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CLINICAL STUDY

Post-surgical use of radioiodine (^{131}I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report

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Abstract

Objective: To determine, based on published literature and expert clinical experience, current indications for the post-surgical administration of a large radioiodine activity in patients with differentiated thyroid cancer.

Design and methods: A literature review was performed and was then analyzed and discussed by a panel of experts from 13 European countries.

Results: There is general agreement that patients with unifocal microcarcinomas = 1 cm in diameter and no node or distant metastases have a $<2\%$ recurrence rate after surgery alone, and that post-surgical radioiodine confers recurrence and cause-specific survival benefits in patients, strongly suspected of having persistent disease or known to have tumor in the neck or distant sites. In other patients, there is limited evidence that after complete thyroidectomy and adequate lymph node dissection performed by an expert surgeon, post-surgical radioiodine provides clear benefit. When there is any uncertainty about the completeness of surgery, evidence suggests that radioiodine can reduce recurrences and possibly mortality.

Conclusion: This survey confirms that post-surgical radioiodine should be used selectively. The modality is definitely indicated in patients with distant metastases, incomplete tumor resection, or complete tumor resection but high risk of recurrence and mortality. Probable indications include patients with tumors >1 cm and with suboptimal surgery (less than total thyroidectomy or no lymph node dissection), with age <16 years, or with unfavorable histology.

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Introduction

Most patients with differentiated (papillary or follicular) thyroid carcinoma (DTC) are treated with large activities of radioiodine (131-iodine; ^{131}I) after initial surgery (total or near-total thyroidectomy). The main rationale for this practice is based on the following assumptions: (a) ^{131}I treatment of microscopic residual post-operative tumor foci may decrease the DTC recurrence and, possibly, mortality rates. Indeed, post-surgical ^{131}I treatment is also used in patients with known macroscopic disease in the neck or at distant sites; (b) ^{131}I ablation of residual normal thyroid tissue facilitates the early detection of recurrence based on serum thyroglobulin (Tg) measurement and eventually on ^{131}I total-body scan (^{131}I-TBS) (1) and (c) a large activity of ^{131}I allows a highly sensitive post-therapy TBS to be obtained 2 to 5 days after radioiodine administration. This TBS may reveal previously undetected tumor foci outside the thyroid bed.

Two recent developments prompted a re-appraisal of these assumptions and of the indications and methods of post-surgical radioiodine administration. First, meta-analyses addressing the assumptions have recently been published (2, 3). Second, European regulatory authorities this year approved recombinant human thyroid-stimulating hormone (rhTSH; Thyrogen, Genzyme Corporation, Cambridge, MA, USA) as a preparation for radioiodine ablation of thyroid remnant. Use of rhTSH may avoid hypothyroid symptoms, decrease extra-thyroidal radiation exposure and shorten the frequently anxiety-fraught interval

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between surgery and ablation, but uncertainty remains regarding the success rates of this ablation method, relative to those of thyroid hormone withdrawal, especially when lower radioiodine activities are employed.

Based on analysis and discussion of published literature and expert experience as of May 2005, we assess the validity of the rationale for the post-surgical use of ^{131}I. We also recommend indications and methods for the procedure, and discuss its safety.

Rationale for post-surgical radioiodine administration

Does post-surgical ^{131}I decrease DTC recurrence and mortality rates?

Currently available data regarding the potential benefits of post-surgical use of ^{131}I on DTC recurrence and mortality rates (Table 1) are controversial. No randomized, controlled clinical trial has yet been performed on a large number of patients**.** In addition, to better define this issue, patients should be analyzed according to risk stratification, using scoring systems such as pathological Tumor-Node–Metastasis (pTNM) classification. Staging is optimally defined when initial surgery has included a total thyroidectomy with a central lymph node dissection that permits histological examination of at least six lymph nodes (4). Other prognostic factors, such as tumor histology, may also be relevant. Stratification allows identification of three groups with different risks of DTC recurrence or cause-specific mortality: very low-risk, low-risk and high-risk patients.

Very low-risk patients (unifocal microcarcinoma with size ≤1 cm, N0, M0 and no extension beyond the thyroid capsule) Unifocal tumors up to 1 cm in diameter, with no extension beyond the thyroid capsule or lymph node metastasis, have a very good prognosis. After surgery alone, the long-term recurrence rate is $<2\%$. Thus, the concept that radioiodine ablation is not indicated in such tumors has been widely accepted, because the patient is believed to have been cured by surgery alone (5–7). Also for this reason, long-term thyroid-stimulating hormone (TSH)-suppressive therapy has no indication as a cancer treatment in this setting.

