 50) were treated while hypothyroid; in the second arm, patients (n = 42) were treated while hypothyroid and stimulated in addition with rh TSH; in the third arm, patients (n = 70) were treated while euthyroid on thyroid hormone therapy and stimulated with rh TSH. The outcome of thyroid ablation was assessed by conventional ^{131}I scan performed in the hypothyroid state 6–10 months after ablation. The rate of successful ablation was similar in the hypothyroid and hypothyroid + rh TSH groups (84% and 78.5%, respectively). A significantly lower rate of ablation (54%) was achieved in the euthyroid + rh TSH group. The mean radiation dose delivered during the 1st h of treatment was significantly lower in the euthyroid + rh TSH group (10.7 ± 12.6 Gy/h) compared with the hypothyroid + rh TSH group (48.5 ± 43 Gy/h) and the hypothyroid group (27.1 ± 42.5 Gy/h). The study of Pacini et al. [59] indicates that by using stimulation with rh TSH, a 1.1-GBq (30 mCi) standard dose of radioiodine is not sufficient for a satisfactory thyroid ablation rate. Possible reasons for this failure rate may be the low 24-h radioiodine uptake, the low

initial dose rate delivered to the residues, and the accelerated iodine clearance observed in euthyroid patients. Possible alternatives for obtaining a satisfactory rate of thyroid ablation with rh TSH may consist of increasing the dose of radioiodine or using different protocols of rh TSH administration, producing more prolonged stimulation of the thyroid cells.

The clinical use of recombinant human TSH in patients with advanced metastases of thyroid cancer has been described by several centers [6,30,32,36,39,53,62]. The observation studies provide preliminary evidence that rh TSH safely aids radioiodine treatment of advanced differentiated thyroid cancer. The use of rh TSH may reduce the effective half-life of ^{131}I, mainly due to a reduced renal iodine clearance in the hypothyroid state [53]. The therapeutic consequences of this changed bioavailability of ^{131}I is an open point of discussion. As prospectively controlled clinical trials have not been carried out, Thyrogen is not yet recommended as the therapeutic standard for the purpose of radioiodine therapy of metastatic thyroid cancer. Rh TSH is suitable in advanced recurrent or metastatic thyroid cancer patient who may be intolerant to TSH stimulation by levothyroxine withdrawal or who suffer from severe comorbidity.

6.4.3 Low-Iodine Diet

The total body iodine pool should be as low as possible. A low daily intake of iodine (approximately 50 μg) can increase the ^{131}I uptake and can double the thyroid dose in Gy per each 3.7 GBq of ^{131}I administered [41, 43]. A daily iodine intake of 50 μg can be achieved by restricting the use of iodized salt, dairy products, eggs, and seafood (Table 6.3). It appears to be practical to limit the time patients spend on the diet to approximately 2 weeks prior to therapy. Iodine excretion in the urine should be measured in doubtful cases.

Table 6.3. Instructions for low-iodine diet

Avoid the following foods for 1–2 weeks
Iodized salt, sea salt
Milk or other dairy products (e.g., cheese, chocolate, ice cream, yogurt)
Eggs
Seafood (e.g., fish, kelp)
Foods that contain the additives carrageenan, algin, alginate, agar-agar
Cured and corned foods (e.g., ham, lox, corned beef, sauerkraut)
Breads made with iodate dough conditioners
Foods and medications containing red food dyes (found in cereals, candies, and vitamins)
Soy products (e.g., soy sauce, soy milk)
Additional guidelines
Avoid restaurant foods and 'fast' food
Foods that contain small amounts of milk or eggs may be used
Consult doctor before discontinuing any red-colored medication

Exogenous stimulation using recombinant human TSH (rh TSH) enables the continuous substitution of levothyroxine, which contains 65.4% of its molecular weight in iodine. Thus, a substantial source of iodine intake is maintained during exogenous stimulation. Although this amount of stable iodine is comparable with the iodine intake in regions of normal iodine supply, it may reduce the accumulation of radioiodine in thyroid carcinoma tissue [37]. Park and Hennessey [61] compared a 7-day and a 14-day low-iodine diet for outpatient preparation for radioiodine rh TSH scanning in patients taking levothyroxine. Measuring urine iodine to creatinine ratios (I/Cr), the 2 weeks of preparation resulted in 71% of patients having a urinary iodine-to-creatinine ratio in the adequate range (<100 μg I/g Cr) versus 41% after 1 week. The authors [61] suggest that rh TSH protocols for monitoring residual thyroid tissue or recurrent thyroid carcinoma may have an improved efficacy if patients are prepared with a low-iodine diet. This study also supports the necessity of a 2-week diet preparation for adequate reduction in total body iodine.

