Aus der Klinik und Poliklinik für Nuklearmedizin

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The course of differentiated thyroid carcinoma in patients in whom the initial I-131 ablative treatment was successful.

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Der Promovend ist Arzt

Contents

Introduction

Historical perspective

In 1942, Dr. Seidlin of the Memorial Hospital in New York was faced with a 51-year-old patient who had undergone a thyroidectomy in 1923 (1). At the time, the histologic diagnosis was a 'malignant adenoma' of the thyroid. In 1938 the patient returned with overt signs of "thyroid hyperfunction" (hyperthyroidism) and lower back pain. A metastasis was found in the lower spine, and surgically removed. Over the next years the patient remained hyperthyroid and developed more bone metastases. At the time of presentation to Dr. Seidlin, the patient was in an extremely poor condition: he was in severe pain, severely hyperthyroid, and severely underweight. At this time radioiodine therapy had just reached the clinical arena. In 1937 Hertz, Roberts and Evans investigated the rabbit's thyroid function using I-128 (2). Later they pursued therapeutic goals for e.g. Graves' disease using I-130. They used dosages that we now know would have been merely diagnostic if it were not for a probable 10% I-131 contaminant (3). Livingood and Seaborg identified I-131 as a separate isotope. In 1942 two groups independently reported on the successful treatment of hyperthyroidism with I-131 sodium iodide (4;5). Radioiodine was so rare that it was recovered from the urine, purified and re-administered to the patient. The patient responded favourably to the radioiodine treatment, and he received several more courses of I-131. Geiger-counter examination of the patient revealed two previously unknown metastases, thereby indicating the diagnostic capabilities of radioiodine. The patient did very well on these courses: the hyperthyroidism subsided, the body-weight kg increased from 38 to 53 kilograms, and the pains diminished.

This report of a potential cure for terminally ill patients fuelled the public imagination to a degree that it hit the political agenda. Effective on August 1, 1946, the Atomic Energy Act (AEA) made radioisotopes available for medical use in the USA. This date marks the beginning of 'atomic medicine', later named nuclear medicine.

Incidence of thyroid carcinoma

Thyroid carcinoma is more frequent in females than in males (see also *etiology*), with reported incidences of 1.2-2.6 per 100,000 in males and 2.0-3.8 per 100,000 in females (6). The incidence of thyroid carcinoma is increasing (7). The mean age of

onset is 45 years. Mortality varies from 0.2 to 1.2 per 100,000 in males and from 0.4 to 2.8 per 100,000 in females (6). These gender differences are most prominent in the reproductive period.

Etiology

The only clearly established external etiologic factor for thyroid cancer is irradiation of thyroid tissue (8-12), especially at a younger age (13). External electron-beam irradiation for benign or malignant disorders in the neck region during childhood results in an elevated risk of thyroid cancer, occurring at least 5 years after radiation; the risk remains elevated even 40 years after exposure (12). With increasing age at the time of exposure, this risk decreases significantly (little elevated risk if age >20 years). For age <15 years at the time of exposure a linear model best describes the dose response, even down to 0.1 Gy. At doses of >10 Gy, the risk appears to level off or decrease (12). Irradiation of the thyroid by exposure to high dosages of radioiodine also increases the risk of thyroid cancer (11;13;14), as became apparent after the Chernobyl accident. Especially in children the incidence rose dramatically after the incident (14;15).

Iodine deficiency is a less certain etiologic factor, although different ratios of papillary, follicular and anaplastic thyroid carcinoma have been established in iodine deficient and iodine sufficient populations (14;16;17).

Estrogens most likely play a pivotal role in the different incidence between male and (younger) female patients. Estrogens increase the expression of the cyclin D1 protein, mitogen-activated-protein (MAP) 1 and 2 kinases (18), and the anti-apoptotic Bcl-xL protein (19). Even though these are strong pointers to a cause of gender differences, estrogens most likely are not the only factor. In a case-control matched population study, limited support was found for the hypothesis that reproductive and hormonal exposures are responsible for the marked excess of thyroid cancer risk in adult females (20). To date no other mechanisms are known for the gender bias in thyroid cancer incidence.

Histology

Papillary thyroid cancer

PTC is an unencapsulated tumor with papillary and follicular structures; it is characterized by overlapping cell nuclei that have a ground-glass appearance and

longitudinal grooves, with invaginations of cytoplasm into the nuclei (21;22). Variations include encapsulated, follicular, tall-cell, columnar cell, clear-cell, diffuse sclerosing, solid or trabecular, oxyphilic forms of papillary thyroid cancer (23;24). Papillary carcinomas are often multicentric. Many of these multicentric carcinomas are of different clonal origin; i.e., the various centers originate independently (25). Metastasis is preferentially lymphogenous, first spreading to the cervical, and sometimes mediastinal, lymph nodes before spreading to the lungs.

Follicular thyroid cancer

FTC is characterized by follicular differentiation, without the nuclear changes characteristic of papillary thyroid carcinoma (21;22). They are encapsulated masses, and are distinguished from follicular adenomas by the presence of invasion of the capsule and vessels. According to the pattern of invasion they can be divided into two categories: minimally invasive and widely invasive carcinoma. Follicular carcinomas are less often multicentric. A variety of the follicular carcinoma is the Hürthle cell carcinoma, which consists of at least 75% oxyphilic cells (24). An important characteristic of Hürthle cell carcinomas is their poor or even absent iodine uptake, which renders them much harder to treat. Follicular thyroid carcinoma preferentially metastasizes hematogenously, and less frequently spreads to regional lymph nodes than papillary thyroid carcinoma.

Treatment

In the treatment of differentiated thyroid cancer multiple modalities are involved, each of which will be discussed separately.

Surgery

Primary surgery for differentiated thyroid carcinoma (DTC) consists of (near) total thyroidectomy. Only for papillary microcarcinoma the optimal extent of surgery is still subject to discussion (25-33). Very few authors found the therapy effect unrelated to the extent of surgery (26). Relapse free survival and thyroid cancer-specific survival are better after (near) total thyroidectomy than after unilateral thyroid lobectomy. Moreover, in over 50 percent of all patients who have a completion thyroidectomy after initial unilateral lobectomy, malignant tissue is found in the thyroid remnant (33).

This is in agreement with the multifocal, multiclonal nature of papillary carcinoma (25). Arguments against total thyroidectomy are also available. Papillary thyroid carcinoma is often found in post mortem studies without a single clinical symptom during life. This raises questions with regard to the clinical relevance of papillary microcarcinomas. The most serious complications include hypoparathyroidism and recurrent laryngeal nerve damage**.**

The final step in the treatment of DTC is the application of a high ('ablative') I-131 dosage, usually 3700 MBq, to destroy thyroid remnants after surgery. The prognosis of DTC and the effectiveness of the additional treatment with I-131 are so good that without at least cytologic proof a radical neck dissection (which is associated with significant morbidity) is unjustifiable. A modified radical neck dissection should be performed only after a diagnosis of lymph node metastases (23).