Low-risk patients (TI > 1 cm N0, M0, or T2, N0, M0 or T1 multifocal) This is an area of significant controversy and debate because studies have been mainly retrospective and limited in size, and have mixed patients with different treatment and prognostic factors (8). A meta-analysis of published studies was recently performed to determine if post-surgical radioiodine decreases disease recurrence or cause-specific death in adults with papillary or follicular thyroid carcinoma (2). In four large series included in the meta-analysis, the recurrence rate was significantly lower in ^{131}I-treated patients, but six other series did not show any statistical benefit with respect to this outcome. This meta-analysis was subject to many limitations and the populations studied were heterogeneous. The authors concluded that post-surgical radioiodine may reduce recurrence and mortality, but that these observations are not definitively verified.

The only large study (9) that found a significant beneficial effect of ablation on cause-specific mortality deserves further comment. Thirty years after ablation, Mazzaferri observed a DTC recurrence rate of 16% in 350 patients submitted to ^{131}I ablation for a primary tumor ≥ 1.5 cm in diameter, significantly lower ($P < 0.001$) than the 38% rate in 802 patients treated with levothyroxine (L-T4) alone. Cancer-related death was observed in 3% of the ^{131}I-treated patients, which was significantly less ($P = 0.03$) than the 8% rate in patients not receiving radioiodine; no death from thyroid cancer was seen among the 138 patients

Table 1 Benefits of radioiodine ablation (adapted from references 2, 6, 9, 16 and 18).

			Statistical benefit (ablation group vs. non-ablation group cause-specific DTC)	
Study	***n***	**Median follow-up** (years)	mortality	recurrence
Illinois Registry, USA	2282	6.5	NS	NS
MD Anderson, USA	1599	11.0	NS	$P < 0.001$
Ohio State, USA	1510	16.6	$P < 0.0001$	$P < 0.016$
Pisa, Italy	964	12.0	NS	$P < 0.001$
Hong Kong, Hong Kong	587	9.2	NS	NS
Toronto, Canada	382	10.8	NS	NS
Gustave Roussy, France	273	7.3	NS	NS
Mexico, Mexico	229	5.0	NS	NS
UCSF, USA	187	10.6	NS	$P < 0.0001$
Gundersen/Lutheran, USA	177	7.2	NS	NS
Mayo Clinic, USA	2444	>25	NS	NS

DTC, differentiated thyroid cancer; NS, not statistically significant.

in the ^{131}I group who lacked evidence of residual disease following surgery.

These favorable results were not confirmed by the same type of analysis performed on a similar population ($n = 1542$) treated at the Mayo Clinic (10). Thirty years after ablation, recurrence rates were comparable in the ^{131}I group and the group not given radioiodine (17% vs. 19%, $P = 0.89$); cause-specific mortality rates were also similar (5.9% vs. 7.8%, $P = 0.43$). Indeed, the 30-year recurrence rate in the no radioiodine group at the Mayo Clinic was considerably lower than those reported by other institutions. The extent and completeness of surgical excision might account for the differences between the Mayo Clinic results and those reported by Mazzaferri and other centers.

High-risk patients (any T3 and T4 or any T, N1 or any M1) When the patient is known to have residual cancer in the neck, distant sites or both, or persistent disease is strongly suspected, the benefits of post-surgical administration of a large radioiodine activity are clear. A prospective multicenter study (11) demonstrated this in 385 patients with high-risk thyroid cancer (age ≥ 45 years with large tumor, tumor extension beyond the thyroid capsule, multifocal follicular tumor, or lymph node/regional metastases; or any age with distant metastases or poorly differentiated follicular cancer). ^{131}I therapy significantly reduced cancer-specific mortality and progression rates in patients with papillary cancer and likewise in patients with follicular cancer, with an additional improvement in disease-free survival. A multicenter Canadian study in similar patients also demonstrated significantly improved recurrence and mortality rates at 20 years after ^{131}I treatment (12). In addition, an earlier study at the Institut Gustave Roussy resulted in the same conclusion (13).