6.4.4 Optimal Diagnostic Scan Dose

The studies of Jeevanram et al. [31] and Park et al. [60] suggested that a 'non-cancericidal' dose of ^{131}I may impair the ability of thyroid tumors to concentrate subsequent therapeutic doses, a phenomenon later termed 'stunning.' The optimum dose of ^{131}I for diagnostic scanning allows visualization of the thyroid remnant and all local and distant metastases without causing a sublethal radiation stunning of the thyroid tissue.

Arnstein et al. [3] performed a series of phantom studies to evaluate the ^{131}I dose that would be sufficient to detect metastatic deposits. Detectability depends on lesion volume and depth, the radioiodine uptake, background activity, and imaging equipment. With assumptions made for these variables, they found that 10- and 30-μl lesions (lesion volumes assumed to represent treatable tumor) with uptakes of 0.05% or more of ^{131}I/g of tissue would only be detected by a 74-MBq diagnostic dose if the lesion was at the surface and in the absence of background activity. Investigating this troubling hypothesis even further, they concluded that some potentially treatable lesions probably cannot be detected even with a diagnostic dose of 1.1 GBq ^{131}I.

Park et al. [60] published retrospective data comparing pretherapy and post-therapy scans done with ^{123}I and ^{131}I. Twenty-six patients were included in the ^{131}I diagnostic scan group (receiving 110–370 MBq ^{131}I) and 14 patients underwent ^{123}I diagnostic scanning. Subsequently, ^{131}I therapy was given to all of these patients. Uptake was compared by visual inspection on a posttherapy scan performed approximately 48 h after the large dose of ^{131}I was given. The uptake of the therapeutic dose was found to be impaired (defined as a qualitative visual decrease in lesion) in 20 of 26 patients in the ^{131}I diagnostic dose group and in none of the 14 patients previously scanned with ^{123}I. It was suggested that ^{123}I may be a better diagnostic agent for use before ^{131}I therapy.

McDougall [51] compared 147 scintiscans, completed 48–72 h after 74 MBq ^{131}I, with scintiscans done on average 7.8 days after therapeutic doses of ^{131}I. The therapeutic doses ranged from 1,100 to 7,400 MBq ^{131}I. The posttreatment scans showed less uptake in one region in 2 of the 147 patients (1.4%), and showed more lesions in 12 patients (8%). McDougall [51] concluded that 74 MBq ^{131}I seldom interferes with subsequent therapy and does not cause stunning.

Based on the important goals of optimal imaging of treatable lesions and subsequent maximum therapeutic dosing, doses of 100–400 MBq ^{131}I should be used for diagnostic scanning, with the higher range preferred when therapeutic dosing is not likely (e.g., for scans used in yearly posttherapy follow-up). Prompt therapeutic dosing following diagnostic scanning is important. The radiation effect of the diagnostic dose on thyroid uptake and function takes place over time, and prompt therapeutic dosing will allow little time for the physiological effects of early radiation damage. Practically, this means that ^{131}I therapy should be administered within 1 day after diagnostic scanning. Low-dose scans may be adequate for therapeutic decision-making but are not sensitive enough for imaging to determine the extent of disease.

6.4.5 Redifferentiation Therapy and Future Therapeutic Options

Retinoic acid [8, 22, 23, 82, 83] or chemotherapy [53, 67] should be considered in patients with radioiodine-negative metastases for tumor redifferentiation in preparation for radioiodine therapy. A decrease in thyroglobulin level and an increase in radioiodine uptake has been found in up to one-third of the study groups of Grünwald et al. [23], Börner et al. [8], and Simon et al. [83]. But the results from other clinical observations are inconsistent [22], and the general use of isotretinoin in all patients with otherwise untreatable thyroid cancer cannot be recommended [18]. Haugen et al. [26] have investigated the mRNA expression of the six retinoic acid receptor and retinoid X-receptor isoforms (RARα, -β, -γ and RXRα, -β, -γ) in human thyroid cell lines. The RARβ and RXRγ isoforms seem to predict response to retinoid therapy in thyroid cancer cell lines. These experimental data offer a future perspective on a more selective use of retinoid therapy in patients in whom retinoid therapy may be beneficial. For widely metastatic disease, high-dose adriamycin therapy provides a 30–40% partial response of disease, but long-term cures are rare. Octreotide and tamoxifen therapies are currently being studied as future therapeutic possibilities, but these agents are still experimental [25]. Further details are included in Chap 10.

