Journal of Nuclear Medicine, published on November 23, 2022 as doi:10.2967/jnumed.122.264660

Radioiodine ablation of thyroid remnants in patients with Graves' orbitopathy.

Michael Oeverhaus[1]

Jana Koenen [2]

Nikolaos Bechrakis[1]

Mareile Stöhr[1]

Ken Herrmann[2]

Wolfgang P. Fendler[2]

Anja Eckstein[1]

Manuel Weber[2]

[1] Department of Ophthalmology, University Hospital Essen, Germany

[2] Department of Nuclear Medicine, University Hospital Essen, Germany

First author:

Michael Oeverhaus, MD

University Hospital Essen

Hufelandstr. 55

45147 Essen

Germany

Phone: +49201 723 2913

Fax: +49201 723 5641

Michael.oeverhaus@uk-essen.de

Corresponding Author:

Manuel Weber, MD

University Hospital Essen

Hufelandstr. 55

45147 Essen

Germany

Phone: +49201 723 2031

Fax: +49201 723 5964

Manuel.weber@uk-essen.de

Short title: Ablation of thyroid remnants

ABSTRACT

Purpose: To assess response following ablation of thyroid remnants (ATR) with radioactive iodine therapy (RAIT) in patients with unstable Graves' orbitopathy (GO) after (subtotal) thyroidectomy.

Methods: 30 patients with mild (n=4, 13%), moderate-to-severe (n=25, 83%) and very severe GO (n=1, 3%) were analyzed in this retrospective study. Primary endpoint was the improvement of GO-related symptoms as assessed by clinical activity score (CAS), NOSPECS, and soft-tissue inflammation score 3 and 12 months after ATR. Ablation success was defined by a decrease in ^{99m}Technetium-uptake (TcTU) on thyroid scintigraphy, remnant volume, and TSH-receptor antibody levels (TRAb) 3 months after ATR.

Results: Twelve months after ATR CAS, NOSPECS, and soft-tissue inflammation scores showed a significant decrease from 3.4 to 1.3 (p=<0.0001), 5.9 to 4.9 (p=0.007), and 4.7 to 2.1 (p=0.0001), respectively. After 3 months 27/30 (90 %) patients had inactive GO and 29/30 (97 %) after 12 months. No new activation of GO occurred. Remnant volume (1.4 vs. 0.4ml, p=<0.0001), mean TRAb titer (19.02 IU/l vs. 13.37 IU/l, p=<0.0001), and TcTU (0.5% vs. 0.1%; n=12; p=0.04) decreased significantly until 3 months after ATR.

Discussion: RAIT after thyroidectomy can successfully ablate residual thyroid remnants leading to an improvement of GO, reduction of inflammatory activity and stabilization of thyroid function. Thus, unstable GO patients after thyroidectomy should be considered for a scintigraphy to rule out thyroid remnants.

Keywords: Thyroid eye disease, radioactive iodine therapy, RAIT, total thyroid ablation, GO, TED, ATR

INTRODUCTION

Graves' orbitopathy (GO), the most common extrathyroidal manifestation of Graves' disease, is a disorder of autoimmune origin. Typically, patients show symptoms of inflammation of the orbital soft tissues, inflammatory triggered fibrosis of the ocular muscles and adipogenesis *(1-3*). These changes are mediated by autoantibodies against the TSH receptor, which stimulate the receptors on orbital fibroblasts. In conjunction with the induction of crosstalk with IGF-1 receptors this leads to a cascade of inflammatory conditions (*4*). Antibodies and autoimmune T-cells stimulate orbital fibroblasts to release inflammatory cytokines to produce hyaluronic acid and to differentiate into adipocytes and myofibroblasts (*5-9*). Consequently, patients suffer from signs of inflammation (pain, swelling), diplopia (due to fibrosis of extraocular muscles) and proptosis (due to adipogenesis), which has a serious impact on the quality of life of the affected patients (*10,11*). Most severely afflicted GO patients can suffer from vision loss due to optic nerve compression (*12*). Despite recent advances in targeted therapy there is none available in Europe yet. Therefore, current treatment can often only reduce symptoms, but cannot prevent the need of rehabilitative surgery (*13-16*). Management of GO comprises two main therapeutic principles: Reducing risk factors for deterioration and anti-inflammatory treatment. According to the EUGOGO (European Group on Graves Orbitopathy) 2021 guideline patients with moderate-to-severe GO are treated with immunosuppression by intravenous glucocorticoids alone or in combination with mycophenolate sodium (*17*). The aim of this anti-inflammatory therapy is to temper inflammation and prevent further deterioration. Poor control of thyroid function and high TSH receptor antibody levels can lead to new development of GO or worsening of pre-existing GO (*18-21*). Consequently, rapid achievement of euthyroidism is crucial (*8,17,20-22*). Primarily hyperthyroidism is treated with antithyroid drugs. Definitive treatment with radioactive iodine (RAI) ablation or thyroidectomy (Tx) is performed in case of relapse or poor thyroid control despite antithyroid drug treatment (*13,17,23*). The status of GO has an impact on the choice of procedure, thyroidectomy is recommended in the presence of active GO stages, though RAI might be used with sufficient corticosteroid prophylaxis (*17,23,24*). Near-total thyroidectomy is performed in patients with Graves' disease in some cases even minimally invasive with video-assisted thyroidectomy (*25*). Small remnants are left to preserve the recurrent laryngeal nerve. Scintigraphy is not always performed (*26*). Therefore, sometimes ectopic thyroid tissue is left

