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Follow-Up after Treatment for Differentiated Thyroid Cancer – The Risk of Recurrences

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Abstract

Background: Differentiated Thyroid Cancer (DTC) is characterized by a good prognosis, and radical surgery has been questioned, especially in cases with small tumors. But size alone cannot possibly predict the prognosis: All tumors were small once. Recurrences occur after several decades, and further risk factors are needed when to choose the optimal treatment.

Methods: A consecutive series of 231 patients with DTC were treated in 2004-2016: In 63/231 (27.3%) there was no preoperative suspicion of malignancy; 214 patients were thyroidectomized. Follow-up was performed in 2023 after mean 10.7 years (range 6.5-19.1). Medical records were scrutinized: Mode of surgery, radioiodine treatment, thyroglobulin levels, deaths and recurrences were registered as were possible risk factors. Patients with negative thyroglobulin after treatment were compared with those who had measurable thyroglobulin or high levels of anti-thyroglobulin.

Results: There were 181 patients with negative thyroglobulin after treatment and 33 patients had measurable thyroglobulin and/or anti-thyroglobulin. All 15 patients deceased in DTC were in the latter group. Significance was confirmed for five risk factors: Size, multifocality, angioinvasion, extra-thyroidal growth and metastases. All ten patients with recurrences had minimum two of these risk factors, which also were found in microcarcinomas (≤ 10 mm). Complication rate was low.

Conclusion: There is good reason for thyroidectomy or hemithyroidectomy in DTC, preferably including the closest lymphatic glands. Thyroidectomy has the advantage of follow-up with thyroglobulin tests, useful even after several years, to alleviate anxiety and to possibly find recurrences in time for treatment.

Keywords: DTC; Follicular tumor; Oncocytic carcinomas

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Introduction

Differentiated Thyroid Cancer (DTC) is known to have a good prognosis, and treatment has gradually changed, from total thyroidectomy with central lymph node dissection that previously was the routine, to lobectomy in selected cases, or simply active surveillance, the latter in cases with tumor diameters of 10 mm or less [1-6]. Still, in spite of accurate surveillance with ultrasonography small tumors and metastases ≥ 2 mm might escape detection [7,8]. Furthermore, the patients' quality of life is lowered because of anxiety many years after treatment [9-11]. Follow-up using the specific tumor marker thyroglobulin is useful only if total thyroidectomy is performed [12], but only a minority is followed long-term [13] in spite of the fact that recurrences may occur after several decades [14]. The aim of this follow-up of a consecutive series of thyroid cancer patients is to show the necessity of being aware of the risks of recurrences, and how to possibly identify them in time to minimize their consequences.

Methods

In 2004-2016 there were 252 patients diagnosed with a thyroid malignancy at the public hospital in Borås, responsible for 290,000 inhabitants in the Southern part of Västra Götaland County in Sweden, and 250 were operated on. After exclusion of anaplastic cancer (n=11), medullary cancer (n=6), a non-Hodgkin lymphoma and a plasmocytoma in the thyroid (n=2), 231 patients with DTC remained for follow-up. Information on the patients' present addresses, and their families' addresses were received from the Swedish authority for National registration. If the patient was deceased, the date of death was provided. Clinical data were retrieved from medical records. A second opinion of all histopathological specimens was a routine procedure; TNM classification of Malignant Tumors, the 7th edition [15], was used and three subgroups were identified: Papillary tumors, including those

described as a follicular variant, pure Follicular tumors and Oncocytic carcinomas. If information at follow-up was incomplete, the patient or a relative was contacted and asked to elucidate.