6.4.6 Lithium

This drug enhances tumor ^{131}I retention by reducing release of iodine from normal thyroid and tumor tissue [64]. In a dosage of 400–800 mg daily (10 mg/kg) for 7 days, lithium increases ^{131}I uptake in metastatic lesions while only slightly increasing ^{131}I uptake in normal tissue. Serum lithium concentrations should be measured frequently and maintained between 0.8 and 1.2 mmol/l. Radiation of tumors in which the biological half-life of iodine is short can be enhanced by lithium without increasing radiation to other organs. Mazzaferri [47] recommended using lithium in this setting generally, but larger groups of patients were not studied. Thus, the clinical benefit was not clearly documented in the radioiodine therapy for thyroid cancer.

6.4.7 Further Optimization of ^{131}I Imaging

Decreasing background activity may be important for visualizing small metastases, and delaying the imaging beyond 72 h is necessary. Constipation should be treated with cathartics. The efficiency of a system for imaging ^{131}I is dependent on the collimator and the thickness of the crystal. A gamma camera equipped with a high-energy collimator and a thick crystal is most important:

- Whole-body images should be acquired for a minimum of 30 min and/or should contain a minimum of 140,000 counts.
- Scanning times for single (spot) images of body regions should be 10–15 min or less if the minimum number of counts is reached sooner (e.g., 60,000 counts for a camera with a large field of view, 35,000 counts for a small field of view).

The diagnostic ^{131}I scan is most sensitive and specific for treatable metastases. Although the specificity of ^{131}I imaging is approximately 99%, false-positive scans may result from body secretions, pathological transudates and inflammation, non-specific mediastinal uptake, or tumors of nonthyroidal origin. Misleading scans can be caused by physiological secretion of ^{131}I from the nasopharynx, salivary and sweat glands, and stomach, from genitourinary excretion or spilling, and from skin contamination with sputum. Pathological pulmonary transudates and inflammation due to cyst and lung lesions caused by fungal and other inflammatory disease may produce false-positive scans.

Given a therapeutic ^{131}I dose, an additional posttreatment scan should always be performed. About 25% of these post-treatment scans show lesions not detected by the diagnostic scan done before therapy, which may or may not be clinically important. Posttreatment ^{131}I scans are especially likely to yield the most information when diagnostic scans are negative and serum thyroglobulin concentrations are elevated.

6.4.8 Diuretic-Enhanced ^{131}I Clearance

Because renal excretion of ^{131}I may be reduced in patients with hypothyroidism, diuretic-enhanced ^{131}I renal clearance offers a potential method for decreasing whole-body radiation burden. In the study by Seabold et al. [81], the enhanced clearance appeared primarily due to the effect of furosemide and not to a water diuresis. Oral hydration alone did not substantially alter the mean posttreatment ^{131}I clearance from the mean pretreatment clearance in the patients who did not receive diuretics.

6.5 Side Effects of ^{131}I Therapy

6.5.1 Radiation Thyroiditis

Radiation thyroiditis occurs in about 20% of patients, most often in patients with large thyroid remnants given doses of ^{131}I that deliver about 500 Gy. It usually appears 2–4 days after ^{131}I administration and is characterized by neck and ear pain, painful swallowing, and thyroid swelling and tenderness. Patients with mild pain can be treated with salicylate or diclofenac, but those with severe pain or swelling should receive corticosteroid therapy; for example, prednisone 30 mg daily for several days.

6.5.2 Painless Neck Edema

Painless neck edema within 48 h after ^{131}I administration is a much less common problem than radiation thyroiditis. It responds to corticosteroid therapy.

6.5.3 Sialadenitis

Pain, tenderness, and dysfunction of the salivary glands is a well-recognized early complication of ^{131}I therapy. Acute and chronic sialadenitis occurred in 12% of patients in the prospective study by Allweiss et al. [1]. Symptoms included dry mouth, bitter taste, recurrent salivary tenderness, and swelling. Onset of symptoms occurred at a median of 6 days after therapy and lasted a median of 2 years.