Levothyroxine medication

After surgery patients are followed-up intensively by their endocrinologists. As by definition the production of endogenous thyroxine is discontinued by the surgical procedure, these patients require thyroid hormone (levothyroxine, LT4) replacement. Differentiated thyroid cancer cells still react to TSH stimulation; for this reason LT4 is usually administered in such high doses that TSH levels fall to immeasurably low levels (<0.01 µU/ml). The ideal degree of TSH suppression, however, hasn't been established. Although complete TSH suppression seems to result in a longer relapse free survival (34), there is no effect of the *degree* of TSH suppression on relapse free survival and cancer specific mortality. Especially for low-risk patients TSH suppression is not generally advocated (35;36). The exact dose of LT4 required to achieve TSH suppression varies from patient to patient, and depends in part from the body weight. In case of failure to suppress TSH by LT4 medication in doses well tolerated by the patient, administration of octreotide may be considered (37).

Radioiodine (I-131) treatment

Iodine (atom number 53) belongs to the group of halogens. Because of its high reactivity it does not occur in a pure form in nature. In its natural state, iodine occurs as I_2. Of all 37 iodine isotopes (with atomic masses ranging from 108 to 144) I-127 is the only stable isotope. An overview of all iodine isotopes that are currently used in medical practice is given in table 1.

The therapeutically useful I-131 is produced by neutron bombardment of tellurium-131, and decays to xenon-131. I-131 emits beta-radiation (energy: 807 keV) with an average range (in soft tissue) of 1 mm, and a maximum range of about 3 mm. It also emits gamma-rays (19 gammas ranging from 80 to 637 keV; most abundant (83%): 364 keV), which are suitable for imaging with a gamma camera.
Iodine is administered as sodium iodide, either orally or by intravenous injection. Iodine is excreted from the body both with urine and with faeces. It is also secreted in milk (38), so breastfeeding will have to be discontinued at least one week before administering I-131 to a patient. This serves two objectives: (1) to prevent I-131 ingestion by the baby, and (2) to prevent unduly high radiation doses to the mother's breasts. Discontinuation of breastfeeding stops the milk production, and consequently also prevents iodine uptake from the blood by the mammary gland.
Iodine-131-NaI closely approaches the ideal drug for oncologic purposes: it is specific for one type of cancer cell, rarely has side effects, emits therapeutically useful beta-radiation and gamma rays suitable for imaging the drug distribution.
Following (near) total thyroidectomy, patients with differentiated thyroid cancer are usually treated with I-131 ablation of residual normal and neoplastic thyroid tissue. This serves multiple purposes: firstly, it destroys remaining (normal or neoplastic) thyroid tissue, thereby increasing the specificity of thyroglobulin measurements during the follow-upS. Secondly, I-131 may destroy occult microcarcinoma, thereby minimizing the incidence of recurrence. Thirdly, a high I-131 dose permits post-ablation I-131 whole body scintigraphy (WBS) which can detect occult metastases (23).
I-131 ablation in addition to (near) total thyroidectomy significantly reduces the risk of recurrence and cancer-specific mortality in patients with differentiated thyroid cancer (26;29;39). The effect of I-131 ablation may be partially dependent from differences in surgical techniques (40). The preferred I-131 dosage for remnant ablation is still a matter of debate (41-47). Although good results may be obtained with a dosage of 1.1 GBq (42;43), they seem to improve further with increasing dosages (47). A plateauing of the dose-response curve of I-131 has been noted for dosages over 1.85 GBq (41).
Diagnostic scintigraphy with I-131 preceding ablation is controversial; it may or may not cause 'stunning' of the remaining thyroid tissue (i.e., diminished I-131uptake) and thus reduce the efficacy of the I-131 ablative dosage (47-54). The benefit of pre-

ablation scintigraphy is uncertain, as residual thyroid tissue is seen in virtually all patients (47;51). Should pre-ablation scintigraphy nonetheless be performed then I-123 seems to be the safer choice to prevent a 'stunning' effect (51;55;56).
Serious complications of I-131 therapy include radiation thyroiditis (especially in the case of large thyroid remnants), salivary gland problems ranging from sialoadenitis to complete xerostomia (occurring in a minority of patients), transient loss of taste or smell, and hematological abnormalities. The incidence of these complications depends from the administered dosage (57;58). Recently evidence was found of earlier onset of menopause in women treated with I-131 for differentiated thyroid cancer (59).

External beam radiation

Radiotherapy to thyroid remnants doesn't enhance the survival as effectively as I-131 (29;30;60;61). It is indicated only in cases of incomplete or impossible surgical excision of tumours lacking I-131 uptake (62). External beam radiation therapy in addition to I-131 is advocated in cases of microscopic residual disease after surgery (63).

Follow-up

Contrary to most other cancer patients, thyroid carcinoma patients conventionally are never considered 'cured' in the oncological sense. Even though most recurrences are observed in the first years after diagnosis and treatment, they may occur more than 30 years after the initial treatment (29;40;64;65). Therefore, the follow-up of patients with differentiated thyroid cancer should be life-long.
Successful ablation has been shown to be a good indicator for a favourable prognosis (66). The American Thyroid Association guidelines (67) and several consensus statements (36;68) state that after I-131 ablation in patients with a favourable prognosis, a negative first TSH-stimulated measurement of thyroglobulin (Tg), possibly combined with I-131 whole-body scintigraphy, TSH-stimulated follow-up can be omitted. Further follow-up in these patients should consist of at least annual Tg-measurement during TSH-suppressive therapy, preferably combined with ultrasound of the neck.

Thyroglobulin measurements

As thyroglobulin is produced only by (normal or neoplastic) thyroid follicular cells, detectable serum levels signal the presence of recurrent or metastatic disease. Thyroglobulin (Tg) is the best available tumor marker for PTC and FTC after a (near) total thyroidectomy and subsequent radioiodine ablation of remaining thyroid tissue (69-71).

The methods in use for measuring Tg are either immuno(radio)metric assay (IMA/IRMA) or radioimmunoassay (RIA). The former is often preferrred as it allows for shorter incubation times and automation. There are, however, problems with the measurement of Tg.

- The presence of circulating auto-antibodies against Tg (TgAb) is a problem for the detection and the interpretion of serum thyroglobulin levels. TgAb can cause either over- or underestimation of Tg-levels. Tg tests should therefore always be combined with TgAb tests; if TgAb test positive, Tg-values are unreliable (72-74). Tg-antibodies themselves have been proposed as a tumor marker . Indeed, Tg-antibodies react to the presence or absence of thyroid cells and of Tg (75;76).
- Heterophilic antibodies can interfere with Tg measurements (77).
- There is a significant inter-assay variation. Despite CRM-457 standardization, this variation supersedes within-person variability (74). Most likely these differences reflect differences in assay specificity for circulating Tg isoforms (78-80).
- The most sensitive Tg-measurements are obtained during TSH stimulation (81). On the other hand, high TSH levels also induce thyroid (cancer) cell proliferation.

In recent years, Tg-mRNA in peripheral blood has emerged as a potential marker of recurrent or metastatic PTC and FTC. This technique doesn't suffer interference by antibodies, nor does it require TSH-stimulation to obtain a sufficiently sensitive measurement. The Tg-mRNA technique seemed very promising at first (82-84), but more recently the reliability and usefulness of this test have been questioned (85-88). Doubt was cast by the phenomenon of 'illegitimate transcription': a low but measurable level of transcription of any gene in any cell. Illegitimate transcription of Tg-mRNA seems to occur in leukocytes (89).

