REVIEW ARTICLE

Radioiodine Therapy in Differentiated Thyroid Cancer

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Abstract

For many years the recommended therapy for differentiated thyroid carcinoma (DTC), with the exception of unifocal papillary carcinoma ≤1 cm in diameter, has consisted of (near) total thyroidectomy followed by postoperative radioiodine ablation of thyroid remnant tissue. Even though results from randomized controlled trials are still missing, this combination has proven its worth as a safe and very effective treatment that resulted in an improved life expectancy and reduced recurrence rate for DTC patients in many observational studies.

Preparation for I-131 ablation using standard activities between 1-3 GBq requires low iodine diet for 2-3 weeks and TSH-stimulation by withdrawal of thyroid hormone medication for 3 weeks following thyroidectomy or by use of recombinant human TSH alternatively. The advantages of exogenous TSH stimulation are a maintained quality of life and a lower radiation dose to the remainder of the body.

In case of metastastic spread, higher activities of radioiodine in the range of 4-11 GBq are necessary; if possible, individual dosimetry is recommended. The standard approach for preparation of I-131 therapy in patients with metastases is endogenous hypothyroidism after thyroid hormone withdrawal.

Indications, contraindications and practical aspects of radioiodine treatment will be discussed in this review.

Keywords: Differentiated thyroid cancer, radioiodine therapy, dosimetry, side effects, recombinant human thyrotropin, guidelines.

INTRODUCTION

Radioiodine thyroid remnant ablation can be defined as the postsurgical therapeutic administration of I-131 to patients with differentiated thyroid carcinoma (DTC) with the primary goal of eliminating residual thyroid tissue following thyroidectomy. As a gamma- and beta-ray-emitter with a physical half-life of 8.1 days, radioiodine [iodine-131 (I-131)] is also suitable for post-therapeutic imaging.

The procedure's potential benefits include:

- Eradicating any microscopic tumor deposits, which may reduce both the frequency of regional recurrences and overall mortality in patients
- Permitting sensitive "post-therapy" imaging that may reveal previously occult metastases
- Improving the sensitivity and specificity of follow-up testing for DTC persistence or recurrence, i.e. of serum Thyroglobulin testing, diagnostic radioiodine scanning, or both.

Adjuvant postsurgical ablative radioiodine therapy is recommended in most countries for differentiated thyroid cancer with tumor diameters >1 cm. In smaller primaries with a so called very low risk profile I-131 ablation is generally not performed and may only be beneficial in special settings: Familial history of thyroid cancer, previous external beam radiation to the neck and unfavorable histological variants.

In most centers, standard fixed activities between 1-3 GBq are commonly used for I-131 ablation. Preparation for the procedure with such activities requires a low iodine diet for 2-3 weeks and endogenous TSH stimulation by thyroid hormone withholding for approximately 3 weeks following thyroidectomy or exogenous TSH increase using i.m. injections of recombinant human TSH. The advantages of recombinant TSH are avoidance of morbidity associated with clinical hypothyroidism and a maintained quality of life, as well as a lower radiation dose to the remainder of the body, e.g. the bone marrow.

I-131 is administered in large activities depending upon patient/disease characteristics also in patients with advanced disease, for curative or palliative treatment of tumor recurrences, metastases or both.

In case of distant metastatic spread, higher activities of radioiodine in the range of 4-11 GBq are generally accepted; if feasible, individual "patient specific" dosimetry should be considered. The standard preparation approach for I-131 therapy in patients with metastases is endogenous hypothyroidism after thyroid hormone withdrawal.

RECENT GUIDELINES

In the last few years, several updated sets of guidelines or consensus reports on the diagnosis and treatment of DTC have been introduced by various international and national

Table 1: Differentiated thyroid cancer: Risk classification[1,3,4]

Organization	*Risk classification characteristics*		
	Pts. < 45 years		**Pts. ≥ 45 years**
ATA			
Stage I	any T or N, M0		T1, N0, M0
Stage II	any T or N, M1		T2, N0, M0
Stage III	Not applicable		T3 N0M0 or T1/T2 N1M0
Stage IV	Not applicable		all other TNM categories
	Very low risk	**Low risk**	**High risk**
ETA	T1(≤ 1 cm) N0M0	T1(> 1 cm) N0 M0 T1m N0M0 T2 N0M0	T3 and T4 N1 M1

AJCC, American Joint Committee against Cancer; ATA, American Thyroid Association; ETA, European Thyroid Association; UICC, Union Internationale Contre Le Cancer

organizations.[1-5] Though, generally following the prerequisites of "evidence-based medicine" these recommendations were put together using different approaches including systematic literature searches, various review processes, expert rounds and other methodology. Current guidelines also differ in their definitions of high- and low-risk patients. However, this risk stratification is largely based on the initial pTNM stage, in which low-risk tumors are usually defined as thyroid cancers confined to the thyroid gland, without evidence of lymph node or distant metastases. In contrast, high-risk tumors are usually defined as those with locally invasive or metastasized disease.