Radiation sialadenitis appears to occur secondary to direct radiation injury to the glands. Salivary glands concentrate iodide, resulting in high iodide concentration in saliva 30–40 times higher than in plasma. Salivary gland scintigraphy with pertechnetate has been used to quantify the damage done

to the salivary glands by ^{131}I therapy. A dose-dependent reduction in salivary function was found due to ^{131}I therapy (cumulative doses less than 10 GBq). It was estimated that complete loss of salivary gland secretion may occur after a cumulative dose of 18.5 GBq ^{131}I [87].

Radiation exposure can be reduced one-fifth to one-tenth by the use of salivary flow-increasing foods such as lemons. Sufficient fluid intake is also important. Patients are encouraged to drink enough to stimulate urination at least hourly when awake over the 24 h following radiation dosage. Transient salivary gland pain can be treated with anti-inflammatory agents, but patients with more persistent pain are referred to ear, nose, and throat specialists for a full evaluation.

Parenchymal damage in salivary glands can significantly be reduced by amifostine, an organic thiophosphate, thus preventing patients from xerostomia. In 25 control patients [9], the parenchymal function of parotid and submandibular glands was significantly reduced by 40% at 3 months after the administration of 3 GBq or 6 GBq ^{131}I. Nine control patients developed grade I and two grade II xerostomia. In 25 amifostine-treated patients, parenchymal function of salivary glands was not significantly altered and xerostomia did not occur in any of these patients. On the other hand, the effect of amifostine (radiation protector) on the tumor uptake is not clearly documented. The experiences from other centers should be published. Thus, generally accepted guidelines regarding the use of amifostine have not been implemented so far. An increased incidence of salivary gland tumors in patients previously treated with radioiodine has been observed by Dottorini et al. [19].

6.5.4 Taste Dysfunction

Varma et al. [93] report a 48% incidence of taste dysfunction, described as loss of taste with or without taste distortion (phantom, metallic, or chemical taste). Onset was usually after 24–168 h, transient in a majority but persisting for 4 weeks to 1 year in 37% of the patients. This potential side-effect should be mentioned to patients.

6.5.5 Gastrointestinal Symptoms

Nausea is an early side-effect of ^{131}I therapy and is thought to be caused by radioiodine uptake in the stomach wall. In a report by van Nostrand et al. [56], gastrointestinal complaints were noted in 67%. These patients experienced mild nausea without vomiting as early as 2 h following therapy and usually within 36 h. The symptom lasted 1 h to 2 days and was well-controlled with antiemetics in most cases. The prophylactic use of metoclopramide can be recommended.

6.5.6 Testicular Function and Male Fertility

Because thyroid cancer strikes at all ages and long-term survival is excellent, the effect of ^{131}I therapy on fertility is an important consideration. Young men may develop permanent testicular damage with a reduction in sperm count that is roughly proportional to the ^{131}I dose administered. According to gamma-dose measurement by thermoluminescent dosimeters and MIRD calculation of beta contribution from blood, the absorbed radiation dose to the testes is 30–43 mGy/GBq ^{131}I for thyroid cancer [13]. The detrimental effect of ^{131}I on spermatogenesis appears to be, in a majority of cases, reversible in the long term. Reports of infertility from ^{131}I treatment with complete and permanent aspermia are rare despite the frequency of transient impairment of testicular germinal cell function [90].

Sarkar et al. [73] interviewed 33 patients (13 males and 20 females) with respect to their reproductive histories and the health of their children. All patients had undergone ^{131}I therapy when they were younger than 21 years of age and had received a mean total dose of 7.25 GBq. The average follow-up period was 18.7 years. The incidence of infertility (12%) was not significantly different from that in the general population.

Exposure of the testes can be diminished somewhat by good hydration and frequent urination during the first 24 to 48 h following therapy. Long-term storage of semen has been suggested for patients in whom high-dose cumulative therapy is anticipated [57].

6.5.7 Ovarian Function and Female Fertility

There are only a few reports on the possible damage to the gonads of females treated with ^{131}I [11, 38]. Dottorini et al. [19] found no significant difference in fertility rate, birth rate, and prematurity between 627 women treated with ^{131}I and 189 untreated women.