behind. There is evidence that larger thyroid residues are associated with poorer control of thyroid function, ongoing GO activity and persistent TRAb levels (*27,28*). In accordance, several studies have shown a higher rate of stable GO/inactivation of GO, if thyroidectomy is combined with postoperative RAIT (total ablation) (*29-31*). This beneficial role might be due to the complete removal of thyroid antigens, which is associated with a reduction in antigenic stimulation, a drop in antibody levels and cell-mediated immunoreactivity to TSH-R and improvement of GO (*31,32*). To evaluate the benefit of ablation of a significant thyroid remnant in patients with unstable GO and persistence of unstable thyroid function in terms of GO activity and severity, we performed an interdisciplinary retrospective study in our tertiary GO referral center.

MATERIALS AND METHODS

Study population

For this retrospective study we searched the institutional database of our EUGOGO (European Group On Graves' Orbitopathy) tertiary referral center from January 2005 until October 2020 (n=4641) for patients who underwent ablation of thyroid remnants (ATR) for persistent/worsening GO and thyroid dysfunction after (subtotal) thyroidectomy. Only patients with (i) active GO at baseline, (ii) comprehensive eye and thyroid examinations prior to ablation of thyroid remnants (ATR), as well as 3 and 12 months afterwards, (iii) elevated TRAb, and (iv) significant uptake on baseline thyroid scintigraphy were included in this study. The retrospective study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the University of Essen (reference number: 17-7542-BO).

Outcome measures

Primary outcome measures were an improvement of GO-related symptoms as assessed by clinical activity score (CAS), modified NOSPECS score (*33*), and soft-tissue score 3 and 12 months after ATR (*17*).

For this study, a successful ablation was defined as decreases in TRAb, ^{99m}Technetium-uptake (TcTU), ultrasound-derived thyroid volume as well as an increase in levothyroxine dose 3 months after ATR.

Clinical assessment

Eye examinations were performed using a modified EUGOGO case record form and Color Atlas in a standardized manner (*34*). All patients were evaluated by a highly trained orthoptist and by one of two specialized ophthalmologists (A.E., M.O.). Follow-up examinations were done by the same ophthalmologist 3 and 12 months after ATR, to ensure homogeneity and reproducibility. GO was diagnosed by the presence of typical clinical signs on examination, including slit-lamp biomicroscopy, applanation tonometry, funduscopy, Hertel exophthalmometry, assessment of subjective diplopia and objective measurement of deviation using the prism-cover-test and measurement of monocular excursions. GO activity was evaluated using the CAS (Clinical activity score) classification system established by Mourits et al. (*35,36*). By analysis of personal photos of the patients and patient history concerning double vision and visual acuity, we determined the dynamic of the disease and scored CAS up to 10 points at baseline. GO was classified active with CAS values of ≥4/10 points. Additionally, classification of the severity of GO (modified NOSPECS) was carried out according to the proposed criteria of the EUGOGO, as previously described (*33,37*). A maximum of 14 NOSPECS points was possible, with no signs of GO classified as 0 points. In addition, we scored the soft tissue inflammation signs derived from CAS more gradually as follows: Spontaneous retrobulbar pain (0-1), Upper lid edema (0-2), Lower lid edema (0-2), conjunctival injection (0-1), chemosis (0-1), lid redness (0-1) and swelling of caruncle or plica (0-1). The sum builds the clinical soft tissue score.

Thyroid examinations were carried out/supervised by a board-certified nuclear medicine physician at baseline and 3 months after RAIT. The examinations included patient history, ultrasound and a thyroid panel including thyroid hormones and thyrotropin receptor antibodies (TRAb) in all patients. Follow-up ^{99m}Tc-pertechnetate thyroid scintigraphy of residual thyroid gland tissue was performed for a subgroup (n=12).