I-131 Whole body scintigraphy

6-12 months after I-131 ablation, whole body scintigraphy (WBS) is performed during TSH stimulation to evaluate whether the ablation was successful. If I-131 uptake is still observed, a second dosage of I-131 is administered to achieve complete ablation. Afterwards, different follow-up strategies co-exist. At selected intervals TSH-stimulated I-131 WBS or ultrasound of the neck is used for the detection of recurrent or metastatic cancer. Either option should be combined with Tg measurements.
The I-131 dosage used for follow-up WBS ranges from 74 to 370 MBq (47). Higher dosages increase the sensitivity of the test, but may also induce stunning of thyroid remnants and consequently lessen the efficacy of a therapeutic I-131 dosage.
With the advent of more sensitive Tg tests, diagnostic I-131 WBS has become controversial; negative I-131-WBS may be observed in the presence of detectable serum Tg levels. In most of these cases foci of iodine uptake can be observed after administration of a therapeutic I-131 dosage (90-92). This is illustrated in figure 5. Positive I-131 WBS at undetectable serum-Tg levels has become a rare observation. Furthermore, ultrasound of the neck is more sensitive than I-131 WBS for detecting lymph node metastases.
I-131 WBS during LT4 suppression medication is quite insensitive. To achieve adequate sensitivity TSH stimulation is required. Until recently this could only be realized by prolonged discontinuation of LT4 medication, but the issuing hypothyroid state was poorly tolerated by many patients. This clinical problem can now be circumvented with recombinant human TSH (rhTSH), both in diagnostic and in therapeutic settings (93-99). Similar sensitivity, specificity, positive and negative predictive figures are observed after LT4 withdrawal or administration of rhTSH.
It might become feasible to confine the follow-up to Tg-measurements after rhTSH stimulation; only those patients with detectable serum Tg-levels should then be subjected to further investigation with I-131 (93;97).

Ultrasound

The use of ultrasound (US) for the evaluation of thyroid nodules was first described in the early 1970s (100). US was primarily used to distinguish between cystic and solid thyroid lesions. Over the years the spatial resolution of ultrasound imaging has progressively improved, and hence its clinical usefulness has expanded. As discussed previously, US guided fine-needle aspiration of thyroid nodules has a

distinct role in the primary diagnostic process of thyroid carcinoma. Also during the follow-up ultrasound has a clear added value: ultrasound imaging is presently the most sensitive imaging modality for the early detection of locoregional recurrence and/or metastases, especially cervical lymph node metastases. Size and location of cervical lymph nodes are the most important predictors of metastatic disease (101). The US procedure may be easily combined with FNA biopsies from suspected lesions. US of the neck has been recommended as a standard procedure during follow-up of thyroid carcinoma (36).

Prognosis

Survival

Generally, patients with differentiated thyroid cancer have a good prognosis. Nevertheless the overall survival is lower than in a reference population of the same age and sex (64;102). The 10-year survival for patients with differentiated thyroid cancer is between 70 and 98 percent; patients with PTC do somewhat better than those with FTC (64;102-104).

Prognostic factors

Many clinical researchers have tried to define prognostic factors at the time of diagnosis to predict outcome in patients (29;64;102-111). The identification of patients at high risk of recurrent disease or of thyroid cancer death is important to establish the most appropriate treatment of individuals. Prominent prognostic factors are the patient's age at the time of diagnosis, and the presence of distant metastases. This may partly explain why FTC has a slightly worse prognosis than PTC: at the time of diagnosis patients with FTC follicular carcinoma are older on average than patients with PTC (112). Prognostic factors found in one study cannot be simply transferred to another. Furthermore, various analyses were based on populations from different parts of the world, and therefore with different ethnicity. This may lead to contradicting prognostic factors: in a study based on a north-American population, male sex was associated with poorer prognosis (105). Others, in a study based on a Japanese population, reported a poorer prognosis for females (111). The treatment of patients may vary between different centers. This empirical fact has a great influence on the prognosis. The prognosis of patients with papillary thyroid cancer is influenced significantly by the extent of surgery and by I-131

ablation (29;31). Different prognostically important variables are sometimes identified when identical methodologies from previous studies are applied to a new population (113).

Prognostic systems

In attempts to further stratify the prognosis, many prognostic systems have been developed to categorize patients with regard to the risk of thyroid cancer related death (29;31;64;103;105;106;108;109;111;114-118). There are several methods for comparing these systems (119). A staging system does not merely serve to predict the outcome in individual patients, but also to compare different populations for initial disease characteristics. Therefore wide acceptation of a system is essential before it can be applied to a population. The International Union Against Cancer and the American Joint Committee on Cancer's TNM system (Table 2) fulfills that requirement (118), and has been shown to be as good as other systems (119).

Objective of this dissertation

As successful ablation has been shown to be a good indicator for a favourable prognosis (66), the American Thyroid Association guidelines (67) and several consensus statements (36;68) state that after I-131 ablation in patients with a favourable prognosis, a negative first TSH-stimulated measurement of thyroglobulin (Tg), possibly combined with I-131 whole-body scintigraphy, TSH-stimulated follow-up can be omitted. Experimental and epidemiological evidence for this position is still relatively scarce.

The aim of this study is to investigate whether and if so when recurrences occur after a negative first TSH-stimulated follow-up after I-131 ablation. Secondary objectives are to study the modalities by which recurrences are discovered as well as determine risk-factors for recurrence after successful ablation.

Patients, materials and methods

Hospitals

In this study three hospitals participated: the University Clinic Würzburg (UKW), in Germany, the Leiden University Medical Center (LUMC) and the University Medical Center Utrecht (UMCU) University Clinic, both in the Netherlands. All three hospitals are referral centers for post-surgical I-131 treatment of DTC patients.

Patients

In this study we included patients who had undergone (near) total thyroidectomy and subsequently received their initial I-131 treatment in one of our centres, and in whom TSH-stimulated Tg-measurement and I-131 whole body scintigraphy (WBS) 4-12 months after initial treatment was completely negative. Data were reviewed retrospectively.

Initial staging and treatment

Ablative dosages and protocols used varied widely over time. In the LUMC patients received an uptake-related dosage of 1110, 1850 or 2800 MBq I-131 until 2002 (120). After 2002 the patients in the LUMC, like the patients in the UMCU, received a fixed dosage (47) of 3700 MBq in case of T1-3N0M0 non-Hürthle cell carcinoma, 5550 MBq in case of TxN1M0, T4NxM0 or Hürhtle cell carcinomas, and 7400 MBq in case of TxNxM1 carcinomas. In the UKW patients received 2500-3500 MBq, depending on the size of the thyroid remnant.

Laboratory analyses

Over time, in all three hospitals various kits were used for the measurement of Tg and Tg-antibodies. Test results for Tg may not be considered reliable in the presence of antibodies (74;77), the presence of which was shown either through direct measurement or through determination of Tg-recovery rates. As all assays were IRMA assays, the interference by antibodies against Tg generally would have resulted in underestimation of Tg-values. Therefore, patients were excluded from analysis in the presence of measurable Tg antibodies or insufficient Tg-recovery and a corresponding Tg value below the cut-off level at the first follow-up. As results of Tg-measurements are not interchangeable between kits (74), for the purpose of this

study Tg-levels in any patient were considered undetectable if they were below the lower detection limit of the method used.