6.5.8 Pregnancy Outcome

Schlumberger et al. [78] obtained data on 2,113 pregnancies by interviewing female patients treated for thyroid carcinoma. The incidence of miscarriages was 11% before any treatment for thyroid cancer; this number increased slightly after surgery for thyroid cancer, both before (20%) and after (20%) ^{131}I, but did not vary with the cumulative ^{131}I dose. Miscarriages were more frequent (40%) in the 10 women who were treated with ^{131}I during the year preceding conception. Incidences of stillbirth, preterm birth, low birth weight, congenital malformation, and death during the 1st year of life were not significantly different before and after ^{131}I therapy. The incidence of thyroid disease and nonthyroidal

malignancy was similar in children born either before or after their mothers were exposed to ^{131}I.

Therefore, it is recommended that conception be postponed for 1 year after treatment with ^{131}I . There is no evidence that pregnancy affects tumor growth in women receiving adequate thyroxine therapy [75]. In women of childbearing age, pregnancy must be ruled out before radioiodine therapy by using a pregnancy test (beta-human chorionic gonadotrophin).

6.5.9 Bone Marrow Suppression

Temporary bone marrow suppression is seen in patients treated with ^{131}I [80]. Bone marrow depression is usually maximal at 1 month to 6 weeks after therapy. However, the baseline leukocyte count may be decreased even 1 year after high-dose therapy. Patients with skeletal or extensive metastases or those who have received external radiation or chemotherapeutic agents may be more susceptible to this side-effect.

Menzel et al. [52] treated 26 patients suffering from advanced differentiated thyroid cancer with repeated activities of 11.1 GBq. Use of repetitive highactivity, with a maximum of 44.4 GBq ^{131}I applied during 1 year and a maximum of 99.9 GBq accumulated activity resulted in a significant increase in hematotoxicity. Thirty-eight percent of patients had mild hematotoxic side effects (WHO I), 8% evinced moderate hematotoxicity (WHO II), and one patient developed severe leucopenia and thrombopenia (WHO III). None of these patients revealed clinical symptoms during the mean follow-up period of 4 years.

The separation and transplantation of autologous hematopoietic stem cells appear to be in an experimental stage. The feasibility of separation should be discussed before a large cumulative dose of ^{131}I has been administered. The long-term benefit for patients in whom the administration of large ^{131}I doses is expected needs to be evaluated by future studies.

6.5.10 Leukemia

Acute myeloid leukemia, the type associated with ^{131}I therapy, may occur within 10 years after treatment in patients given ^{131}I every few months and in whom the total blood doses per administration are more than 2 Gy or when cumulative doses are greater than approximately 37 GBq ^{131}I [66]. The absolute risk of life lost because of recurrent thyroid carcinoma exceeds that from leukemia by 4-fold to 40-fold, depending on the age at which the patient is treated [95].

Treatment regimes that include individual ^{131}I doses of as much as 7.4 GBq at intervals of greater than 6 months, with 12 months preferred, and that do not exceed 30 GBq per total patient dose probably do not significantly increase the risk for leukemia [4].

6.5.11 Solid Tumors

There is a low incidence of bladder cancers following repeated high-dose radioiodine therapies [20]. Attention to adequate hydration for urine dilution and emptying the bladder hourly during waking hours over the first 2 days following administration will reduce the bladder wall exposure to radiation and, perhaps, decrease the frequency of bladder cancer.

The risk of second primary malignancies was evaluated in a Swedish, Italian, and French cohort of papillary and follicular thyroid cancer patients. The study concerned 6,481 thyroid cancer patients, diagnosed during the period 1934–1995, at a mean age of 44 years [70]. In all, 17% were treated with external radiotherapy and 62% received radioiodine therapy. In total, 576 patients were diagnosed with a second primary malignancy. The mean interval of time between thyroid cancer diagnosis and second primary cancer was 15 years (range: 2–55 years). Compared with the general population of each of the three countries, an overall significantly increased risk of second primary malignancy of 27% (95% confidence interval: 15–40%) was seen in the European cohort. An increased risk of both solid tumors and leukemias was found with increasing cumulative activity of ^{131}I administered, with an excess absolute risk of 14.4 solid tumors and 0.8 leukemias/GBq of ^{131}I and 10^5 person-years of follow-up. A relationship was found between ^{131}I administration and occurrence of bone and soft tissue, colorectal, and salivary gland cancers. No interaction was evidenced between external radiotherapy and ^{131}I administration for the risk of secondary primary malignancy. The excess relative risk for solid tumors did not vary widely with time after exposure to ^{131}I: among the 3,211 patients followed for at least 10 years after thyroid cancer treatment, the excess relative risk of a second primary malignancy more than 10 years after the last ^{131}I treatment was 6% (95% confidence interval: 1–12%) per gigabecquerel of ^{131}I administered.

