^{131}I Therapy for Treatment of Differentiated Thyroid Carcinoma

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1. Introduction

Differentiated thyroid carcinoma comprises papillary and follicular thyroid carcinomas. The mixed papillary/follicular type is regarded on (cyto)pathological grounds as papillary thyroid carcinoma and behaves clinically as such. The incidence of clinically manifest differentiated thyroid carcinoma in The Netherlands ranges from 2 to 4 per 100.000 inhabitants per annum. The relative frequency of papillary thyroid carcinoma is ± 65%, that of the follicular thyroid carcinoma ±15%. The remainder consists of medullary carcinoma (±10%) and anaplastic thyroid carcinoma (±10%), which has not changed over the years. Papillary thyroid carcinoma occurs primarily in patients aged between 10 and 60 years and follicular thyroid carcinoma is primarily seen between the ages of 30 and 70 years. With adequate treatment the 10-year survival rates are respectively 85-95% and 50-70%. Treatment of well differentiated thyroid carcinoma consists primarily of a (near) total thyroidectomy followed by an ablative dose of radioactive iodine (^{131}I). Hemi-thyroidectomy alone may only be considered in very small (<1 cm), unifocal, papillary thyroid carcinomas without metastases (pT1N0M0). In such cases, ablation is not indicated.

The aim of ablation with ^{131}I is to ensure that all remaining thyroid tissue is eliminated, so that on follow-up reliable use can be made of the thyroglobulin concentration (Tg) in the serum. Also, the post-ablative total body scintigraphy (approximately one week after administration of the ablation dose) can provide information about any existing ^{131}I-accumulating metastases and is therefore used for staging. Ablation with ^{131}I should take place about 4-6 weeks after the total thyroidectomy. To guarantee a sufficiently high TSH level (TSH > 30 mU/L) the patient receives no thyroid hormone supplementation during this period. In low-risk thyroid cancer patients, TSH stimulation can be achieved by the administration of recombinant TSH (rhTSH).

Prior to the ablation, a post-operative scintigraphy can be made. In so doing, either ^{123}I (185-370 MBq) or a low dose of ^{131}I (< 74 MBq) should be used. There is little evidence in support of the usefulness of making a pre-ablation scintigraphy. In recent studies, the usefulness of the pre-ablation scintigraphy has been brought into question, because it is rarely negative (no iodine accumulation in the thyroid bed or elsewhere) and following on from that, virtually all patients receive an ablative dose of ^{131}I. Furthermore, by administration of diagnostic quantities of ^{131}I, stunning can occur, consequently reducing the uptake of the subsequent ablative dose of ^{131}I and decreasing the effectiveness of the ablation. Significant stunning can be prevented by using a small amount of ^{131}I (< 74 MBq) or by using ^{123}I. After using a diagnostic amount of ^{123}I, (minor) stunning was seen in just one study. The relevant authors attributed this to self-stunning, i.e. stunning by the therapy dose itself, and not to the previously administered diagnostic quantity of ^{123}I.

The pre-ablation scintigraphy can be useful if one has doubts about the completeness of the (near) total thyroidectomy. If a great deal of residual activity is found, repeat surgery should be considered, although this is generally regarded as a challenge.

Treatment with ^{131}I is most effective with small amounts of thyroid and/or thyroid carcinoma tissue. Indeed, the larger the remnant, the higher the chance of additional treatments being required. In recent studies, it has been shown that in low-risk thyroid cancer patients 1100 MBq ^{131}I achieves complete ablation in a majority of the patients. In high-risk patients, higher activity is recommended.