Follow-up after ablation

4-12 months after I-131 ablation, patients returned to our hospitals for TSH-stimulated follow-up. High TSH-levels were induced either by LT4 withdrawal or, upon availability, intramuscular injection of recombinant human TSH. During TSH-stimulation Tg-levels were measured and a diagnostic WBS using 185-370 MBq of I-131 was acquired. In the LUMC and UKW TSH-stimulated follow-up was performed at least once more within 5 years after diagnosis. In the UMCU patients routinely received TSH-stimulated follow-up 4 years after ablation, and after that at 5-year intervals.

Definitions

TNM-stage of all patients was analysed according to the 5th edition of the UICC/AJCC TNM staging system (121).

High-risk patients were defined along the lines of the 2006 European consensus (122), in which all patients with T3 or T4 tumours, as well as patients with N1 or M1 disease, were considered at high risk for recurrence.

By definition, all patients included in this study were considered disease-free. Recurrence was defined as any of the following occurring after a documented disease-free period:

- cytologic / histologic evidence of disease
- detectable Tg-levels
- positive I-131 scintigraphy

Analysis

Statistical significance was defined as $p < 0.05$.

Survival times were assessed using the method of Kaplan-Meier. Differences in survival times were assessed with a log rank test. Multivariate analysis was performed using a Cox-regression on any variable that had $p \leq 0.20$ in univariate Cox-regression

Results

Out of 1993 patients with differentiated thyroid carcinoma seen in our hospitals, 526 patients fulfilled the inclusion criteria and were included in the present study: 312 from the UKW (start of inclusion: 1980),102 from the UMCU (start of inclusion: 1990) and 112 from the LUMC (start of inclusion: 1990). Details of these patients can be found in table 1. Mean follow-up was 79,6 months after ablation, median follow-up was 61 months (range: 4-306 months). 12 patients (2.3%) developed a recurrence after a mean interval of 35 months (range: 12-59 months) following administration of the ablative activity of I-131 (figure 1), of whom 2 eventually died of DTC. Recurrence was first discovered by Tg-measurement during TSH suppression in 7/12 patients, and by TSH-stimulated Tg-measurement in 5/12 patients. Only one patient showed a concurrent positive diagnostic I-131 whole-body scan; in none of the patients was a recurrence first detected only by means of a I-131 WBS.

In 6/12 patients an anatomical substrate for the recurrence was found: 4 patients had distant metastases, and two patients had a local recurrence.

In the remaining patients we were unable to identify a focal source for the elevated Tg-levels: one patient died of cardiac causes before a diagnosis could be made, one patient received a “blind” therapeutic dosage and Tg-levels were undetectable ever since, and in four patients no anatomical correlate for the elevated Tg-levels has been found thus far. The overall 5-year and 10-year disease-free survival both were 96.6 $\pm$ 1.0 % (figure 1). No recurrences occurred at more than 60 months after ablation. There were no differences in survival times between the participating hospitals (figure 2, p=0.26) patients with different T-stages (p=0.73), between patients with or without lymph node metastases (p=0.53) or between men and women (p=0.33). Neither the presence of lymph node metastases (p=0.53) or tumours infiltrating outside of the thyroid (p=0.18) at initial staging led to a significantly lower disease-free survival rate, nor did the participating centers (p=0.31) show a difference in disease-free survival.

High risk patients did not have a higher recurrence rate than low-risk patients (p=0.61): the long-term survival-adjusted risk of recurrence in low-risk patients was 3.4% $\pm$ 1.3% while the risk in high-risk patients was 3.7% $\pm$ 1.7%. Patients aged $\geq$ 45 years had a slightly, but significantly lower disease-free survival rate (5-year disease-free survival: 94.4 $\pm$ 1.8 %) than patients under 45 years of age ate the time of ablation (5-year disease-free survival: 98.4 $\pm$ 0.9 %, figure 4, p=0.03).

Patients with papillary thyroid cancer did significantly better than those with follicular thyroid carcinoma (p=0.04) (figure 5). The various stages according to the TNM-system showed a significant difference with regard to disease-free survival (p=0.03) (figure3). Multivariate analysis showed that age TNM-stage (p=0.015) and histology (p=0.032) were independent predictors of disease-free survival.

Mean Age (years)	44.1
No. patients with age < 45 years	283
No. patients with age ≥ 45 years	243
Histology	
Papillary thyroid carcinoma	381
Follicular thyroid carcinoma	142
Unknown histology	3
TNM stage (5th edition)	
I	309
II	160
III	49
Unknown	8
Nodular metastases	
Node negative	449
Node positive	76
Unknown	1
Low / High risk	
Low risk	329
High risk	177
Unknown	20
Extrathyroidal tumour invasion	
No invasion	473
Invasion present	53

Table 1. Basic characteristics of the patients included in this study.