Is post-surgical follow-up with Tg measurement and ^{131}I-TBS improved after radioiodine ablation of normal thyroid remnants?

In patients with thyroid residues, detectable serum Tg levels may derive from the normal thyroid cells of the residues or from previously unknown neoplastic thyroid cells. In contrast, after ^{131}I remnant ablation, detectable Tg can derive only from tumor. Thus, a definite advantage of ^{131}I ablation is that Tg measurement will be more specific for detection of persistent or recurrent disease, as there will be no confounding factor. Indeed, a recent meta-analysis demonstrated that the accuracy of Tg follow-up was increased in patients who had undergone ablation (3).

However, experience has shown that Tg levels remain undetectable during long-term follow-up in the vast majority of non-ablated patients with low thyroid bed ^{131}I uptake, i.e. $<1-2\%$ uptake after total thyroidectomy in 95% of such patients during L-T4 treatment and 80% after thyroid hormone withdrawal (14). This observation has two implications. First, even in the absence of ^{131}I ablation, accurate Tg measurement can be used to follow up low-risk totally thyroidectomized patients, provided they have undetectable stimulated serum Tg after surgery and no serum Tg autoantibodies. Second, after total thyroidectomy, ^{131}I ablation may be indicated in otherwise low-risk patients with detectable Tg on L-T4 or after TSH stimulation, if the Tg level increases in serial measurements. Of note, Tg may remain detectable several weeks after thyroidectomy and then become undetectable, indicating that measurement of serum Tg should not be performed too soon after surgery.

Serum Tg is detectable during L-T4 treatment in most patients with distant metastases. Rare false negative serum Tg determinations are usually due to isolated neck node metastases. Currently, the most sensitive tool to discover lymph node metastases is neck ultrasonography (15–17), which should be performed in all thyroid cancer patients, even if there is no ablation. Therefore, in low-risk patients who have not been ablated because they have low thyroid bed uptake and undetectable Tg and Tg autoantibodies following surgery, follow-up is based on serum Tg determination on L-T4 plus neck ultrasonography.

Diagnostic ^{131}I-TBS is also more sensitive after radioiodine ablation of normal thyroid remnants, because visualization of neoplastic foci with low uptake may be masked by thyroid remnants with high uptake. However, thyroid bed ^{131}I uptake is typically under $1-2\%$ after total thyroidectomy performed by an experienced surgeon, and this level of uptake does not hamper visualization of foci outside the thyroid bed, provided an appropriate gamma camera is used for scintigraphy (18). Thyroid bed uptake will be much higher when less than total thyroidectomy has been performed. In such patients, the diagnostic TBS may not be informative and serum Tg will be detectable on L-T4 treatment. These considerations should lead to ablation, even in low-risk patients.

Patients who are Tg antibody positive may be followed up with neck ultrasonography and ^{131}I-TBS. In the majority of patients without persistent disease, serum Tg antibodies will progressively disappear (19) as a result of antigen elimination, and at this point, patients can be considered cured.

Is post-ablation ^{131}I-TBS worthwhile?

A number of studies have shown that the sensitivity of ^{131}I-TBS for detecting thyroid cancer is improved following administration of a high activity of ^{131}I, and a TBS should be performed whenever such an activity is given (20, 21).

Post-ablation ^{131}I-TBS may reveal useful information, provided an appropriate gamma camera is

used (high energy collimator with a thick crystal) and thyroid remnant uptake is low (<1–2%). High ^{131}I uptake in a remnant may produce a starburst effect that prevents visualization of any tumor in the neck. If a large residue has been documented before ablative ^{131}I administration, completion thyroidectomy may be indicated, particularly when the risk of persistent disease is high. However, if ^{131}I has already been administered, it is better to consider the need for a second operation or radioiodine treatment after 9–12 months. Indeed, by that time, the initial radioiodine treatment frequently obtains successful ablation even in residues producing thyroid bed uptake up to 10%.

Post-ablation ^{131}I-TBS can demonstrate the completeness of surgical excision and in other patients, may show uptake outside the thyroid bed, in lymph node areas or at distant sites. Findings of extra-thyroidal uptake may prompt further treatment and thus influence the final outcome. However, it is important to remember that some tissues physiologically take up iodine, including the salivary glands and mouth, the esophagus due to swallowing of radioactive saliva, the axilla due to radioactive perspiration, the liver due to concentration of radiolabeled iodoproteins, the stomach, colon, bladder, and less frequently, the thymus and the breasts in young women. Uptake in these sites must not be erroneously considered as metastatic disease.