Metastases of differentiated thyroid carcinoma generally have good uptake of iodine. In terms of survival rates, the benefit of ^{131}I cannot be demonstrated by prospective controlled trials. Schlumberger described the largest retrospective series (n=283 and n=394). These showed that the ability to take up ^{131}I is an important prognostic factor. The 10-year survival rate in patients with iodine-absorbing metastases was 54%, while it was only 9% in patients who had no ^{131}I uptake (p=0,0001). It also appeared that ^{131}I had less impact on bone metastases than on lung metastases (10-year survival rate 27% versus 57%, p=0,0001). Consequently, in the treatment of bone metastases, where possible, radical surgery is preferable, and other treatments such as external radiotherapy and embolization can be considered. Patients with bone metastases removed through radical surgery, were reported to have a better survival rate (n=41). Bernier confirmed this in a larger group of patients (n=109). The 5-, 10- and 20-year survival rates in this group with bone metastases was 41%, 15% and 7% respectively. In an early stage and where there are still few bone metastases, ^{131}I can bring about a cure, especially in young patients. The treatment of lung metastases is most effective in so-called micronodular metastases, namely lung metastases that are so small that they are not yet visible on an ordinary chest x-ray. Macronodular metastases, has a poorer prognosis. In the Schlumberger series, the 10-year survival rate for micronodular metastases appears to have been as high as 95%. The prognosis of patients with metastases is therefore determined, to a significant extent, by this ability to absorb ^{131}I. It is also important to give ^{131}I treatment as early as possible in the phase in which the metastases are still small. There are no good systemic alternatives for the treatment of metastatic disease. Because treatment with ^{131}I is a relatively safe form of therapy, after surgical treatment, this should be the treatment of choice. Also, when pathological lymphomas cannot be surgically removed, ^{131}I should be considered. Pacini reported a cure rate of over 75% in patients with lymph node metastases who were treated with ^{131}I. The dose given is generally 5550-7400 MBq (150-200 mCi) and is continued until remission is achieved or until there is no further iodine uptake in the tumour. In patients with recurrent disease in the head and neck region, retreatment with ^{131}I after surgery is questionable, especially when normalization of Tg-levels has been achieved.
Treatment with ^{131}I is also effective in children and should be considered, especially when there are lung metastases. Isolated bone metastases in this group are also preferably treated surgically. The time interval between ^{131}I treatments is usually 4 to 6 months. Even if ^{131}I is persistently absorbed in the tumour, treatment with ^{131}I is nonetheless warranted because it affords the possibility of prolonged palliation. Where there is strong progression under ^{131}I treatment, further treatment with ^{131}I must be abandoned.

Although ^{131}I is a relatively safe form of therapy, a slightly increased risk of second primary malignancies is nonetheless described (14,4 solid tumours and 0,8 cases of leukemia per GBq of ^{131}I at 105 patient years of follow-up). The necessity for treatment must therefore be constantly weighed up against these risks. In recent reports, a maximum of 22,2 GBq of ^{131}I has been described.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

- Ablation of thyroid (carcinoma) residues after (near) total thyroidectomy
- Treatment of iodine-absorbing recurrences or metastases of differentiated thyroid carcinoma
- Treatment of inoperable iodine-absorbing differentiated thyroid carcinoma

4. Relation to other therapies

Over the past years, many tracers and techniques have become available for the initial staging and the detection of recurrent differentiated thyroid cancer.
Gamma-camera based procedure: Many studies have appeared that relate to the sensitivity and specificity of thallium (^{201}Tl), sestamibi (or tetrofosmin) for the detection of recurrences in the neck or distant metastases of differentiated thyroid carcinoma. However, the set-up for most of these studies can be criticised in some respect, such as too small or selected patient populations, lack of or inconsistent and blind use of a gold standard. Routine use of the aforementioned nuclear imaging in the follow-up of patients with differentiated thyroid carcinoma is not sufficiently supported scientifically. However, the aforementioned nuclear techniques can be usefully employed in those patients suspected of having recurrence or metastases of differentiated thyroid carcinoma on the basis of an elevated thyroglobulin level, but in whom a whole body scan with ^{131}I (preferably in a therapeutic dose) yields no localisation. In this setting sestamibi/ tetrofosmin, thallium and FDG-PET may be used. As far as can be judged, the tracers sestamibi, tetofosmin and thallium do not differ from each other a great deal as far as precision is concerned. Advantages of the ^{99m}Tc tracers sestamibi and tetrofosmin relative to thallium are a better image quality (due to the higher energy of ^{99m}Tc than of thallium) and the possibility of administering much higher doses. In patients with Hurthle cell carcinoma, sestamibi is also a good choice because of the accumulation of sestamibi in mitochondria which are present in relatively high density in Hurthle cell carcinoma. Octreotide scintigraphy for the localization of recurrences/metastases of differentiated thyroid carcinoma has been researched in a number of studies. Its sensitivity appears to be limited. Should experimental therapy with radiolabelled octreotide be considered in otherwise end-stage patients, preliminary octreotide scintigraphy is of course a necessity. In all other cases, the afore mentioned tracers would appear to be preferable. Because of the predominantly osteolytic character of skeletal metastases of thyroid carcinoma, the sensitivity of the bone scintigraphy is inadequate for it to be adopted in the routine follow-up of these patients. If there are skeletal pains, then this should of course be considered.