With the exception of the American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi recommendations,[2] all the publications deal extensively with the treatment of DTC with a special focus on radioiodine therapy.

The guidelines / consensus reports by the European Thyroid Association[3,4] are especially helpful for the practitioner, since the risk classification and the description of procedures is closely related to routine clinically settings (Table 1).

INDICATIONS

Comprehensive retrospective long-term studies[6] with over 10 years of follow-up demonstrated a decrease in the frequency of locoregional recurrences and disease-associated mortality.

The American Thyroid Association[1] recommends I-131 ablation in patients age < 45 years only in the presence of distant metastases, and in patients age ≥ 45 years, if tumor stage is T2-4, N0-1, M0-1. In contrast, the European Thyroid Association[3,4] advocates routine ablation for stages T3/T4, N1 or M1 disease and defines a relative indication in young patients (below age 18 years) and in primary tumors between 1 and 2 cm in diameter without lymph node or distant metastases.

Although, some retrospective follow-up studies showed a reduction of the locoregional recurrence rate after adjuvant ablative radioiodine therapy in unifocal, papillary carcinomas with a diameter ≤ 1,[7] the procedure seems not to be justified in the very-low-risk group. A recent study, however, reported a significantly increased probability of lymphogenic micrometastases in papillary thyroid cancer above a tumor diameter cut-off of 5 mm.[8] After near-total thyroidectomy, adjuvant radioiodine therapy may facilitate follow-up procedures and should be individually evaluated[9] taking into account other relevant patient specific prognostic factors. The same holds true, although rarely encountered, for small follicular thyroid cancers.[8,10]

PROCEDURES

Pretherapeutic Imaging

The application of a diagnostic activity of I-131 before radioiodine treatment may induce "stunning" that is, reduced uptake or altered kinetics of I-131 during subsequent radioiodine therapy, which may substantially impair the efficacy of that therapy.[11] Therefore the use diagnostic activities exceeding 10-20 MBq for pretherapeutic scanning should be avoided before ablation. Alternatively, 24-hour uptake measurements with low I-131 activities (< 10 MBq) may be performed in an attempt to roughly estimate the thyroid remnant volume.[3,4] Because I-123 is a pure gamma emitter, this radionuclide is routinely used in some institutions to substitute I-131. Due to the relatively short half-life (13.2 hours) late scans (i.e. > 24 hours after administration) is not the rule.

Recently, I-124 (half-life 4.2 days) positron emission tomography (PET) has been introduced by some groups with special interest in pretherapeutic dosimetry.[12]

TSH Stimulation [Recombinant Human TSH (rhTSH), Thyroid Hormone Withdrawal (THW)]

Adequate uptake of a radioiodine in thyroid remnants or tumor tissue is dependent on serum TSH levels above 30 mU/l; this may be accomplished by two different modes:

- Endogenous TSH stimulation induced by withholding levothyroxine for approximately 3 weeks.[13] In an attempt to mitigate hypothyroid symptoms, some authors recommend

intermittent administration of short-lived T3 (pharmacological half-life approximately 10 hours) for 1-2 weeks.
- Exogenous TSH stimulation by rhTSH injection while patients remain on T4 therapy.

In the past, TSH elevation has been achieved by weeks-long thyroid hormone withdrawal (i.e. temporarily stopping thyroid hormone therapy) or withholding (i.e. delaying starting thyroid hormone therapy after thyroidectomy). Thyroid hormone withdrawal or withholding, however, renders patients clinically hypothyroid, a state that frequently induces morbidity that can have important negative effects on patients' ability to work, study and pursue leisure activities, on their quality-of-life (QOL) and on their concomitant psychological, cardiac, cerebrovascular, lipidemic, renal and other disorders.