Interestingly, after total thyroidectomy, post-ablation ^{131}I -TBS results are closely related to Tg levels on the day of ^{131}I administration (22, 23). An undetectable serum Tg at that time is a good predictor of the absence of neoplastic foci.

When ablation is performed, the highly sensitive post-ablation TBS is considered the first step in post-operative monitoring. Patients with no uptake outside the thyroid bed will not need TBS during subsequent follow-up, in fact a control TBS with a small, diagnostic radioiodine activity will have a lower sensitivity (18, 24). However, depending on the Tg levels or the anti-Tg antibody status, a diagnostic TBS may be performed some months later to confirm completeness of ablation and absence of uptake outside the thyroid bed.

Indications for post-surgical radioiodine administration

Post-surgical use of ^{131}I should be selective (Table 2), given that uncertainty persists concerning its benefits in decreasing recurrence rates and cause-specific mortality. Cost, discomfort and inconvenience to the patient may be significant enough to outweigh potential benefits, although the recent approval of rhTSH for thyroid ablation makes a preparation method available that can avoid hypothyroid symptoms and allow performance of the procedure sooner after surgery.

In patients with unifocal papillary thyroid carcinoma less than 1 cm in diameter, no extension beyond the thyroid capsule, and no lymph node metastases, the prognosis is so favorable after surgery alone that adjuvant therapy, including routine ^{131}I ablation, appears superfluous. At present, these individuals account for up to 30% of all DTC patients. Patients with a minimally invasive follicular carcinoma up to 1 cm in diameter also generally have no need for ablation, because such tumors are usually unifocal and lymph node metastases are rare.

In patients with metastases, incomplete tumor resection, or high risk based on the pTNM classification or other well established criteria, radioiodine treatment is definitely indicated. In our opinion, a high activity (3.7 GBq) should be used in these patients because the radioiodine is aimed both at ablating normal thyroid remnants and treating known or suspected persistent neoplastic foci.

In patients with primary tumors that exceed 1 cm in diameter or are multifocal, the benefits of ^{131}I ablation on recurrence and survival rates are still controversial after what appears to be complete surgical excision. ^{131}I ablation may be restricted to patients with incomplete surgical excision or poor prognostic factors for recurrence or death (4). These patients are selected for ^{131}I ablation based on well-established characteristics that take into account the initial extent of the disease, the patient's age, and the surgeon's and pathologist's reports.

However, on the grounds that the consequences of administering 1.1 GBq (30 mCi) or even 3.7 GBq (100 mCi) of ^{131}I are minimal, many clinicians would give ablation to all low-risk patients 'for the certainty

Table 2 Recommended indications for post-surgical radioiodine in differentiated thyroid cancer patients, for definite indications, a high activity (≥3.7 GBq) is administered; for probable indications, a lower activity (1.1 GBq) may suffice.

No indication (low risk of relapse or cancer-specific mortality):
Complete surgery
Favorable histology
Unifocal T ≤ 1 cm, N0, M0
No extra-thyroidal extension
Definite indication (use high activity [≥3.7 GBq (100 mCi)] after thyroid hormone withdrawal):
Distant metastases
Incomplete tumor resection
Complete tumor resection but high risk for recurrence or mortality: tumor extension beyond the thyroid capsule (T3 or T4), extensive lymph node involvement.
Probable indication (use high or low activity [3.7 or 1.1 GBq (100 or 30 mCi)] after withdrawal or rhTSH):
Less than total thyroidectomy,
No lymph node dissection
Age < 16 years
T1 > 1 cm and T2
Unfavorable histology:
papillary: tall-cell, columnar-cell, diffuse sclerosing
follicular: widely invasive or poorly differentiated.

and peace of mind provided by a subsequent negative scan and undetectable serum Tg concentration' (10). Also, when the completeness of surgery is less assured, radioiodine ablation is often performed to reduce concern about tumor recurrence. With time, the number of these patients are likely to decrease as surgeons gain experience with thyroid cancer resection. In these patients, further trials are warranted to establish the minimal activity of ^{131}I and the mode of preparation (withdrawal or rhTSH) that may be successful for ablation.