PET based procedure: Over the past year, FDG-PET has gained significance in detecting and localizing tumour recurrence. The sensitivity of FDG-PET may possibly be greater specifically in distant metastases, especially in patients with elevated Tg-levels and normal ^{131}I total body scans. This so-called flip-flop phenomenon, no ^{131}I uptake and increased FDG uptake, is regarded as sign of dedifferentiation. In this respect, FDG-uptake is correlated with prognosis, in which high standardized uptake values (SUV) correlate with poor outcome. It is preferable for FDG-PET to be performed under TSH stimulation, because in those circumstances its sensitivity is higher and more lesions are depicted than without TSH stimulation. Recently, ^{124}I has been introduced in re-staging differentiated thyroid cancer. ^{124}I-PET proved to be a superior diagnostic tool as compared to low-dose diagnostic ^{131}I scans and adequately predicted findings on subsequent high-dose post-treatment ^{131}I scans. In addition, due to the option of quantification, it might become an additional tool for dosimetry in ^{131}I therapy. Data in literature, however, are still too limited to support a definite role.

5. Medical information necessary for planning

- Relevant prior medical history, date of surgery, contra-indications for thyroid hormone withdrawal. Neurological symptoms caused by metastases
- Report of operation
- Pathological anatomical data (histology, tumour size, growth through the encapsulation, angio-invasion, lymph node metastases)
- Medication use
- Preliminary X-ray (take care iodinated contrast agents!)
- Serum levels of TSH, FT4, thyroglobulin and possibly thyroglobulin antibodies

6. Radiopharmaceutical

Preparation:	Sodium ^{131}I
Nuclide:	Iodine-131
Administration:	Orally or intravenously
Characteristics:	^{131}I decays to the stable Xenon-131 under emission of beta radiation (in 90% of the disintegrations with an average energy of 192 keV) with an average tissue penetration of 0,5 mm (maximum penetration in tissue 2 mm). The physical half-life is 8,0 days

Kinetics: After oral administration, 90% is absorbed via the intestine within 1 h. Excretion takes place primarily with the urine, but also with the faeces (purge, if necessary, at high doses because of radiation exposure of the gut and to promote the interpretability of the post-therapy scintigram). The maximum uptake in the tumour is reached after approximately 12 to 24 h. The biological half-life can be estimated at 4 days. The effective half-life is 2,7 days. When rhTSH is used for stimulation, different kinetics are expected resulting in a more rapid excretion from the body of circulating ^{131}I. Due to this, side-effects as dysfunction of lacrimal and salivary glands may be minimized.

Activity: In the CBO consensus of 2014, the following dosage regimens are recommended: [CBO = Centraal Begeleidings Orgaan - Kwaliteitsinstituut voor de

gezondheidszorg, institution responsible for the quality of healthcare].

- Ablation activity: For ablation of normal thyroid tissue, a standard activity of 1100-1850 MBq of ^{131}I is recommended. In T3-4 tumours, the presence of lymph node metastases and/or non-radical resection of primary tumours, a standard activity of 3700 - 7400 MBq of ^{131}I is advised. With calculated activity: a dose of ≥300 Gy per gram of thyroid tissue should be achieved.
- Therapeutic doses in metastases which continue to absorb radiation after previous ablation: 5550-7400 MBq of ^{131}I is recommended.

7. Radiation safety

Contraindications

Absolute contraindications are pregnancy and breast-feeding.