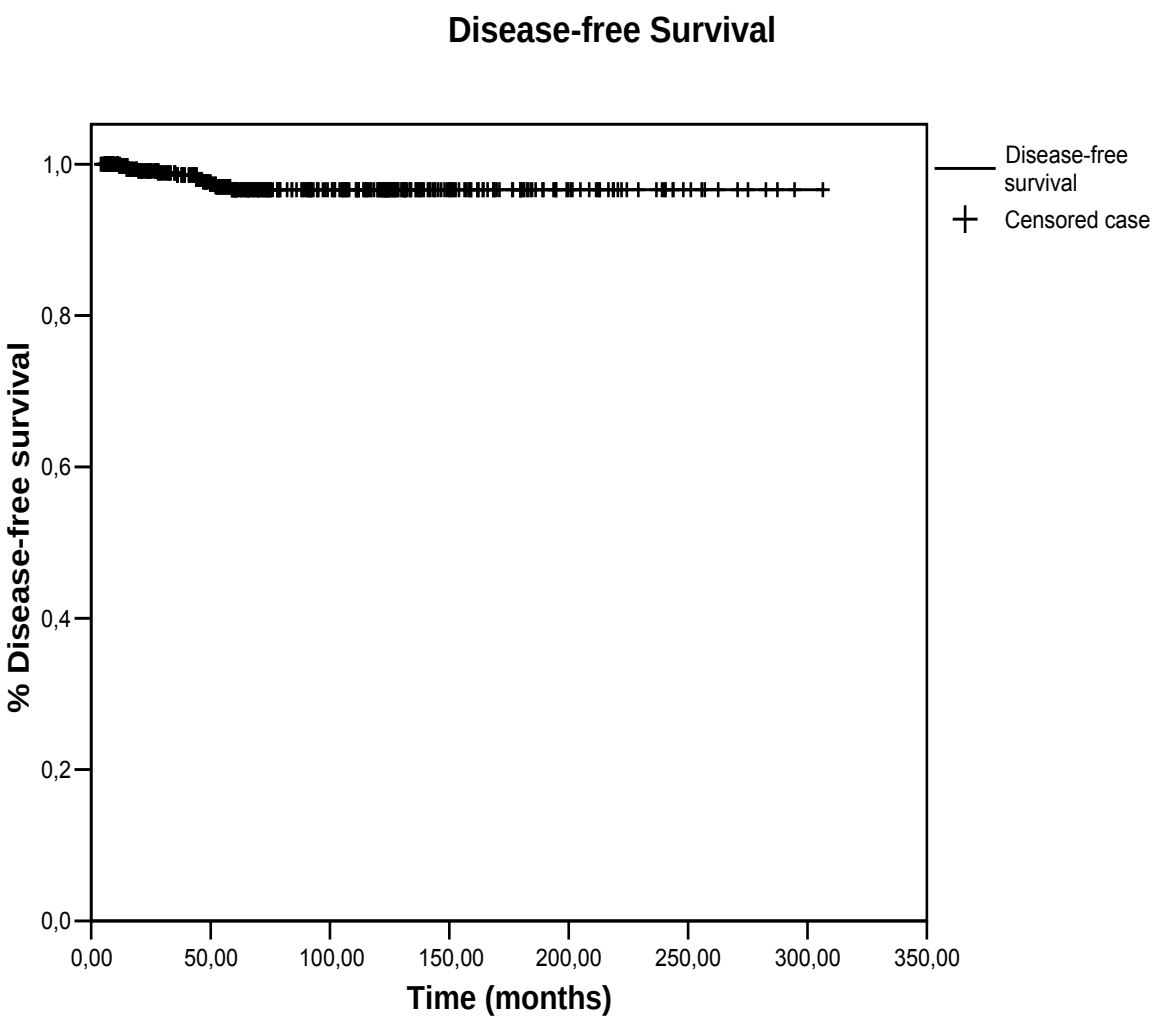

Figure 1: Overall disease-free survival.

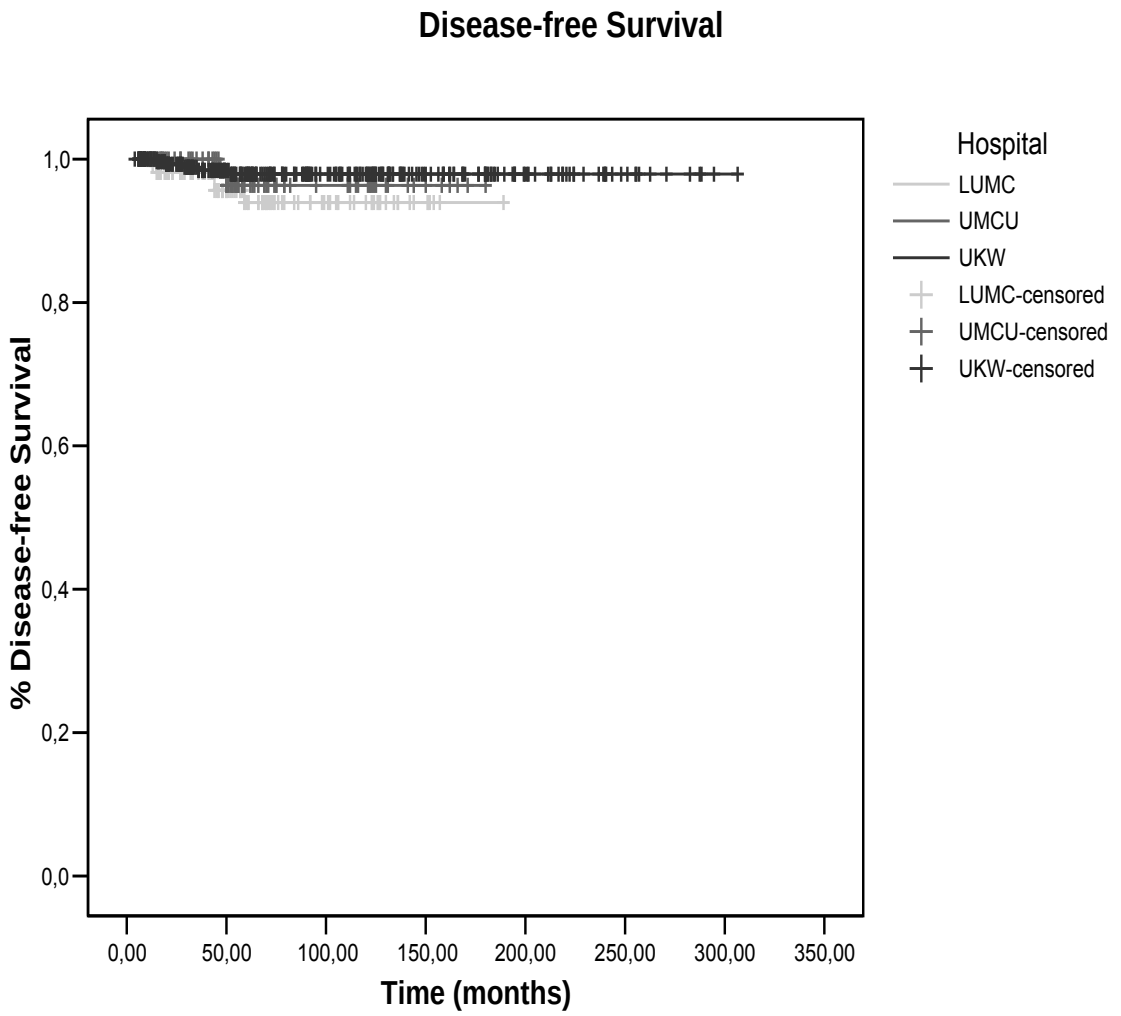

Figure 2. Disease-free survival for patients with treated in each of the participating centers. The difference between the curves is not statistically significant (p=0.26)