Radioiodine ablation of thyroid remnants

The ^{131}I activity was determined with the aim to deliver an absorbed dose of 500 Gy to the thyroid remnants. To this end, two different methodologies were employed:

- In 17/30 patients, a radioactive iodine uptake test (RAIU) was performed, and the treatment activity calculated using the Formula of Bockisch (*38*). If the target dose could only be achieved by use of excessive administered activity (i.e. considerably higher than 500 MBq), 0.09 mg recombinant human TSH (rhTSH) each was administered on the two days leading up to ATR. This was the case in 8/17 patients with a radioactive iodine uptake deemed insufficient (median 192h-uptake 1.6% vs. 7.4% in those who did not receive rhTSH). This approach was mainly favored in later years and in patients with bigger thyroid remnants.
- In 13/30 patients, rhTSH was administered as described above and a ^{99m}Tc-pertechnetate thyroid scintigraphy performed on the day of the second injection. If the Tc-uptake was deemed sufficient by the treating physician, the administered dose was calculated, as follows estimating a radioactive iodine uptake of 10 %:

$$A[MBq] = 3.27 \times \frac{Dose\ [Gy] * Volume\ [ml]}{Uptake[\%]}$$

The second approach was mainly used in earlier years and in patients with small thyroid remnants, where the reliability of a RAIU was considered questionable. Levothyroxine treatment was not withdrawn. ATR was performed with an average activity of 452 MBq ^{131}I and measurements of intratherapeutic radioactive iodine uptake performed twice daily for a minimum of 5 total measurements. These measurements were used to calculate reached thyroid remnant doses following the medical internal radiation dose approach. Additionally, 25 patients received oral glucocorticoid therapy with 30 mg prednisolone for 4 weeks. In 5 patients with highly active GO an i.v. glucocorticoid therapy was necessary. After ATR, thyroid parameters were closely monitored, and medication adapted to ensure normal TSH levels.

Statistical Evaluation

For metric data, median values ($\tilde{x}$) and range or the mean and standard deviation (SD±) were calculated and differences between groups were evaluated with Student's t-test (two-tailed) if D'Agostino-Pearson omnibus-normality-test showed normal distribution, if not with Wilcoxon test. Fisher's exact test was used to evaluate group distributions of binary variables. Level of statistical significance was defined two-tailed as $2\alpha<0.05$. All calculations were performed with SPSS (IBM SPSS Statistics, Chicago, IL, USA, Version 22.0.0,) and Graph Pad Prism (Prism 9 for Windows, Software Inc., San Diego, CA, USA, Version 9.0.0). P-values are given descriptively without α-adjustment for multiple testing.

RESULTS

Study population

Thirty patients who met all inclusion and exclusion criteria were identified and analyzed. Four showed mild (13%), twenty-five moderate-to-severe (83%), and one sight-threatening (3%) GO. Of these, 27 were female, 3 male; the mean age (range) was 52.1 (29-80) years (an overview of baseline characteristics is provided in Table 1). All patients showed an unstable GO and fluctuating thyroid parameters. To increase radioiodine uptake, 21 patients received rhTSH before ATR.

Changes in thyroid parameters

Half of the patients (n=15) showed a remaining pyramidal lobe on pre-ATR ^{99m}Tc-pertechnetate thyroid scintigraphy. Because scintigraphy was not routinely included in follow-up examinations, only six of 15 patients with pyramidal lobe received a second analysis after ATR. In 6/6 patients the pyramidal lobe was not visible on a repeat thyroid scintigraphy 6 months after ATR (s. Figure 1).

Mean TcTU of all patiens with pre- and post-ATR ^{99m}Tc-pertechnetate thyroid scintigraphy showed a decrease from 0.5 % to 0.1 % 3 months after ATR (n=12, p=0.04; s. Figure 2).

The average thyroid volume (n=28) shrank from 1.4 ml to 0.4 ml from baseline to 3 months after ATR. The mean TRAb titer (n=21) decreased from 19.02 IU/l to 13.37 IU/l. Both changes were highly statistically significant (p=<0.0001). All patients showed a positive TRAb titer at baseline. In no case a complete regression in antibodies could be measured after ATR.

Compared to baseline, average TSH increased from 1.3 to 1.42 mU/l (p=0.75), despite increasing levothyroxine therapy (81.5 µg vs. 101.3 µg after 3 months, p=0.002; vs. 108 µg after 12 months, p=0.006), which emphasizes the loss of functional thyroid tissue and the success of ATR. An overview of the assessed thyroid parameters before and after ATR is provided in Table 2 and an overview regarding the RAI therapy parameter in Table 3.