A relative contraindication is an insufficiently high serum TSH level (<30 mU/l) after at least 4 weeks of thyroid hormone withdrawal or after rhTSH stimulation. In this situation, treatment should be postponed.

a. Short-term side-effects

- Sialadenitis: Transient sialadenitis occurs quite frequently after a treatment with a high activity of ^{131}I (±10%). The cause is the high concentration of ^{131}I in the salivary glands. Symptoms are pain and swelling in the first three days after therapy. Sometimes patients complain about a dry mouth and a metallic taste that may last from several weeks to months. The excretion of ^{131}I from the salivary glands after the administration of a therapeutic dose is stimulated by allowing patients to eat sweets or other products that stimulate saliva production, but this should be initiated not earlier than 1 day after the administration of ^{131}I.
- Gastrointestinal symptoms: Ten to sixty percent of patients treated with high activity ^{131}I (5500-7400 MBq) will suffer from radiation-induced gastritis, characterized by nausea, sometimes leading to vomiting. These symptoms usually begin 8 h after administration , can last 2 to 3 days and are easily treated with anti-emetics.
- Local effects: A high dose of ^{131}I can lead to a radiation thyroiditis, if there is still a lot of residual tissue present. This presents a few days after therapy with a painful, sometimes red neck. The pain may spread to the ear. Aspirin is often an effective treatment. In some cases, corticosteroids are indicated.
- Edema: In the case of brain metastases, ^{131}I treatment may lead to edema. Therefore, major cerebral metastases must preferably first be treated neurosurgically with the aid of external radiotherapy. If, after all, ^{131}I is primarily decided upon, the patient must be pre-treated with corticosteroids, mannitol or glycerol to prevent edema.
- Myelosuppression: Myelosuppression may occur one month after the administration of ^{131}I. This myelosuppression is mild and reversible. Myelosuppression is more frequently seen in patients with a high cumulative dose and where there is extensive skeletal metastasis.

b. Long-term side-effects

- The emergence of second primary malignancies The most recent publication reported a slightly increased risk of second primary malignancies (14,4 solid tumours

and 0,8 cases of leukemia per GBq ^{131}I and per 105 patient years of follow-up). The necessity for treatment must therefore be constantly weighed off against these risks.

- Genetic effects and effects on fertility:
  Females: Casara described 70 women who were treated for thyroid carcinoma with high dose ^{131}I and became pregnant after a mean period of 5,3 ± 2,8 years. No increased incidence of miscarriages or malformations was found. The cumulative doses ranged from 1,85 to 16,55 GBq of ^{131}I. However, in a single study by Sawka et al. , an increased risk on miscarriages was observed in the first year after treatment. Therefore, despite limited data, pregnancy should be avoided within the first year after initial therapy according to the recently updated CBO consensus. Especially in high-risk patients it may also interfere with risk stratification and subsequent treatment.
  Males: High doses of ^{131}I can, in rare cases, lead to (reversible) azoospermia or testicular atrophy. This occurs mostly with very high doses and/or with metastases in the pelvic area, but in some cases it has been observed already after one administration. Therefore, this aspect should be discussed with all male patients and cryo-preservation should be offered in all cases prior to treatment. Given the short timeframe of spermatogenesis, it will be sufficient to advise a male patient against reproduction for a period of 4 months.

8. Patient preparation

Standard care prior to ^{131}I therapy:

a. Stopping levothyroxine Iodine uptake in the thyroid (carcinoma) tissue depends on the TSH level in the serum. To obtain sufficient TSH stimulation (TSH > 30 mU/l), the patient should stop taking levothyroxine at least 3 weeks prior to a diagnostic scintigram with radioactive iodine or before treatment with ^{131}I. If the hypothyroid phase is poorly tolerated by the patient, triiodothyronine (Cytomel®, for example 0,0125 mg t.d.s.) may be given after stopping levothyroxine until 14 days before the ^{131}I treatment. An alternative for TSH stimulated ablation in low-risk patients is the use of rhTSH. The standard dose is 0,9 mg i.m. per day, administered on day 1 and 2 followed by ^{131}I therapy on day 3. Recombinant TSH has already been registered for diagnostic use and for ablation; it can also be extremely useful for therapeutic use in selected patients.
b. Both when diagnosing patients with suspected thyroid carcinoma and when monitoring patients with thyroid carcinoma, administration of iodinated x-ray contrast agents (CT scan with iodinated contrast!) must be avoided. This makes treatment with ^{131}I over a long period of time impossible due to the blocking effect which the excess iodine in the contrast materials has upon the uptake of ^{131}I.
c. Prior to the ablation, a post-operative scintigram can be made. In so doing, either ^{123}I (185-370 MBq) or a low dose of ^{131}I (< 74 MBq) should be used. A post-operative scan is recommended in case there is doubt about the completeness of thyroid resection and, consequently, adaptation of the treatment activity can be expected.
d. Limitation of dietary iodine: An iodine-restricted diet (see appendix), can double the effective tumour dose in favorable circumstances. It is therefore desirable to give patients an iodine-restricted diet from four days before treatment with ^{131}I and to

continue this for at least one day after administration of ^{131}I.