Among the 344 patients aged less than 20 years at thyroid cancer diagnosis, 13 second primary malignancies occurred. Compared with the general population, the overall risk of second primary malignancies was significantly increased (standardized incidence ratio 2.5), independent of the therapy. In all, 61% of the young patients were treated by ^{131}I and no carcinogenic effect of ^{131}I was found in this subgroup (relative risk 1.1). As the dose-response relationships for ^{131}I administration were linear, it seems necessary to restrict the repeated use of radioiodine therapy to thyroid cancer patients in whom clinical benefits are expected.

6.5.12 Pulmonary Fibrosis

Pulmonary fibrosis is seen in patients with diffuse pulmonary metastases from differentiated thyroid carcinoma who have been treated with ^{131}I in doses that exceed 9.25 GBq [20]. Although rarely observed, this potential side effect must be considered in patients with disseminated pulmonary metastases.

6.5.13 Neurological Complications

Because brain metastases in thyroid cancer are rare, screening measures are not common. However, because of the dire consequences of cerebral edema, certain precautions are recommended. The head should always be included in pretherapy diagnostic scanning with ^{131}I. Furthermore, in patients with widespread metastatic disease or bulky local disease, a magnetic resonance imaging study is appropriate before ^{131}I therapy. Surgical debulking of spinal lesions may be prudent before ^{131}I is given.

Pretreatment with corticosteroid, as used in preventing cerebral edema in patients receiving external beam therapy, is suggested in patients with brain metastases who are to be treated with ^{131}I.

6.5.14 Parathyroid Dysfunction

Anatomical location of the parathyroid glands outside the thyroid bed may be protective due to the physical properties of the beta-radiation from ^{131}I. Overall, the parathyroid gland can be considered relatively radioresistant, and parathyroid glands seem clinically unaffected by high-dose ^{131}I therapy. However, the management of patients should include long-term follow-up of calcium levels due to possible operative damage.

6.5.15 Lacrimal Gland Dysfunction

The symptoms from radiation-induced ocular dryness are rather discrete, in contrast to the symptoms caused by salivary gland dysfunction. Lacrimal gland dysfunction might be permanently impaired after high-dose radioiodine therapy. Zettinig et al. [96] investigated 88 patients with a history of radioiodine therapy for thyroid carcinoma and compared them with a sex- and age-matched control group. The mean administered activity was 5.3 ± 4.7 GBq ^{131}I (range: 3.0–22.3 GBq), and 66 of the patients (75%) had a single radioiodine treatment. A total of 81 patients (92%) had at least one abnormal function test indicating impaired lacrimal gland dysfunction. Schirmer's test was decreased (<10 mm/5 min) in 47 of the 88 patients and definitely abnormal (< 5 mm/5 min) in 35 patients. A tear film breakup time of <10 s was found in 78 patients and 62 patients had a definitely abnormal breakup time of <5 s. The lacrimal lipid layer was impaired in 43 patients. The following symptoms of dry eye were recorded: xerophthalmia (16%), epiphora (11%), or epiphora and photophobia (1%). Similar results were reported by Solans et al. [85] using a standardized questionnaire (n = 79 patients): Xerophthalmia persisted to the 2nd year of follow-up in 17.7% of cases and was still present in the 3rd year of follow-up in 13.9% of cases. Keratoconjunctivitis sicca persisted in 11 patients (13.9%) to the 2nd year of

follow-up but was only present in 6 patients (7.6%) more than 3 years after the last radioiodine application. A dependence on cumulative dose of radioiodine was significant for subjective xerophthalmia, with a linear trend to cumulative activity. The data indicate that lacrimal gland dysfunction (sicca syndrome) is relatively frequent after radioiodine therapy. In most cases this is a transient side-effect, but in some patients it may persist for a long period or appear late.

6.6 Radiation Considerations in the Treatment of Thyroid Cancer

Sodium iodide ^{131}I is available in capsule and liquid forms for oral and intravenous administration. The capsular form is associated with easier handling. Recommendations for inpatient therapy and whole-body scintigraphy with ^{131}I in Germany are outlined by the 'Strahlenschutzverordnung,' the 'Richtlinie Strahlenschutz in der Medizin' [33] and the 'Strahlenschutzkommision' [88].

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