Recombinant, human thyroid-stimulating hormone was developed to provide TSH elevation to stimulate radioiodine uptake, Tg secretion, or both while sparing patients THW and consequent hypothyroid morbidity and QOL impairment.

A randomized prospective Phase III study in mainly low-risk patients proved that a standard activity of 3.7 GBq I-131 induced comparable ablation rates of approximately 86% after endogenous (TSH >25 mU/l after THW) or 96% after exogenous TSH-stimulation (two consecutive daily IM injections of rhTSH, 0.9 mg). These rates were obtained when successful ablation was defined as the combination of radioiodine neck uptake < 0.1% on a diagnostic WBS and of serum Tg < 2 ng/ml under rhTSH stimulation at 8 ± 1 months after ablation.[14] Long-term follow-up of the patients enrolled in this pivotal trial also demonstrated a favorable outcome.[15]

Very likely because of improved renal function and, as a consequence, more rapid excretion of peripheral I-131 under euthyroid versus hypothyroid conditions, rhTSH appears to decrease radiation exposure (-35% on average) of extrathyroidal tissues and blood after radioiodine therapy. This decreased exposure potentially may reduce length of stay under radioprotection conditions, the long-term risk of second primary malignancies, or both. rhTSH administration also provides more rapid and predictable TSH elevation than does THW.[16-18]

Based on pharmacoeconomic model calculations from a societal perspective rhTSH as compared to THW resulted in a gain of 0.05 quality adjusted life years (QALYs) per course, which was mainly due to less time off work and an extrapolated lower rate of secondary malignancies.[19] In addition, short-term hypothyroidism secondary to T4 withholding after thyroidectomy leads to disturbances of lipid metabolism and increased arteriosclerotic risk.[20]

Since rhTSH is not approved up for radioiodine treatment of metastases, endogenous TSH stimulation currently should be preferred in high-risk patients, especially when histopathology, clinical status or imaging procedures are suspicious for metastatic spread.[3,4] On the other hand, a recent retrospective analysis from the Memorial Sloan-Kettering Cancer Center[21] included a higher-risk population than the pivotal Phase III trial, demonstrating that, with a median 2.5 years of follow-up, rhTSH- and withdrawal-aided ablation were associated with statistically not different, low rates of clinical recurrence.

Radioiodine Activities for Thyroid Remnant Ablation

The amount of activity which should be administered for radioiodine therapy is still a matter of debate and reported data are somewhat conflicting; randomized trials that are currently underway in Great-Britain and France might give an answer to this question. Some approaches also use a patient-specific tailoring of the activity based on the radiation absorbed dose to the blood or the target dose to the lesion(s). Presently, no data correlating the whole body absorbed dose to radiation induced cancer risk are available. The importance of blood based dosimetry, however, is to avoid unwanted bone marrow toxicity when treating patients. In the widely used range of 1 GBq to 3.7 GBq I-131, higher activities seem to coincide with higher success rates.[6] A recent prospective, randomized, controlled investigation[22] suggests that rhTSH-aided ablation with 1.85 GBq of I-131 may achieve a statistically noninferior ablation success rate to that accomplished with rhTSH-aided ablation using 3.7 GBq, even in the presence of node metastases. Two prospective trials[23,24] suggested equivalent ablation success rates with rhTSH-aided versus withdrawal-aided ablation using 1.1 GBq, whereas, another investigation did not show similar findings.[25]

If higher radioiodine activities, e.g. > 11 GBq, are considered for treatment, dosimetric approaches should be used to estimate the radiation dose to the blood, to ensure that this dose not exceed 2 Gy, a generally accepted safety limit to avoid serious myelotoxicity.[26-28]

Low-iodine Diet

A low-iodine diet for 2-3 weeks before iodine administration is strongly recommended, even more important is the avoidance of iodine-containing drugs (e.g. X-ray contrast media, reagents for disinfection, ophthalmologic agents, amiodarone, iodide medication) or food or food additives with high iodine content (e.g. seaweed, kelp, dietary supplements).[1,3,29]

Family Planning

Use of effective contraception over the 6-12 months following radioiodine therapy is recommended to avoid pregnancy in female patients of child-bearing age. If conception occurs during this period, the rates of early deliveries and still births seem to be higher as compared to conception $\geq$ 12 months after radioiodine therapy.[30] In male patients, the quality of sperm may be transiently reduced.[31] Due to the 4-month lifespan of spermatozoa, it is recommended to avoid procreation for that interval after ablation. Additionally, if higher cumulative therapeutic activities of radioiodine (> 15 GBq) are expected, cryoconservation of sperm should be considered.[32] Females seem to experience lesser impairment of gonadal function and

fertility.[30,33] Sufficient hydration with frequent voiding reduces radiation exposure of the reproductive organs in both females and males.