e. Laxatives: To reduce the radiation exposure of the intestine, it is recommended that purging be undertaken (e.g. with magnesium oxide) if patients suffer with constipation (stool less frequently than 1 to 2 times daily). This will also avoid the patient suffering from troublesome bowels during the post-therapeutic whole body scintigram.
f. Hydration: To reduce the absorbed dose of ^{131}I in the bladder wall and surrounding structures (gonads!) the patient must be advised to drink sufficiently (at least 2 l a day) during the admission.
g. Pregnancy test: Pregnancy is an absolute contraindication to treatment with ^{131}I. Just as in the case of ^{131}I therapy for hyperthyroidism, it is necessary in women of childbearing age to exclude pregnancy by means of a pregnancy test before administration of the therapeutic dose.

Standard care after ^{131}I therapy:

a. After a total thyroidectomy and ^{131}I ablation, levothyroxine is started. This is to ensure that the patient becomes euthyroid and that the TSH level is suppressed (TSH can encourage tumour growth in patients with thyroid carcinoma). Because the uptake of ^{131}I in thyroid (carcinoma) tissue is usually maximal after 12 to 24 h, on day 2 following administration of an ablation dose or a therapeutic dose of ^{131}I, patients may be started on a suppressive dose of levothyroxine (2-2,5 µg/kg body weight). In low-risk patients, a replacement dose of levothyroxine is also given. In older patients (> 60 years) and patients with cardiac problems in their medical history, the levothyroxine is administered in scheduled increases (e.g. 50-100-150 µg levothyroxine, increasing from week to week).
b. Approximately one week after any ablative or therapeutic activity of ^{131}I, a whole body scintigram must be performed using the ablative / therapeutic activity of ^{131}I. In this way, metastases not yet known can be visualized and the iodide uptake of known metastases evaluated.
c. Discharge from the therapy department is only allowed with a dose rate < 20 microSv/hr at 1m distance from the patient. Special precautions should be taken to avoid radiation exposure to members of the family, and especially to pregnant women and children.
d. Pregnancy should be avoided in the first year after initial treatment. In female patients with progressive thyroid cancer, it is recommended to prevent pregnancy

Follow-up:

Long-term follow-up of patients with differentiated thyroid carcinoma is indicated because recurrences may still occur many years after the initial treatment. In this respect, the diagnostic whole body scan after thyroid hormone withdrawal was the mainstay for monitoring patients with differentiated thyroid carcinoma. This was also true for the subgroup of patients with thyroid carcinoma who had a relatively good prognosis and low risk of recurrent thyroid carcinoma. The spectrum of patients with thyroid carcinoma has changed in recent years, because many carcinomas are being discovered earlier in their development. The majority of patients nowadays have a low risk of recurrence. In a majority of the patients presenting with recurrent disease, however, it is detected in the

head and neck region. As sensitivity of ultrasonography of the neck to detect locoregional nodal metastases of thyroid carcinoma appears, at least in specialized centers, to be high, it is currently regarded as the first imaging tool in the follow-up. In addition, it has become apparent that determination of the serum thyroglobulin level, especially where there is a high TSH level in the blood, is very sensitive for detection of recurrences and metastases of differentiated thyroid carcinoma. It is apparent that the sensitivity of the whole body scan with diagnostic quantities of ^{131}I (80-370 MBq) for the detection of recurrent thyroid carcinoma is limited. The aforementioned developments are incorporated in most updated guidelines on the follow-up after initial treatment of patients having differentiated thyroid carcinoma with a relatively good prognosis.
Three months after ablative therapy with ^{131}I, patients are definitively identified who have a relatively low risk of recurrent thyroid carcinoma. For them, the following criteria apply: patient aged 20-45 years, pT1-2 (no extrathyroidal extension), well differentiated histological type carcinoma (papillary thyroid carcinoma with the exception of a few aggressive variants, minimally invasive follicular thyroid carcinoma), complete resection of the primary tumour, thyroglobulin level at the time of ablation with ^{131}I relatively low and 3 months after ablation whilst under thyroid hormone suppression undetectable and no antibodies to thyroglobulin, no evidence of metastases in lymph nodes (N0) or at distance (M0), thus also not on whole body scan 3-7 days after the ablative treatment with ^{131}I.
In low-risk patients, thyroid cancer follow-up comprises a combination of (TSH stimulated) Tg measurement and ultrasonography of the head and neck region 6-12 months after ablation. Yearly follow-up is recommended when there is no indication for tumour recurrence. Since the risk on tumour recurrence after 5 year is in a range of 0,8-0,9%, further follow-up can be stopped after this initial period.