There were 175 women and 56 men with DTC (Figure 1). They were diagnosed because of goiter in 87 cases or a thyroid nodule in 96 cases. Six patients had a nodule that revealed a metastatic lymphatic gland and five had distant metastases as the first sign. Various symptoms strengthened the indication for surgery: Unpleasant pressure affecting ability to breathe or swallow, signs of recurrent laryngeal nerve dysfunction, and toxic goiter. In eight cases the tumor was discovered at surgery because of hyperparathyroidism. In some the enlarged thyroid gland was found En Passant at computer tomography: In three cases the trachea was compressed to 4 mm to 8 mm, and in four the thyroid tumor penetrated larynx or the tracheal wall. In four cases ultrasonography revealed small tumors and two of them were diagnosed by cytology. In all the others Fine Needle Aspiration Cytology (FNAC) was guided by palpation. The classification used derived from the British Thyroid association [16]. From 2011 the Bethesda system [17] was introduced, which then by retrospective scrutiny was applied to the whole patient series: BII (n=43), BIII (n=17), BIV (n=67), BV (n= 21), BVI (n=48). Thus, the indication for surgery was in part, or definitely, motivated in 153 cases, BIII-BVI (66.2%). In 63/231 cases (27.3%) there was no preoperative suspicion of malignancy: Intrathoracic goiters unsuitable for FNAC, ten cases with large thyroid glands (mean 200 g; range 124-259), 42 patients with small tumors out of whom 17 had toxic goiters with tumor diameters 2 mm to 8 mm (mean 5.2). Bi- or multi-focality occurred in 65/231 cases (28.1%).

Mean age at surgery for DTC was 56.3 years (SD 18.9; median 58.8; range 16.7-91.8). They had Papillary carcinomas in 186 cases, 98 the follicular variant, 25 had Follicular carcinomas and 20 Oncocytic carcinomas.

Mode of Surgery: Total thyroidectomy was primarily performed in 130 cases (56.3%). Since eight patients were previously operated on with hemithyroidectomy altogether 138 patients (59.7%) were completely thyroidectomized. One patient with toxic goiter had a subtotal thyroidectomy. In 92 cases a hemithyroidectomy was performed, and after the diagnosis was confirmed, the remaining thyroid tissue was removed in 75 cases.

Lobectomy only: Seventeen patients were left without further surgery (7.4%). In 13/17 cases 1 to 16 lymphatic glands were investigated (mean 5.7; SD 4.8), all without metastases. One lady, 91 years of age, with an oncocytic 52 mm tumor, wanted as little treatment as possible. She lived ten years after that. The remaining 16 patients had papillary tumors, one had a 10 mm tumor, and the others had tumor diameters 0.5 mm to 6 mm. They had all benign ultrasonography performed one year after surgery.

A modified central neck dissection: was performed when there were signs of malignancy *i.e.* the tissue adjacent to the thyroid was removed En bloc with the thyroid gland. In several cases also lateral nodes on the tumor side were removed primarily, in eleven cases at a separate occasion. Fifteen glands or more were investigated in 43 patients (mean 23.3; SD 7.9) and 29/43 had metastases (67.4%). For reliable TNM classification at least 6 lymphatic glands should be examined [15], and in 163/231 cases that criterion was fulfilled (70.6%). Of the remaining 68 patients, eight had follicular tumors, eight had toxic goiter, 21 had cytology Bethesda II and 35 patients had tumor diameters ≤ 10 mm. The number of lymphatic glands examined in the 214 patients operated on bilaterally varied from 0 to 54: No glands in 14 patients with toxic goiter (n=4), with BII (n=6), and with trachea compromised by tumor growth (n=4). Mean number of glands examined in the other 200 patients was 10.9 (SD 8.32) and in 63/200 (31.5%) there were metastases. In the majority, with ≥6 glands examined [13], 58/159 had metastases (36.5%).

Postoperative complications: were one reoperation due to bleeding and one due to leakage from the thoracic duct. Two patients had temporary recurrent laryngeal nerve dysfunction. Seven patients had recurrent laryngeal nerve paresis before surgery, six of them because of tumor growth, and one recovered within one year after surgery as the tumor was small and within the large thyroid gland weighing 165 g. Seven patients had postoperative hypoparathyroidism with adjusted medication with calcium and vitamin D (7/214; 3.3%) [18]. Another 20 patients take extra calcium as a dietary supplement.