Ophthalmological assessment

Three months after ATR CAS decreased significantly from an average score of 3.4 to 1.9 (p=0.0003; s. Figure 3). The rate of active forms decreased to 10 %. Three patients needed glucocorticoids in addition to the glucocorticoids all patients received during ablation to reach an inactive status. After 12 months 96 % of patients were inactive. CAS further improved significantly to an average score of 1.3 (p=<0.0001). Worsening of CAS was only observed in 1/30 patients (4 %), who was a heavy smoker and showed unstable thyroid function and high levels of TRAb before ATR.
The Soft-tissue-score decreased 3 months after ATR to an average score of 3.4 (p=0.002). After 12 months there was a highly significant improvement to an average score of 2.1 (p=0.0001).

Compared to baseline, after 3 months NOSPECS was reduced to 5.2 vs. 5.9 (p=0.013; s. Figure 3). A significant reduction in NOSPECS was also observed at the evaluation 12 months after ATR (4.9, p=0.007). Worsening of NOSPECS was only observed in the aforementioned risk patient after 3 months as well as after 12 months.

For the proptosis analysis we excluded all patients who received a decompression during the follow-up period and included only patients with clinically significant exophthalmos ≥ 20mm or side differences ≥ 2mm. This left at baseline 27% (n=8) patients. Three months after ATR 3 of these 8 patients improved clinically significant (reduction ≥2mm), 4 patients were stable and 1 patient showed a deteriorated situation (increase ≥ 1mm). This was the same at 12 months

follow-up. All patients who were inconspicuous at baseline (n=16) underwent no changes in proptosis during follow-ups.

An improvement or worsening of ocular motility was defined by an increase/reduction of total motility ≥ 8 °. Patients who received an orbital decompression and/or eye muscle surgery during the follow-up period were excluded from this analysis. This left 19 patients (63%). At the 3 months follow-up visit 26% of these patients showed improved motility, 74% stable and 2 patients decreased motility. Changes in ophthalmological parameters are shown in Table 4.

DISCUSSION

The results of this retrospective study show a clinical benefit of ATR in patients with unstable GO after prior thyroidectomy. Because of the complicated anatomical location small remnants of thyroid tissue can persist after surgery and subsequently trigger hyperthyroidism and GO (*39,40*). The results encourage to perform ATR in these patients with unstable thyroid function and consecutive unstable GO. This is in concordance with therapeutic principle to aim for stable euthyroidism in GO (*11,41*).

Ophthalmological assessment

Corresponding to the improvement of thyroid parameters an early response assessment 3 months after ATR, already showed significant reductions in CAS, NOSPECS, and soft-tissue score, with further improvements occurring until the 12-month follow-up. Worsening can be mostly prevented with concomitant glucocorticoid treatment (oral or intravenous depending on the activity and severity of GO prior ATR). Only one patient showed worsening of CAS and NOSPECS during the follow-up trial. This individual was a heavy smoker (30cig/d) which might be the reason for insufficient treatment response. The significant reduction of inflammatory activity is less likely due to the corticosteroid treatment patients received during ATR due to the short nature (4-6 weeks) and previous unsuccessful attempts to stabilize the GO with corticosteroids. However, a beneficial effect cannot be ruled out and should be subject to further investigation in the future.

These findings are in line with the results of prior studies: A retrospective analysis of 55 GO patients who underwent thyroidectomy, showed that the prevalence of inactive GO was significantly higher in the fraction of patients treated with additional adjuvant ATR. This has been confirmed in subsequently performed randomized control trials comparing the effects of thyroidectomy vs. thyroidectomy + ATR on GO improvement (*29,30*). Different results have been reported by a longitudinal study on 60 patients with mild to moderate GO undergoing thyroidectomy, thyroidectomy + RAIT, or treatment with antithyroid drugs, without statistically significant differences between the thyroidectomy vs. thyroidectomy +. RAIT group. Still, both groups showed significantly better outcomes compared to the group treated with antithyroid drugs (*42*). The differing results might indicate that not all patients benefit from an ATR following thyroidectomy. Therefore, ATR was in our center not performed immediately post-thyroidectomy but in case of unstable GO after surgery, which entails a negative pre-selector. Our findings therefore indicate a potential role of ATR in this setting as well. In contrast to Menconi et al.(*29*) and De Bellis et al.(*42*), we also included patients with severe GO and in contrast to Moleti et al.(*30*) intravenous glucocorticoids were only administered in 5 patients.