If ^{131}I ablation is not performed postoperatively, it may be administered some months later to patients with persistently elevated, increasing serum Tg levels.

Methodological recommendations

Pre-ablation scintigraphy

As exposure to ^{131}I may 'stun' thyroid tissue and thus decrease the efficiency of subsequent treatment with this radioisotope, a TBS with a diagnostic activity of radioiodine is not recommended before ablation (25, 26). However, if a center desires a scintigraphic map of the thyroid bed, a small activity of ^{131}I in the order of 1.75–3.7 MBq (50–100 μCi) will provide the same information as would higher diagnostic activities, without any stunning effect. Another alternative to avoid stunning may be to use ^{123}I, but this isotope is not widely available and is relatively expensive. A diagnostic TBS, together with an ultrasound measurement of thyroid residue volume, may be useful after a suboptimal thyroidectomy to assess the need for completion surgery.

Preparation

To optimize uptake, radioiodine is administered following TSH stimulation. Historically, to obtain such stimulation, thyroid hormone treatment has been withheld and iodine contamination carefully avoided for 4–6 weeks after surgery. During thyroid hormone withdrawal, many patients suffer hypothyroid symptoms and do not resume work, study, family or leisure activities (27). Serum TSH should be above an empirically determined level (> 25–30 μU/ml) before administration of ^{131}I, otherwise withdrawal should be prolonged by 1 or 2 weeks. Iodine excess should be excluded by careful screening and in case of uncertainty, urinary iodine excretion should be measured. Pregnancy should be excluded in women of childbearing age. If ablation has to be delayed beyond 6 weeks, thyroid hormone treatment with L-T4 or triiodothyronine (L-T3) is initiated and then withdrawn later. Initial use of LT-3 for 5 days will reduce the hypothyroid period following thyroid hormone withdrawal.

Since this year, rhTSH is licensed in Europe for ablation with 3.7 GBq (100 mCi) of radioiodine in low-risk patients. rhTSH has the advantage of allowing thyroid hormone treatment to be started immediately after surgery, avoiding hypothyroid symptoms and improving quality of life (28). In addition, with rhTSH, ablation may be performed a few days after surgery, which may be expected to allow patients to resume work and other activities more quickly, and to shorten the frequently anxiety-fraught period until primary treatment has been completed.

rhTSH is the modality of choice in patients with concurrent major co-morbidity or the inability to tolerate hypothyroidism. There is, however uncertainty over whether ablation success rates differ between patients given rhTSH and those discontinuing thyroid hormone. Retrospective studies reported no difference, but are subject to bias and confounding factors (29, 30). Two prospective trials have been performed with limited numbers of patients. One of these studies (31) using 1.1 GBq (30 mCi) as the standard ablative activity, reported that hypothyroid patients given rhTSH ($n = 42$) had similar ablation rates compared with hypothyroid patients not given rhTSH ($n = 50$), 78% vs 84%, respectively; the ablation rate in euthyroid patients given rhTSH ($n = 70$) was significantly lower (54%, $P < 0.01$). However, this observation could have been due to radioiodine being given 24 h later post-rhTSH compared to other studies, and to the trial's stringent definition of successful ablation, as absence of visible thyroid bed uptake on a diagnostic TBS performed following thyroid hormone withdrawal. When the criterion for successful ablation was no visible thyroid bed uptake on withdrawal diagnostic TBS or undetectable serum Tg following rhTSH, the success rates were similar (95.0% vs. 88.0% vs. 74.1%) in the three groups.

The other prospective trial (28) was randomized, had blinded scintigraphic evaluation, and used an ablative activity of 3.7 GBq (100 mCi). It reported similar rates of ablation success, defined as no visible uptake on an rhTSH-aided diagnostic TBS, in patients on thyroid hormone given rhTSH ($n = 32$) and in those in whom thyroid hormone was withdrawn ($n = 28$), 96% vs 87%, respectively. Based on the primary outcome of no or < 0.1% visible uptake, the ablation rate was 100% in each arm. Dosimetric studies showed that the residence time of ^{131}I in thyroid remnants was similar in the two groups (indicating similar radiation doses to the remnants), but a further advantage of using rhTSH was a one-third reduction in the radiation dose delivered to the blood. The increased iodine intake due to continued thyroid hormone treatment is believed by many experts to be too small to meaningfully decrease the radioiodine uptake observed after rhTSH stimulation. In all rhTSH patients in the randomized prospective ablation trial, iodine excretion remained far below 200 μg/l, a level generally considered to indicate no iodine excess.