Additional treatment: In 2004-2010 adjuvant radioactive treatment with 4000 MBq was given while 2000 MBq was used to eliminate minimal remnants of thyroid tissue in cases with low risk. From 2011 lower doses were used, 3700 MBq and 1100 MBq, respectively. Patients with distant metastases got 8000 or 7400 MBq. Altogether postoperative radioactive treatment [19,20] was given in 159/214 cases (73.8%). One patient got it six years after surgery as her thyroglobulin was continuously measurable at a low level, and it has now been negative since 14 years. Another patient had after surgery and radioiodine in 2015 thyroglobulin 28 μg/L, that turned negative eight months later after her right ovary containing a teratoma with thyroid tissue was removed. Thereafter it was negative.

The importance of avoiding X-ray using Iodine in patients with goiter had been notified, and in 115/159 cases (72.3%) full effect of radioiodine could be expected. In 44 cases treatment was given with a few months delay because of previous iodine administration. There were 55 patients without radioactive treatment, all of them without signs of metastases, 44 with stage T1 tumors, 7 with stage T2, and also four patients with T3 tumors who declined radioactive treatment for different reasons.

Lifelong thyroxine treatment: is a consequence after surgery, the dose determined in relation to the TSH level. In this series TSH was kept as low as possible but within the normal range in order to avoid negative cardiovascular effects [21], with a few exceptions in patients with advanced disease.

Results

Altogether there were 62/231 deceased at follow-up in 2023. Mean age at death was for women 82.0 years (SD 9.8; range 60.7-101.7), and for men 80.1 years (SD 11.2; range 56.8-99.4). For comparison, the average length of life in Sweden in 2021 was for women 84.8 years and for men 81.2 years. Mean follow-up time of the deceased was 6.4 years (SD 4.2; range 0.3-15.9), and of the patients still alive it was 10.7 years (SD 3.7; range 6.5-19.1).

Fifteen patients died because of their DTC (15/231; 6.5%). At the time of diagnosis six had locally advanced disease, one had a pulmonary metastasis and four had skeletal metastases. In one patient symptom from a cerebral metastasis was revealed when in care after her thyroidectomy. Mean age at death was for women 81.0 years (SD 10.0; range 74.2-100), and for men 74.3 years (SD 12.2; range 56.8-89.0). Mean follow-up time of them, 8 women and 7 men, was 4.6

Table 1: The result of significance tests performed using t-test for mean tumor size and Fisher's exact test for categorical variables, comparing occurrence of probable risk factors among patients with negative thyroglobulin after treatment (n=181) and among patients having measurable thyroglobulin or high levels of anti-thyroglobulin after treatment (n=33).

Thyroglobulin after OP/RI	Tg neg; n=181	Tg 0.5-55000/ATg; n=33	p-value
Mean Tumor size (mm)	22.54 (SD 17.5; 1.5-75)	41.58 (SD 25.4; 5-100)	p<0.001
Vascular invasion	52 (28.7 %)	18 (54.5%)	p=0.008
Extrathyroidal growth	25 (13.8%)	20 (60.5%)	p<0.001
≥ 5 met.lymphatic glands	12 (6.6%)	8 (23.2%)	p=0.005
≥ One met.lymphatic gland	50 (29.2%)/n=171	14 (48.3%)/n=29	P=0.053

RI: Radioiodine Treatment; Tg: Thyroglobulin (µg/L); ATg: Anti-Thyroglobulin (kU/L)

Table 2: Ten patients with recurrent Differentiated Thyroid Cancer, 5 women and 5 men, age at diagnosis and time in Years to first measured Thyroglobulin level (Tg) after treatment and to confirmed recurrence. Two patients had high levels of Antithyroglobulin (ATg) instead.