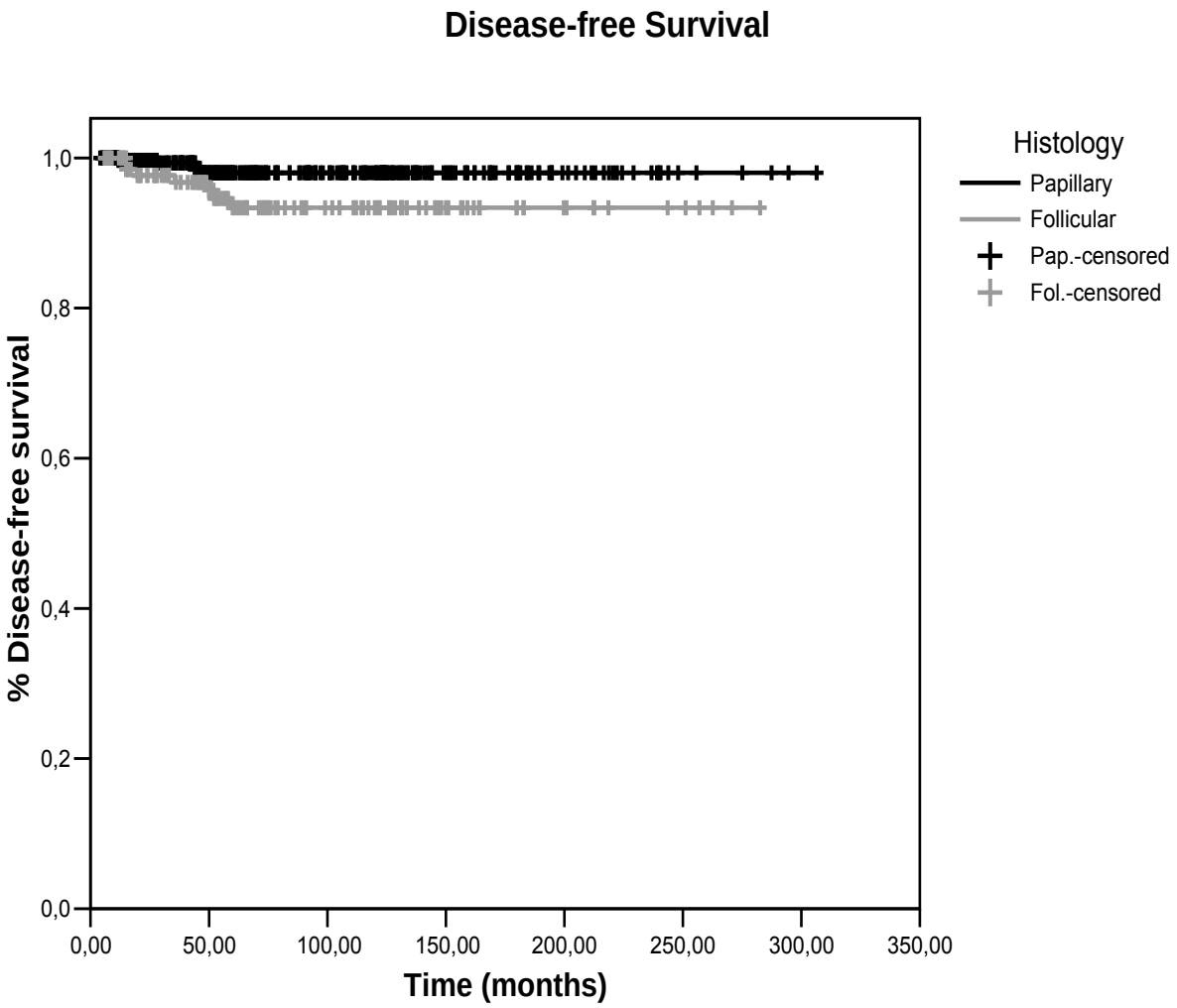

Figure 3. Disease-free survival for patients with papillary or follicular thyroid carcinoma. The difference between the two curves is statistically significant (p=0.03)

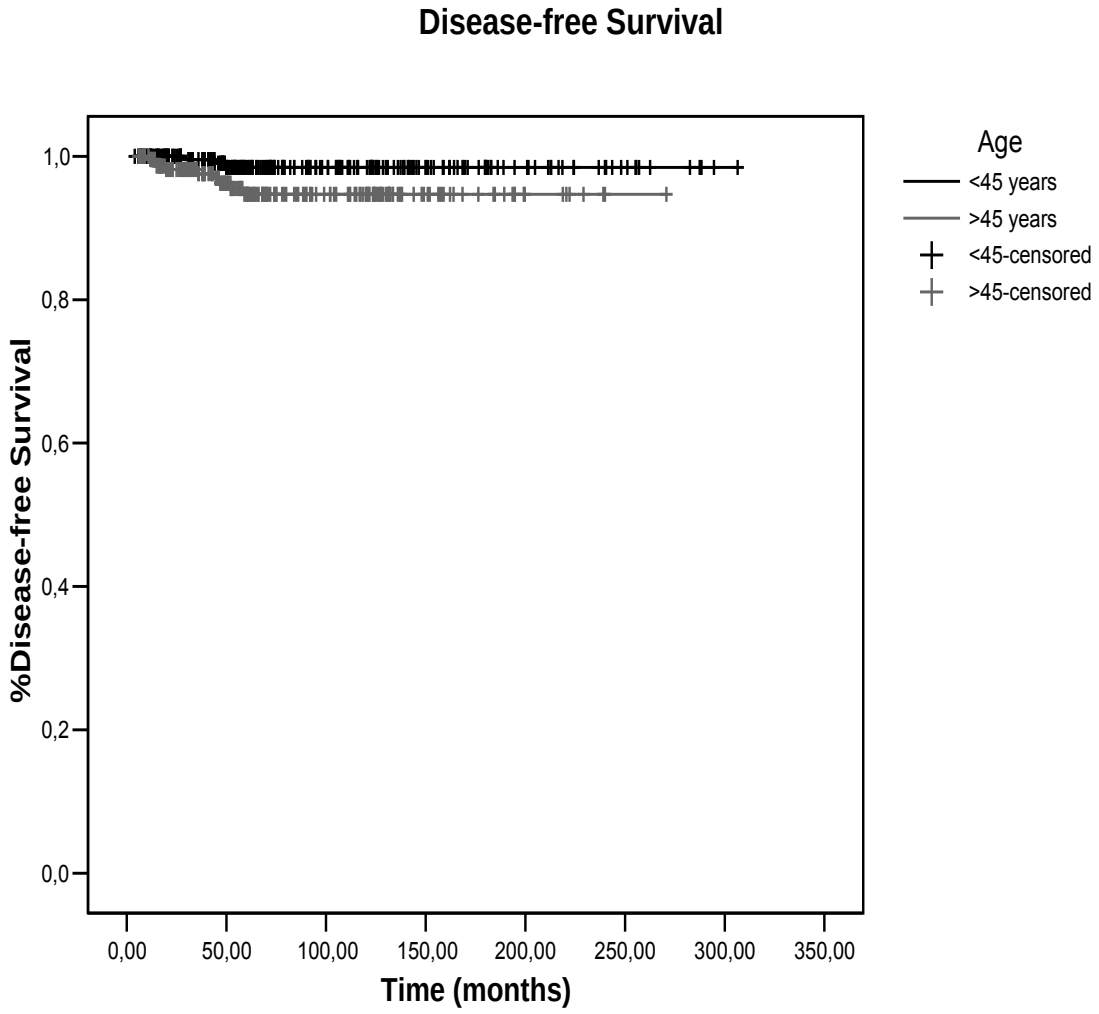

Figure 4. Disease-free survival for patients age up to and including or over 45 years of age. The difference between the two curves is statistically significant (p=0.04)