Assessment of ablation success

In the above-mentioned studies, ablation success was verified 6–12 months after the procedure via a TBS

performed with 74–185 MBq (2–5 mCi) of ^{131}I, and was defined as no or <0.1% visible thyroid bed uptake. Low ^{131}I thyroid bed uptake has no prognostic significance and for this reason, a control diagnostic TBS may be avoided when an informative post-ablation TBS shows no uptake outside the thyroid bed (15–18, 24, 32). Thus, in the absence of anti-Tg antibodies, the current criterion for successful ablation is an undetectable (<1 ng/ml) serum Tg following rhTSH stimulation 9–12 months after ablation.

Ablation activity The ^{131}I activity used for ablation may range according to institutional practice or the patient's clinical or prognostic status from 1.1 GBq (30 mCi) to 5.5 GBq (150 mCi). Dosimetric studies have shown that ablation is successful when a radiation dose exceeding 300 Gy is delivered to thyroid remnants (1), and allow a more precise estimation of the minimum ^{131}I activity required for effective ablation. The result of such studies is that the same rate of total ablation has been achieved with lower activities of ^{131}I (33).

The advantages of using a lower activity include lower cost, shorter hospitalization, reduced environmental radioiodine exposure and lower radiation doses to extra-thyroidal tissues. However, a recent review concluded that a low radioiodine activity was associated with a lower ablation success rate (2). This review was based on 13 studies, of which only 3 were randomized, while 10 were cohort studies. Nine of the 10 cohort studies were small (<100 patients each) and showed that lower activities had a lower success rate, whereas the remaining cohort study was larger (283 patients) and showed similar success rates in the high- and low-activity groups (34). Cohort studies may be subject to bias and results of this review may be unreliable. Our own systematic review of the literature revealed five randomized trials evaluating ablation activity (Table 3). In the only large randomized trial (35), the 565 patients were divided into eight groups, each group receiving a different activity ranging from 0.5 to 1.8 GBq (15 to 50 mCi). A high success rate was reported with activities of 1.1 GBq, which did not increase with higher activities. However, for each activity, the ablation success rate was higher than in other trials. Overall, comparisons of high and low activities are conflicting; the results of these randomized trials are consistent with there being either no difference between the studied activities or with a high activity being more effective. Most published trials have focused on ablation of normal thyroid remnants and have not compared the complication or DTC recurrence rates or the socio-economic consequences according to the activity administered, although these may be more clinically relevant endpoints.

With a standard activity of 1.1 GBq (30 mCi), total ablation is achieved more frequently (>80% success rate) in patients who have undergone total thyroidectomy (<2% thyroid bed uptake) than in patients with larger thyroid remnants (~67% success rate) (36–39). This was confirmed by a recent study (38) that showed a high efficacy of low activities in ablating small remnants (uptake <2%) and an inverse relationship between thyroid uptake and ablation efficacy for each activity. Total thyroidectomy should therefore be strongly considered in all patients who are to be treated with ^{131}I. In more than 80% of cases, an entire lobe can be ablated with a single administration of 1.1 GBq (29.9 mCi) of ^{131}I (40), and a recent study concluded that large-activity ablation is a viable alternative to completion thyroidectomy (41). However, these studies did not provide data on long-term outcome.

Treatment

Where an in-patient stay is required, patients are hospitalized for ablation in a specifically equipped room, until the external dose rate is below limits determined by national radiation protection authorities. Written and verbal information describing the procedure, its potential risks and benefits. Radiation safety measures should be given to the patient before ^{131}I administration. Hospital personnel should be regularly instructed on radiation safety measures and written standard operating procedures should be readily available. Although shortly after administration, the external dose rate is high, normal clearance from the

Table 3 Ablation success rates by radioiodine activity. Ablation success was assessed by a ^{131}I total body scan performed after withdrawal with a tracer dose of 37–150 MBq ^{131}I 6–12 months after ablation and was defined as no visible or negligible uptake (<0.1%).