	Age at Diagn	Preop Ct with	Tumor type Bi-multifocal	Metastases/ investigated	Years to Tg/ATg	Tg. (µg/L)	Years to	Tg (µg/L)	Recurrence
No	Years	Iodine (I)	diam (mm)	Lymph.glands	measured	Anti-Tg (kU/L)	Rec	ATg (kU/L)	measures taken
1	51	Ct+I	Pap/multifocal/ **7**	15/18	1.1	1.5	1.5	Tg 1.5	OP 8/27+RI
2	66	Ct+I	Foll/ **50**	0/14	7.4	0.97	9.5	Tg 7.1	Ct unclear
3	23	-	Pap/ **17**	6/27	12.1	0.6	13.6	Tg 1.1	OP 1/1 + RI
4	68	Ct+I	Pap-foll/ **24**	0/4; Pulm	3.5	0.5	6.2	Tg 0.7	OP2/21; pulm+RIx3
5	67	Ct+I	Pap/ **30**	10/31	1.1	Tg 2.9/ATg 68	1.2	Atg 1279	OP 8/49 + RI
6	26	-	Pap/multifocal/ **26**	20/30	0.3	Tg 0 /ATg 634	1.1	Atg 1795	OP 4/27 + RI
7	33	-	Pap-foll/ **40**	3/16	8.4	0.2	9.6	Tg 0.3	OP 1/9 + RI
8	78	Ct+I	Pap / bifocal/ **22**	10/10	5.2	1.8	6.4	Tg 1.8	Cytol = diff TC
9	24	-	Pap/multifocal/ **13**	5/20	2.3	0.4	5.3	Tg 3.9	OP 1/5 + RI
10	44	Ct+I	Pap/ **50**	1/39	0.9	0.3	2.9	Tg 4.9	Ct neg + Uls neg

Ct: Computer Tomography; Pap: Papillary cancer/Pap-foll: Follicular variant of papillary cancer; Foll: Follicular cancer; RI: Radioiodine treatment; Pulm: Pulmonary metastasis; Cytol: Cytology; Uls: Ultrasonography

years (SD 2.8; range 0.3-11.0).

Five of the seventeen patients who had a hemithyroidectomy were deceased at mean 77.8 years of age (range 61-101) because of death from other causes. There are 12/17 patients, now 27 to 89 years of age (mean 63.6) after mean 9.4 years (range 7.2-14.8). Five of them express uneasiness about their lack of possibility to get specialized medical check-ups.

After treatment: Surgery with or without radioactive treatment, thyroglobulin was negative in 181/214 cases (84.6%). But 33 patients had measurable thyroglobulin levels or high anti-thyroglobulin levels (n=4): 25 patients had papillary tumors, 13 the follicular variant, three had follicular tumors and five oncocytic carcinomas. In one case thyroglobulin declined slowly during six years from 2.2 to <0.1 µg/L after removal of a goiter weighing 252 g with a bifocal tumor without metastases in 15 lymphatic glands, and radioiodine, 1100 MBq. Another two patients mentioned above became negative. Two patients without radioactive treatment have low thyroglobulin levels 0.3 and 1.5 µg/L after 7 and 9 years respectively, as it seems due to aberrant benign thyroid tissue: One at the root of the tongue according to a scintigraphy, and the other was operated on because of a suspicious gland with the finding of an island of benign thyroid tissue instead. One patient is well but lost to follow-up as for thyroglobulin. Eight patients died from other causes, their last thyroglobulin levels were 1.5 µg/L to 2.2 µg/L (n=3), 7.2-22 µg/L (n=3), 200 µg/L (n=1), and one patient had anti-thyroglobulin 378 kU/L. All fifteen patients deceased in DTC were in this group. Skeletal metastases occurred in 11 patients with thyroglobulin levels, 1200 µg/L to 55000 µg/L, and pulmonary metastases occurred in 12 patients with levels 46 µg/L to 2200 µg/L (some of them had both).