Post-therapeutic I-131 Whole Body Scan (WBS)

Performing a WBS 4-6 days after administration of therapeutic activities of I-131 (or even earlier in cases with exogenous TSH stimulation) is mandatory for definitive staging of DTC. Hybrid imaging using single-photon-emission computer tomography (SPECT) in conjunction with computed tomography (CT) has been shown improve the sensitivity of post-therapy scans as compared to conventional planar imaging.[34,35]

RADIOIODINE TREATMENT OF METASTASES

In patients with metastases a multidisciplinary sequential approach is crucial. Surgery, external beam radiation therapy or "novel targeted therapies" or chemotherapy alone or in combination are valuable options.

The results of radioiodine therapy depend on tumor volume and grade of differentiation.[36] I-131 therapy may well prove feasible in a palliative setting with inoperable tumors; again individual dosimetry could be chosen to safely administer maximal tolerated activities.[37-39]

Frequently, young patients with lung metastases of papillary thyroid cancer present with micronodular, disseminated lesions showing intense radioiodine uptake.[40-42] Higher activities of radioiodine should be administered in intervals of 6-12 months, since complete remissions are often achievable, but radiation pneumonitis or fibrosis may be rare complications. In this setting prophylactic steroids should be recommended. In adult patients with follicular thyroid cancer and macronodular lung metastases complete remissions are rare.[41-43]

Criteria for the definition of appropriate treatment strategies in patients with bone metastases are the risk of pathological fractures or neurological complications, the degree of bone pain and the avidity of radioiodine uptake. Complete surgical resection of solitary bone metastases has a better outcome compared to palliative radioiodine treatment.[42,44,45]

In patients with brain metastases, neurosurgical removal of the lesions is the primary option, independent of radioiodine uptake.[46,47]

In patients with metastases, possible complications, e.g. swelling of tumor masses or tumor progression after THW, are limitations for repeated courses of THW-aided radioiodine therapy. In addition, patients with metastases not infrequently refuse repeated courses of radioiodine after THW because of negative impact on the quality of life or severe co-morbidities. In this subgroup radioiodine therapy after exogenous stimulation with rhTSH is an option.[48]

Endogenous TSH stimulation after THW as well as exogenous stimulation by rhTSH may lead an increased tumor volume and edema.[49] In cases of metastatic disease in confined spaces with a risk for compression symptoms, anti-inflammatory premedication is strongly recommended.[5]

For the assessment of metastatic disease, especially in non-iodine avid cases, current algorithms advocate the use FDG-PET to localize tumor foci.[50,51]

CONTRAINDICATIONS FOR RADIOIODINE TREATMENT

Absolute contraindications include pregnancy and lactation. To minimize radiation exposure breastfeeding should be stopped at least 6-8 weeks before radioiodine therapy.

Relative contraindications for radioiodine therapy in patients with thyroid cancer include:

- High-grade bone marrow depression in cases of treatment with high activities of radioiodine
- Considerable reduction of pulmonary function in patients with lung metastases and high radioiodine uptake
- Considerable xerostomia due to proven impairment of salivary gland function.

SIDE EFFECTS OF RADIOIODINE THERAPY

The most frequent permanent side effect of "high-dose" radioiodine therapy is xerostomia due to chronic sialadenitis sometimes leading to a loss of taste and an increased risk of caries.

Nonpermanent early side effects of radioiodine treatment include administered, local neck pain and swelling, sialadenitis and gastritis.

A meta-analysis from Sweden, France and Italy showed a small, dose-dependent increase in the incidence of secondary solid tumors (of the bone, soft tissues, colon, rectum, or salivary glands) and leukemia[52] after high cumulative therapeutic activities (>22 GBq) of I-131. In contrast, a recent American cohort study from the Surveillance, Epidemiology and End Results Registry, that included 10,000 patients and 19,000 control cases, failed to find any increased risk for secondary tumor after radioiodine treatment.[53]

The benefits and potential risks for patients undergoing radioiodine therapy for treatment thyroid cancer, however must be carefully evaluated. High-risk patients with significant cumulative activities should be encouraged to follow age-related follow-up procedures for early diagnosis of secondary malignancies.[54]

REFERENCES

1. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:1-33.
2. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006;12:63-102.