In patients not meeting criteria for a low risk of recurrence (thus including patients in whom antibodies to thyroglobulin have been demonstrated) must be followed up by means of physical examination, half-yearly determination of serum thyroglobulin levels whilst under thyroid hormone suppression and, in the first instance, an annual determination of the serum thyroglobulin level after TSH stimulation (ideally by means of withdrawal of thyroid hormone) and ultrasound of the neck.

Diagnostic, stimulated ^{131}I scintigraphy or ^{124}I PET can be recommended in patients with elevated Tg levels and negative ultrasonography, as well as in patients with normal testing but a high risk profile. In these patients, but also in patients with elevated or rising Tg levels with negative testing, CT/MRI of the neck/chest and/or FDG-PET should also be considered. If no abnormalities are found, the frequency of the aforementioned investigations can be reduced together with a reduction in the duration of follow-up.
In this respect, the exact role of ^{124}I PET/CT is still not established yet. Data so far has demonstrated little additional value

First follow-up in local hospital 3 months after ablative treatment consists of determining the thyroglobulin level whilst under thyroid hormone therapy, determination of TSH, FT4 and, if necessary. FT3, physical examination. If at this first follow-up whilst under thyroid hormone treatment no thyroglobulin and no thyroglobulin antibodies are detectable, approximately 6-12 months after the ablation, apart from a physical examination, an

additional ultrasound scan of the neck is done, during which a cytological puncture is taken from any abnormalities found. If there are any positive findings, neck surgery follows. Subsequent ^{131}I therapy should be given when Tg levels remain elevated thereafter followed by a post-treatment scintigram. When Tg levels normalize after surgery, the role of ^{131}I is not fully clarified. If the ultrasound does not reveal any abnormalities, a follow-up study then takes place in the center where the ablative therapy with ^{131}I took place. At this examination, and after withdrawal of thyroid hormone or after preparation by rhTSH (2 x 0,9 mg rhTSH intramuscularly) a thyroglobulin determination is carried out, if desired in combination with an ^{131}I diagnostic whole body scan with 185-370 MBq ^{131}I (or possibly ^{123}I). If no thyroglobulin is detectable at high TSH levels and there is no other evidence of recurrent or metastatic thyroid carcinoma, the patient remains under follow-up by his own consultant with an annual determination of TSH, FT4 and/or FT3, thyroglobulin and thyroglobulin-antibodies whilst under treatment with thyroid hormones, where indicated supplemented with an ultrasound of the neck. If thyroglobulin is detectable in a titre > 1 ng/ml, blind therapy with high dose of ^{131}I follows. If the post-therapy whole body scan shows no abnormalities, a PET investigation follows, preferably whilst under TSH stimulation, e.g. still in the hypothyroid phase. If this is also negative, the patient is initially followed up by means of a thyroglobulin determination whilst under thyroid hormone suppression together with a physical examination. When indicated, such as for example if there is an increase in thyroglobulin level, the procedure is repeated from the neck ultrasound onward. However, if in so doing a similarly increased thyroglobulin level is found, blind therapy with ^{131}I does not follow automatically. In this case additional imaging such as FDG PET and/or CT/MRI should also be considered. If thyroglobulin is detectable in a low concentration (0,3-1 ng/ml) and there are no other abnormalities, then the patient is initially followed up by thyroglobulin determinations whilst under thyroid hormone suppression together with a physical examination. If indicated, e.g. by an increase in the thyroglobulin levels > 5 ng/ml (expert opinion), the procedure as described above for Tg>1 ng/ml is followed.

9. Literature

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