Statistics: Obviously measurable thyroglobulin or high levels of anti-thyroglobulin after treatment was in most cases a sign of an advanced stage: Mean tumor diameter was 41.6 mm. Eighteen patients had angioinvasion, twenty had extra-thyroidal growth, eight patients had several metastatic lymphatic glands (mean 7.6; range 5-20), five had 1 to 3, twelve patients had no metastatic glands and four were without investigated glands. Significance tests were performed using Fisher's exact test, comparing occurrence of these probable risk factors among patients with negative thyroglobulin after treatment (n=181) and among those who after treatment had measurable thyroglobulin or high levels of anti-thyroglobulin (n=33). Their significance was confirmed (Table 1). Furthermore, the finding of just one metastatic gland at primary surgery compared to none was tested, and a borderline statistical significance was found (14 patients without investigated glands were excluded).

Microcarcinomas: There were 79/231 patients (34.2%) whose tumors were ≤ 10 mm, one was follicular, the others were papillary tumors, 25 the follicular variant. Lymphatic glands were examined in 71/79, and 17 patients had metastases (23.9%). Among the 79 patients with microcarcinomas five had angioinvasion (6.3%), six had extra-thyroidal growth (7.6%), and four had ≥ 5 metastatic glands (5.6%).

Multifocality: Occurred in 29/79 cases (36.7%), and 24/29 had investigated lymphatic glands out of which ten had metastases (41.7%). Therefore, multifocality seems to be a risk factor: Patients with bi- or multi-focal tumors were compared with patients with one single tumor in the whole series (any tumor size): The shares of patients with metastases out of the numbers who had any glands

Table 3: Ten patients with recurrent DTC, 5 women and 5 men, and time in Years after their primary diagnosis to first negative thyroglobulin level (Tg) after treatment for recurrences in four cases. Two of them had again recurrences and a third is not yet investigated.

	Years	Tg (µg/L)	Years	Tg (µg/L)	Events/Recurrences	Years	Tg (µg/L)	The situation in 2023
no	From Diagn	Atg (kU/L)	from Diagn	Atg (kU/L)	measures taken	from Diagn	Atg (kU/L)	Age (years)
1	5	Tg neg	6.5	Tg 0.6	Ct neg/+RI/Tg became neg for >3 years	17.8	Tg 0.7	no check-ups, /71
2	10.6				Age 77/unexpected death, other cause			
3	15.2	Tg 0.5	16.4	Tg 4.1	Age 41/investigation planned	16.6		no data /41
4	8.6	Tg neg	12.3	Tg 2.8	Cytol=DTC/OP declined/no complaints	16.7	Tg 10	Status quo /86
5	5.3	1279	7.9	3200	OP 2/2 + RI; but after 8.1 years pulm + RI	12.7	4000	no complaints /80
6	1.6	1960	1.9	2560	OP 2/5 +RI/ 2.9 years: OP 4/8 noduli	11.5	4000	Scint + Uls neg /38
7	10.2	Tg neg				10.4	Tg neg	Status quo /44
8	6.4	Tg 1.8			Check-ups declined/no complaints	8.9	Tg 1.8	Status quo /88
9	8.6	Tg neg				8.8	Tg neg	Status quo /34
10	3.6	Tg 18	4.1	Tg 25	pulm/RI/4.6 years/OP jugular nodulus	7.4	Tg 111	St quo since 2 years /52

Atg: Antithyroglobulin level; Ct: Computer Tomography; RI: Radioiodine treatment; pulm: Pulmonary metastases; Uls: Ultrasonography; Scint: Scintigraphy with Iodine-123