3. Pacini F, Schlumberger M, Harmer C, et al. Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol 2005;153:651-59.
4. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
5. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008;35:1941-59.
6. Sawka AM, Thephamongkhol K, Brouwers M, et al. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3668-76.
7. Pelizzo MR, Boschin IM, Toniato A, et al. Natural history, diagnosis, treatment and outcome of papillary thyroid microcarcinoma (PTMC): a monoinstitutional 12-year experience. Nucl Med Commun 2004;25:547-52.
8. Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. Cancer 2005;103:2269-73.
9. Dietlein M, Dressler J, Escher W, et al. Procedure guidelines for radioiodine therapy of differentiated thyroid cancer (version 3). [German]. Nuklearmedizin 2007;46:213-19.
10. Rahbar K, Hutzenlaub V, Fischer RJ, et al. Comparative study on the radioiodine ablation in small papillary and follicular thyroid carcinomas (≤ 1cm). Nuklearmedizin 2008;47:179-80.
11. Lassmann M, Luster M, Hänscheid H, Reiners C. Impact of ^{131}I diagnostic activities on the biokinetics of thyroid remnants. J Nucl Med 2004;45:619-25.
12. Stahl AR, Freudenberg L, Bockisch A, Jentzen W. A novel view on dosimetry-related radionuclide therapy: Presentation of a calculatory model and its implementation for radioiodine therapy of metastasized differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 2009;36:1147-55.
13. Serhal DI, Nasrallah MP, Arafah BM. Rapid rise in serum thyrotropin concentrations after thyroidectomy or withdrawal of suppressive thyroxine therapy in preparation for radioactive iodine administration to patients with differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3285-89.
14. Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: Results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91:926-32.
15. Elisei R, Schlumberger M, Driedger A, et al. Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. J Clin Endocrinol Metab Oct 2009;22. Epub ahead of print.
16. Haenscheid H, Lassmann M, Luster M, et al. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: Procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 2006;47:648-54.
17. Luster M, Sherman SI, Skarulis MC, et al. Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone (rhTSH) and after thyroid hormone withdrawal in thyroid carcinoma. Eur J Nucl Med Mol Imaging 2003;30:1371-77.
18. Löffler M, Weckesser M, Franzius C, et al. Iodine excretion during stimulation with rhTSH in differentiated thyroid carcinoma. Nuklearmedizin 2003;42:240-43.
19. Mernagh P, Campell S, Dietlein M, et al. Cost-effectiveness of using recombinant human TSH (rhTSH) prior to radioiodine therapy ablation for thyroid cancer, compared with treating patients in a hypothyroid state: The German perspective. Eur J Endocrinol 2006;155:405-14.
20. Duntas LH, Biondi B. Short-term hypothyroidism afte Levothyroxine-withdrawal in patients with differentiated thyroid cancer: Clinical and quality of life consequences. Eur J Endocinol 2007;156:13-19.
21. Tuttle RM, Brokhin M, Omry G, et al. Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med 2008;49:764-70.
22. Pilli T, Brianzoni E, Capoccetti F, et al. A comparison of 1850 (50 mCi) and 3700 (100 mCi) 131-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3542-46.
23. Barbaro D, Boni G, Meucci G, et al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: Effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. J Clin Endocrinol 2003;88:4110-15.
24. Barbaro D, et al. Recombinant human thyroid-stimulating hormone is effective for radioiodine ablation of post-surgical thyroid remnants. Nucl Med Commun 2006;27:627-32.
25. Pacini, et al. Ablation of thyroid remnants with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. J Clin Endocrinol Metab 2002;87:4063-68.
26. Lassmann M, Hänscheid H. Spatial dose mapping for individualizing radioiodine treatment. J Nucl Med 2007;48:2-4.
27. Lassmann M, Hänscheid H, Chiesa C, et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: Blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging 2008;35:1405-12.
28. Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. AJR 1962;87:171.
29. Maxon HR, Thomas SR, Boehringer A, et al. Low iodine diet in I-131 ablation of thyroid remnants. Clin Nucl Med 1983;8:123-26.
30. Schlumberger M, De Vathaire F, Ceccarelli C, et al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. J Nucl Med 1996;37:606-12.
31. Krassas GE, Pontikides N. Gonadal effect of radiation from ^{131}I in male patients with thyroid carcinoma. Arch Androl 2005;51:171-75.
32. Ceccarelli C, Battisti P, Gasperi M, et al. Radiation dose to the testes after ^{131}I therapy for ablation of postsurgical remnants in patients with differentiated thyroid cancer. J Nucl Med 1999;40:1716-21.