	Proportion of patients successfully treated by activity		
Study	1.1 GBq (30 mCi)	1.8 GBq (50 mCi)	3.7 GBq (100 mCi)
Creutzig, 1987 (36)	50% (5/10)	Not studied	60% (6/10)
Johansen, 1991 (37)	58% (21/36)	Not studied	52% (14/27)
Bal, 1996 (34)	63% (17/27)	78% (42/54)	74% (28/38)
Sirisalipoch, 2004 (39)	Not studied	65% (41/63)	89% (67/75)
Bal, 2004 (35)	83% (61/73)	82% (63/77)	Not studied
Total	71% (104/146)	75% (146/194)	77% (115/150)

body and limited uptake by the thyroid remnant result in a rapid decline of this rate and a limited radiation exposure to clinical staff, and after the patient's discharge, there is exposure to relatives and the public. When uptake is low in thyroid tissue (typically $<2\%$), the effective half-life in the whole body is short following thyroid hormone withdrawal and even shorter in euthyroid patients prepared with rhTSH (typically around 16 and 12 h, respectively) (28).

A post-ablation TBS is performed 2–5 days after ^{131}I administration and uptake is quantified. Discovery of foci of uptake outside the thyroid bed will lead to additional treatment. A prescription for L-T4 is initiated or maintained. The follow-up strategy in patients with no uptake outside the thyroid bed on the post-ablation TBS was discussed previously (42, 43).

Conclusions on methodology

Some uncertainty remains concerning the efficacy of a low activity of radioiodine as compared with higher activities, and also concerning the optimal preparation procedure (rhTSH versus withdrawal), in particular when a low activity is administered. Most prospective studies have addressed the effects of ablation only on normal thyroid remnants, not on long-term DTC recurrence rate. When radioiodine is administered in patients with suspected or known neoplastic foci, preparation with thyroid hormone withdrawal and a high activity of ^{131}I should be used, aimed both to treat neoplastic foci and to eradicate normal thyroid remnants. When radioiodine is aimed only at ablating normal thyroid remnants, it can be administered following rhTSH; whether in these cases, a low activity can be used needs confirmation. Randomized trials are warranted to address both the ^{131}I activity (low or high) and the stimulation method (withdrawal or rhTSH), with endpoints including the ablation success rate, DTC recurrence rate, side effects, and socioeconomic consequences.

Side effects of large radioiodine activities

Side effects of ^{131}I treatment are usually minimal and transient. Nausea and gastric pain may occur, but last only a few days. Sialadenitis is more frequent, with salivary gland pain and enlargement, this may lead to decreased salivary flow or xerostomia (44). Prophylaxis can be achieved in part by getting patients to drink large volumes of fluid and starting on day 2 following ^{131}I treatment to suck lemon drops or candy (45). Loss of taste is a regular feature, which usually persists for a few days. Recently, nasolacrimal drainage system obstruction was reported (46), but this complication may be less frequent than dry eye (47). In cases of large thyroid remnants, the occurrence of radiation thyroiditis is more theoretical than real, and may be prevented with low-dose corticosteroid therapy. Laxative treatment is given to decrease colonic exposure and improve the quality of the post-ablation TBS.

Gonadal irradiation from a single radioiodine activity is limited (48) but in some cases, may lead to transient hypospermia with elevation of serum follicle-stimulating hormone. Permanent damage is observed only after several treatments with cumulative activities exceeding 18.5–22.2 GBq (500–600 mCi) (49). For this reason, young male patients who may require high cumulative activities should be offered sperm banking before ^{131}I treatment. In female patients treated with radioiodine, transient amenorrhea and an early age of menopause have been observed (50). Studies of pregnancy outcome after radioiodine treatment revealed no deleterious effects. The only abnormality was an increased risk of miscarriage when conception occurred fewer than 6 months after the last treatment (51). Therefore the advice is to postpone conception for at least this interval.

Significant carcinogenic effects of ^{131}I have been shown in patients treated with large cumulative activities (>15 GBq). Because there is a linear relationship between the cumulative administered activity of ^{131}I and the risk of a secondary leukemia or other cancer, every effort must be made to use radioiodine only in patients for whom it can be beneficial (52), and when ^{131}I is indicated, to use the smallest effective activity. For a given activity, another potential advantage of using rhTSH is that doing so will decrease the dose to extra-thyroidal tissues by about one-third (26, 28).

Anxiety is commonly reported by thyroid cancer patients and may impair quality of life. Radioiodine exposure may be a contributing factor, and patients should receive extensive reassurance about the safety and potential benefits of the procedure.

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