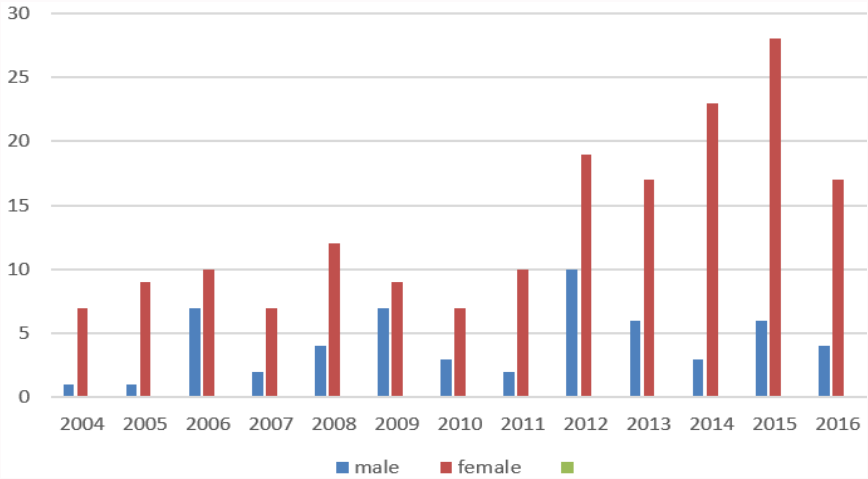

Figure 1: A consecutive series of 231 patients, 175 women and 56 men, treated for differentiated thyroid cancer, DTC during 2004-2016; 186 with Papillary tumors, 98 the follicular variant, 25 with Follicular cancer and 20 with Oncocytic carcinomas.

Data used in Figure 1:

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
male	1	1	7	2	4	7	3	2	10	6	3	6	4
female	7	9	10	7	12	9	7	10	19	17	23	28	17

examined in these groups were calculated. The result was 24/58 (41.4%) and 37/153 (24.2%), with a statistically significant difference: P=0.017 according to Fisher's test. When testing using the same procedure for tumors ≤ 10 mm, the difference was also significant with p=0.006.

Recurrences: In 13/55 patients (23.6%) without radioactive treatment thyroglobulin became measurable at low levels, mean 0.37 µg/L (range 0.1-0.7), after mean 68.8 months (range 3-133). In 27/159 patients (17.0%) who received radioactive treatment thyroglobulin also became measurable, at mean 0.47 µg/L (range 0.1-2.8), after mean 60.7 months (range 11-175), and 12/27 patients had a computer tomography with iodine administration before surgery. Apart from four cases with high levels of anti-thyroglobulin, a few more patients had elevated levels of anti-thyroglobulin that declined during the first years, and follow-up with thyroglobulin was used as usual. Recurrences occurred in ten out of these 27 cases (10/214; 4.7%), after mean 5.7 years (SD 4.2; range 1.1-13.6) (Table 2, 3). In eight cases the primary sign of recurrence was metastatic lymphatic glands in the lateral compartment. In one unfortunate case a jugular nodulus was not found until after pulmonary metastases had occurred. One patient died before the source of measurable thyroglobulin was proven. The thyroglobulin level at which recurrence occurred was mean 2.7 µg/L (range 0.3-7.1). In two cases a second recurrence occurred later on. All had radioiodine treatment after surgery, and all had primarily minimum two of the five risk factors tested above. Another two patients with thyroglobulin 0.3 and 0.7 µg/L, have after more than eight years, small but suspicious lymphatic glands at ultrasonography. At present they decline biopsy.

Only selected cases are followed ten years or more. There is no obvious systematic timetable for follow-up. After the patients

became out-patients without hospital connection, thyroglobulin determinations were not performed at all. In the most recent follow-up after mean ten years 7/13 patients without radioactive treatment had mean thyroglobulin 0.3 µg/L (range 0.1-4.4), and after mean nine years 18/27 with radioactive treatment had mean thyroglobulin 1.1 µg/L (range 0.1-10.0).