33. Dottorini ME, Lomuscio G, Mazzucchelli L, et al. Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. J Nucl Med 1995;36:21-27.
34. Tharp K, Israel O, Hausmann J, et al. Impact of I-131-SPECT/CT images obtained with an integrated system in the follow-up of patients with thyroid carcinoma. Eur J Nucl Med Mol Imaging 2004;31:1435-42.
35. Aide N, Heutte N, Rame JP, et al. Clinical relevance of single-photon emission computed tomography/computed tomography of the neck and thorax in postablation (131)I scintigraphy for thyroid cancer. J Clin Endocrinol Metab 2009;9:2075-84.
36. Durante C, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892-99.
37. van Nostrand D, Atkins F, Yeganeh F, et al. Dosimetrically determined doses of radioiodine for the treatment of metastatic thyroid carcinoma. Thyroid 2002;12:121-34.
38. Dorn R, Kopp J, Vogt H, et al. Dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer : Largest safe dose using a risk-adapted approach. J Nucl Med 2003;44:451-60.
39. Tuttle RM, Leboeuf R, Robbins RJ, et al. Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. J Nucl Med 2006;47:1587-1591. Erratum in: J Nucl Med 2007;48:7.
40. Ilgan S, Karacalioglu AO, Pabuscu Y, et al. Iodine-131 treatment and high-resolution CT: Results in patients with lung metastases from differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 2004;3:825-30.
41. Ronga G, Filesi M, Montesano T, et al. Lung metastases from differentiated thyroid carcinoma. A 40 years' experience. Q J Nucl Med Mol Imaging 2004;48:12-19.
42. Schlumberger, M, Challeton C, De Vathaire F, et al. Radioactive iodine treatment for lung and bone metastases from thyroid carcinoma. J Nucl Med 1996;37:598-605.
43. Reiners C. Radioiodine therapy in patients with pulmonary metastases of thyroid cancer: when to treat, when not to treat? Eur J Nucl Med Mol Imaging 2003;30:939-42.
44. Bernier MO, Leenhardt L, Hoang C, et al. Survival and therapeutic modalities in patients with bone metastases of differentiated thyroid carcinomas. J Clin Endocrinol Metab 2001;86:1568-73.
45. Zettinig G, Fueger BJ, Passler C, et al. Long-term follow-up of patients with bone metastases from differentiated thyroid carcinoma – surgery or conventional therapy? Clin Endocrinol (Oxf) 2002;56:377-82.
46. Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab 1997;82:3637-42.
47. McWilliams RR, Giannini C, Hay ID, et al. Management of brain metastases from thyroid carcinoma: A study of 16 histopathologically confirmed cases over 25 years. Cancer 2003;98:356-62.
48. Luster M, Lippi F, Jarzab B, et al. rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: A comprehensive review. Endocr Relat Cancer 2005;12:49-64.
49. Braga M, Ringel MD, Cooper DS. Sudden enlargement of local recurrent thyroid tumor after recombinant human TSH administration. J Clin Endocrinol Metab 2001;86:5148-51.
50. Leboulleux S, Schroeder PR, Schlumberger M, Ladenson PW. The role of PET in follow-up of patients treated for differentiated epithelial thyroid cancers. Nat Clin Pract Endocrinol Metab 2007;3:112-21.
51. Zoller M, Kohlfuerst S, Igerc I, et al. Combined PET/CT in the follow-up of differentiated thyroid carcinoma: What is the impact of each modality? Eur J Nucl Med Mol Imaging 2007;34:487-95.
52. Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancy in thyroid cancer patients. Br J Cancer 2003;89:1638-44.
53. Bhattacharyya N, Chien W. Risk of second primary malignancy after radioactive iodine treatment for differentiated thyroid carcinoma. Annals of Otology Rhinol Laryngol 2006;115:607-10.
54. Kumagai A, Reiners C, Drozd V, Yamashita S. Childhood thyroid cancers and radioactive iodine therapy: Necessity of precautious radiation health risk management. Endocr J 2007;54:839-47.