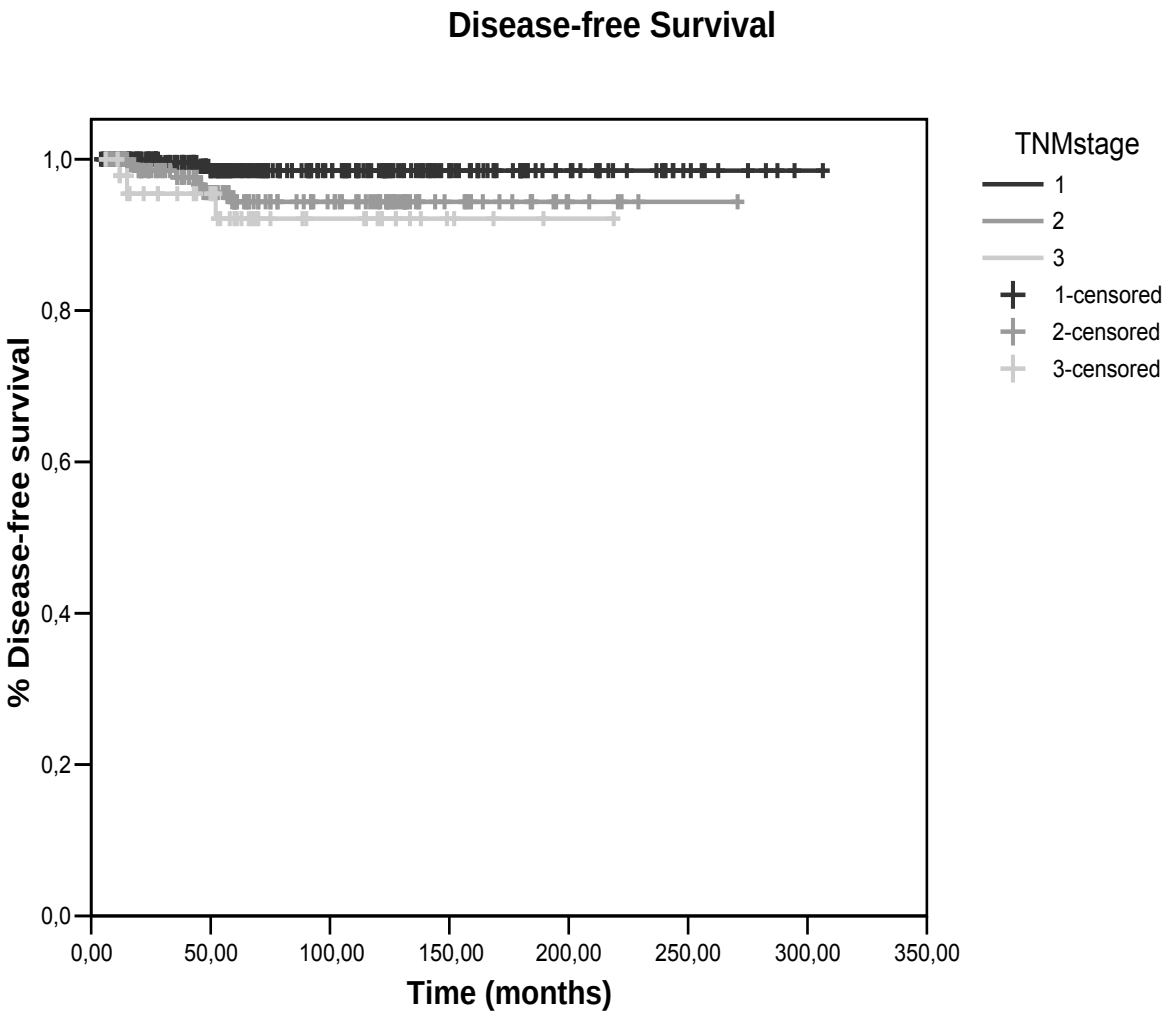

Figure 5. Disease-free survival of patients per TNM-stage. The difference between the three curves is statistically significant (p=0.03)

Discussion

In this study of a large group of differentiated thyroid cancer patients with negative TSH-stimulated Tg-levels and negative diagnostic I-131 WBS after I-131 ablation, tumour recurrence was a rare event. Remarkably all recurrences occured within five years after initial treatment. Elevated Tg-levels, either during suppressive levothyroxine therapy or during TSH-stimulation, were the first sign of recurrence in all patients while diagnostic I-131 WBS provided no pivotal diagnostic information in any of these patients.

Clinicians and scientists alike often quote a number of large studies detailing the risk of late recurrence in DTC when they want to stress the need for a life-long follow-up in DTC-patients (29;40). The strength of all these studies lies first and foremost in the extremely long follow-up of at least a fraction of the patients (>40 years in some cases). However, these studies have started long before modern follow-up methods such as Tg-measurement were available, and base their risk-stratification solely on the initial tumour stage. That such a strategy does not lead to truly accurate risk-stratification is illustrated in a study by Hundahl et al. (123), who reported on a cohort of 9369 papillary thyroid carcinoma patients stratified according to the AMES staging system (105). 8770 patients were classified as low risk and 599 ones as high-risk, but almost two-thirds of tumour-related deaths occurred in the low-risk group.

The advent of Tg-measurement has not only made follow-up of DTC much more sensitive and allowed for a close monitoring of therapy response; it has also opened the possibility for re-stratification of risk based on this monitoring and follow-up. This adaptation of risk-stratification is also propagated in the guidelines of the American Thyroid Association (ATA) as well as two consensus statements (36;67;68) which all recommend reducing the intensity of follow-up for patients with a negative TSH-stimulated Tg-level after I-131 ablation. The results of the present study strongly support such a policy, but go further. The guidelines of the ATA and the various consensus have limited relaxation of follow-up to patients who can be classified, with different criteria, as ‘low risk’ at the time of initial treatment. This study shows that patients who were initially classified as ‘high risk’ (such as patients with lymph node metastases) can be downgraded to being at ‘low risk’ for recurrence as well – even those patients who have one or more risk factors as identified in this study (i.e. follicular carcinoma or higher TNM-stage) will have a long-term disease-free survival rate well above 90 percent. That even such a therapy-response based ‘low risk’

classification does unfortunately not mean ‘no risk’ is not only illustrated by the 12/526 patients who developed recurrence, but especially by the 2/526 patients who eventually died of their disease.

The results of this study are in line with findings by Kloos and Mazzaferri (124) This study with a relatively small group of patients with a negative first TSH-stimulated follow-up (n=68), who were treated in a single center according to a single protocol, found a recurrence rate of ~2% percent in patients with rhTSH stimulated Tg-levels <0.5 ng/ml. A limitation of this study by Kloos and Mazzaferri was a limited follow-up of three to five years. The results in this larger, multicenter, multinational, long-term study of DTC patients also show that a negative TSH-stimulated Tg-measurement and a negative diagnostic I-131 WBS predict a very favourable prognosis with an overall recurrence-rate of about 2 percent. A study by Pacini et al. (125), later confirmed in another study by the same authors (126), concluded that the combination of clinical examination, TSH-stimulated Tg-measurement and ultrasound of the neck would be sufficient to follow thyroid cancer patients, and that I-131 whole-body scintigraphy did not reveal any additional findings except for persistent uptake in the thyroid bed. In this study the long-term disease-free remission rate (89.5%) in patients with a negative first stimulated Tg-measurement was much lower than in the present one. A possible explanation for this lower rate may lie in the inclusion criteria: Pacini et al. included all patients with a negative Tg, regardless of the outcome of a diagnostic I-131 WBS performed concurrently, whereas in the present study patients had to have a negative I-131 WBS as well. The contrast between the results of the present study and the one by Pacini et al. does however highlight the value of I-131 WBS for stratifying patients more accurately according to prognosis after initial treatment: by using I-131 WBS in addition to Tg-measurement our study population showed a recurrence rate that was only one-third of the population studied by Pacini et al. In concurrence with Pacini et al., and foremost with Robbins et al., this study shows that a follow-up I-131 WBS does not contribute any clinically relevant information in patients with a prior negative I-131 WBS.

Based on their observation, Pacini et al. concluded that I-131 WBS can be avoided in the follow-up of thyroid carcinoma patients. This study however also shows that despite the recommendation in recent guidelines to omit I-131 WBS, this procedure may be useful to reclassify risk status after initial treatment. Robbins et al. (127) largely concurred with this opinion: in patients with a negative I-131 WBS, follow-up

WBS did not yield significant information. In concurrence with Pacini et al., and foremost with Robbins et al., this study shows that a follow-up I-131 WBS does not contribute any clinically relevant information in patients with a prior negative I-131 WBS.