Discussion

This presentation of a consecutive series of patients treated for differentiated thyroid cancer illustrates an opposite situation to several presentations on overdiagnosis and overtreatment of this cancer form [1-6,22-24]. These patients were generally diagnosed without ultrasonography. DTC is not an aggressive tumor in comparison with many other cancer forms, but clearly, with the cases described above, and without doubt, early treatment seems preferable to late treatment. The impression is that one complete and precise operation results in better situations for the patients than if further operations will be needed later on, which is the purpose for including removal of the central lymphatic glands primarily. If not, the patients will probably be depending upon ultrasound evaluations with different intervals, which would lead to varying degrees of insecurity. Metastases <3 mm to 4 mm or intra-thyroidal tumor foci with diameters 1 mm to 4 mm, which occurred in more than 30% of the cases, cannot be identified with certainty, if at all, by ultrasound [7,8]. After thyroidectomy with a negative thyroglobulin that would not be a problem, but the frequent occurrence of metastatic lymphatic glands found in this series is justification enough for including the closest lymphatic glands at surgery.

The second possibility, lobectomy including removal of the central lymphatic glands unilaterally, gives confident data on the tumor characteristics and whether there is spread to the closest lymphatic glands. Risk factors will be identified, and in the future further prognostication made possible with gene mutation mapping [25]. Unilateral operation has the disadvantage of follow-up without thyroglobulin determinations that in spite of their variability displayed above, give valuable information and safety that is important for both patients and surgeons [12,26]. Naturally, complications after surgery would be half as frequent, but the complication rate after bilateral surgery in this series may be regarded as low [21], considering the advantage of as many as 85% became thyroglobulin negative.

The third possibility, Active Surveillance, concerns microcarcinomas. It is obvious that the important risk factors cannot be revealed with ultrasound alone, nor with FNAC and cytology. For this reason, together with the small, but not negligible, numbers of findings of multifocality, angioinvasion, extrathyroidal growth and metastatic lymphatic glands, Active Surveillance appears highly uncertain. These observations contradict some descriptions in the literature of microcarcinomas as generally harmless [22-24].

Follow-up using thyroglobulin appears to be a reliable marker in spite of its variability. There does not seem to be any clear limit for the thyroglobulin level at which extended investigations are called for, maybe in part a consequence of the level being related to the TSH level. All thyroglobulin levels given above are basic. Thyrogen stimulated thyroglobulin determinations [26] were also performed, but not during the whole period. A negative basic thyroglobulin level means safety all the same. A low level that is stable may be safe as well, but is no guarantee for tumor growth to have ceased. There is always a risk of recurrence [27-30]. It is worth noticing that some patients had skeletal metastases and/or pulmonary metastases many years, that seemed stationary, or there was slow progress long-term. This slow development of DTC in several cases may be the reason for late recurrences occurring after two or three decades [1,14]. For the time being thyroglobulin tests are in many cases not performed more than a few years after treatment. The patients' anxiety because of fear of recurrence is assuredly of longer duration. A reasonable consequence in clinical practice would be to follow more patients long-term with basic thyroglobulin determinations with intervals of 1 to 2 years instead of just leaving them. With adequate information it would easily be coordinated with the patients' yearly examinations of blood samples for their thyroxine medication, without need of connection with hospital care.

Sweden has guidelines for treatment of Thyroid Cancer in which the three different forms of treatment mentioned above are accepted since 2017 [13]. Still, individual decisions must be made in each case. This suggested improvement with longer follow-up with thyroglobulin tests for out-patients has three purposes: Since recurrences may occur decades after treatment it might be possible to find them in time for treatment with satisfactory result. The costs of these extra thyroglobulin tests would be acceptable when coordinated with the yearly check-ups. The quality of life of the patients would hopefully improve with less anxiety as thyroglobulin in most cases is a reliable tool, easy to interpret.

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Ethics

This study was approved by the Regional Ethical Review Board in Gothenburg in 2018 (D759-18).

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