In the interpretation of the present data several limitations should be considered. First of all the lack of homogenous treatment and follow-up. It is unclear to what extent the initial treatment still influences the chance of recurrence once therapy has been a success, as the incidence of recurrent disease is too small in this patient group to demonstrate any significant influence (or lack thereof) that differences in initial treatment may have. In literature some support can be found for the premise that inhomogeneities in the follow-up of patients with regard to method of TSH stimulation and precise diagnostic I-131 activity can largely be disregarded. rhTSH-mediated follow-up has already been shown to yield equivalent results to follow-up after LT4 withdrawal (93). Phan et al. showed however that using different activities for follow-up does not significantly influence the result of diagnostic whole body scanning (128). Secondly there is a large number of patients with limited long-term follow-up in our study; median follow-up was only about five years. This is largely explained in that in all three centers a large part of our patients are referred to us for in-patient treatment and I-131 follow-up by specialists from all over our countries, who perform the out-patient follow-up themselves. Any time these collegues indicate a need for I-131 treatment for diagnostic or therapeutic purposes these patients will return to us. Even though we have no data collected in our hospitals, and can therefore not include these patients after they were last seen, the non-return of many of these patients might even be interpreted as them still being free of disease many years after initial treatment. Thirdly, the results of this study and the resulting recommendations are for now limited to those patients who had successful ablation after one I-131 treatment. Whether the same high rate of disease-free survival also exists in patients who require more than one I-131 therapy to become disease free is subject to further study.

The results of this study show that in our study population no more recurrences occur >5 years after ablation. As this study shows clearly, and as has before already been shown by Pacini et al. and Robbins et al. (93;127), it is useless to perform an I-131 WBS if the first, ablative, I-131 treatment was successful; this practice is therefore

best avoided. Pacini et al. and Cailleux et al. (125;129) have even stipulated that possibly even the first I-131 WBS can be left out.
Further follow-up should then consist of Tg-measurement and ultrasound (126). Whether a TSH-stimulated Tg-measurement (whether with recombinant human TSH (rhTSH) or after withdrawal) should take place can be subject of debate. In our study only 5 recurrences were found with TSH-stimulated follow-up. Whatever way TSH-levels are stimulated, this will mean that to find one additional recurrence, 100 patients need to be withdrawn from levothyroxin or given rhTSH, which may incur considerable costs and/or burden to the patient (130-133). This result is in agreement with a recent study by Castagna et al (134), who reported finding only one patient with a positive Tg-measurement after rhTSH stimulation in a group of 67 patients with a prior negative rhTSH-stimulated Tg.
As a last question, what to do with these patients after 5 years of being disease-free? In many forms of cancer patients are discharged from follow-up after 5 years, and are told that they have been ‘cured’. Even though it could be considered giving the patients a message that they have been ‘cured’, at the same time the patient should be told that a life-long follow-up is still necessary to control the iatrogenic hypothyroidism and possible co-morbidity such as post-operative permanent hypoparathyroidism. Whether or not to give the patient such a two-faced message will largely depend on the attending physician and the individual patients character and needs.

Conclusions

After successful ablation, established by negative Tg-levels and negative I-131 scintigraphy, disease-free survival rates in patients with differentiated thyroid carcinoma are high; even in those patients that would initially be classified as high risk. I-131 WBS is useful for re-stratification of risk but thereafter does not yield additional diagnostic information and is therefore best avoided if the initial one is negative.

Abstract

Objective: The objective of this study was to study recurrence in patients with differentiated thyroid carcinoma who after initial therapy consisting of total thyroidectomy and I-131 ablation, were cured defined as a negative TSH-stimulated Tg-levels and a negative I-131 whole body scan (WBS) at the first follow-up after ablation.

Methods: Retrospective data for differentiated thyroid carcinoma patients from three university hospitals were pooled. Out of 1993 patients, 526 cured patients were included. All patients received at least one more TSH-stimulated WBS and Tg-measurement within 5 years after initial treatment.

Results: 12 patients (2.1%) developed a recurrence after an average interval of 35 months (range: 12-59 months) following administration I-131 ablation. Overall disease-free survival according to the method of Kaplan-Meier was 96.6%. There was no difference in disease-free survival between high- and low-risk patients (p=0.61). Recurrence was first discovered by Tg-measurement during levothyroxin therapy in 7 patients, and by TSH-stimulated Tg-measurement in 5 patients. I-131 WBS did not contribute to the detection of recurrences. Multivariate analysis showed that age TNM-stage (p=0.015) and histology (p=0.032) were independent predictors of disease-free survival.

Conclusion: Recurrence is a rare event in patients with DTC who received total thyroidectomy with subsequent I-131 ablation, and who had a negative first follow-up TSH-stimulated I-131 WBS and negative concurrent Tg. In the study population there were no recurrences after more than 5 years of follow-up.

Zusammenfassung

Ziel: Das Ziel dieser Studie war es, die Rezidivrate zu untersuchen bei Patienten mit einem differenziertem Schilddrüsen-Karzinom (DTC), die nach der ersten Behandlung, bestehend aus totaler Thyreoidektomie und I-131 Ablation, geheilt wurden. Heilung wurde definiert als eine negative TSH-stimulierte Tg-Messung und eine negative I-131 Ganzkörperszintigrafie (GKS) im ersten Follow-up nach der Ablation.
Methoden: Retrospektive Daten für Patienten mit einem differenziertem Schilddrüsen-Karzinom aus drei Universitätskliniken wurden gemeinsam analysiert. 526 von 1993 Patienten wurden geheilt. Alle Patienten erhielten mindestens eine weitere TSH-stimulierte GKS und TG-Messung innerhalb von 5 Jahren nach der ersten Behandlung.
Ergebnisse: 12 Patienten (2,1%) entwickelten ein Rezidiv nach einer durchschnittlichen Zeitdauer von 35 Monaten (Bereich: 12-59 Monate) nach der I-131-Ablation. Das rezidiv-freie Überleben berechnet mit der Methode von Kaplan-Meier lag bei 96,6%. Es gab keinen Unterschied im rezidiv-freien Überleben zwischen Hoch- und Niedrig-Risiko-Patienten ($p = 0,61$). Ein Rezidiv wurde zum ersten Mal entdeckt mittels Tg-Messung während Thyreosuppressiver Levothyroxin-Einnahme bei 7 Patienten, und mittels TSH-stimulierter Tg-Messung bei 5 Patienten. Die I-131-GKS führte nicht zur Erkennung von Rezidiven. Multivariate Analysen zeigten, dass TNM-Stadium ($p = 0,015$) und Histologie ($p = 0,032$) unabhängige Prädiktoren für das Rezidiv-freies Überleben waren.
Fazit: Ein Rezidiv ist ein seltenes Ereignis bei Patienten mit DTC, die nach totaler Thyreoidektomie mit anschließender I-131-Ablation einen negativen ersten Follow-up bestehend aus TSH-stimulierter I-131 GKS und gleichzeitiger TG-Messung hatten. In der untersuchten Patientengruppe ergaben sich keine Rezidive nach mehr als 5 Jahren Nachsorge.

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