Despite the large amount of GO patients in our tertiary referral center only relatively few patients could be included in this trial. This is probably due to multiple reasons, e.g. the high amount of mild GO cases and many externally performed ATR due to the tertiary referral status of our center and long journeys to it. Furthermore, it might suggest that thyroidectomy alone is mostly sufficient.

Most patients in our analysis showed a moderate-to-severe GO probably since mild patients are less often referred to a university eye hospital. It could also indicate that mild forms need extensive thyroid treatment less frequently. However, this cannot be extrapolated from our data and should be investigated in a larger study. Our cohort had only one patient with sight-threatening since these patients are rare even in a tertiary referral center.

The less beneficial effect on proptosis and motility was not unexpected since fibrotic changes of the extraocular muscles and proptosis due to adipogenesis react less to inactivation of GO, as demonstrated in clinical trials of anti-inflammatory agents (*16,17*).

Changes in thyroid parameters

In line with prior observations, ATR showed a good safety profile and the administration of rhTSH was not associated with any severe ophthalmological side effects. (*30*) Follow-up examinations after 3 and 12 months showed reductions in TRAb titer, thyroid volume and TcTU implicating successful irradiation of thyroid remnant tissue. We also observed increases in levothyroxine requirements, which could be interpreted as an additional marker of successful ablation but may also be attributable to other causes, such as e.g. weight gain, which is commonly observed in patients treated with corticosteroids.

The therapeutic effect of ATR affirms prior observations that even small thyroid remnants can play a role in mediating GO and that its irradiation reduces autoimmune activity (*43,44*). Of note, half of our patients displayed a prominent pyramidal lobe on pre-treatment Tc scintigraphy suggesting that its non-resection may play a relevant role in the course of post-thyroidectomy hyperthyroidism and GO. However, since Tc scintigraphy is not performed as routine follow-up examination after thyroidectomy it remains unknown how many patients with residual pyramidal lobes may experience no complications.

Regarding TRAb Levels, most patients (93 %) showed TRAb levels above 2 IU/l (median: 18.4) at baseline 2 years after beginning of the thyroid disease. This is in concordance with previous studies showing that patients with severe, progressive GO have persistent TRAb of at least 2-6 IU/l even 2 years after onset of Graves' disease. In contrast, less severely afflicted patients showed at this time point already negative TRAb levels (*8,21*). Our patient cohort confirms these findings and represents an at-risk cohort regarding the progression of GO. Still, ATR was able to reduce TRAb levels in median from 18.4 to 13.4 IU/l after 3 months. Furthermore, the fact that 96 % patients show inactivation after ATR even in this at-risk group regarding TRAb levels, underlines the effectiveness of ATR.

Lastly, we observed a wide range of reached thyroid remnant doses in our cohort. Interestingly, in all patients, in whom the thyroid remnant dose of 500 Gy was exceeded by 20% or more, (i) the activity calculation was performed using the pre-therapeutic ^{99m}Tc-pertechnetate thyroid scintigraphy or (ii) rhTSH was administered after the RAIU meaning that the conditions during TRA and RAIU were not comparable.

The patients, in whom the target thyroid remnant dose was undershot by 20% or more (n=10) had a lower radioactive iodine uptake during TRA than in the previously performed RAIU (n=7) or than the assumed radioactive iodine uptake of 10 % in the patients, in whom no RAIU was performed (n=3).

Limitations

Limitations of this study include its retrospective design and the lack of a control group, in which the course of GO without additional ATR could be observed. Additionally, follow-up thyroid scintigraphy was missing in a subgroup of patients. Furthermore, the treatment protocol within the collective was variable, with some patients being treated following a RAIU, whereas in others a radioactive iodine uptake of 10 % was assumed if the Tc-uptake was rated sufficient by visual assessment. Based on the small sample size, caution is warranted with regards to a comparison of these two approaches. Yet, insufficient thyroid remnant doses were more commonly observed in the cohort that underwent pre-therapeutic RAIU (7/17 vs. 3/13) implying that a clear benefit of RAIU cannot be stated.

CONCLUSION

Our data indicate that radioiodine ablation of thyroid remnants is a viable treatment option in patients with unstable GO and persistence of thyroid dysfunction after thyroidectomy. Therefore, patients with unstable GO after thyroidectomy and fluctuating thyroid parameters should be considered for a scintigraphy and in case of a significant thyroid remnant an additional ablation should be performed. The persistence of the pyramidal lobe after surgery may play a pivotal role in the pathogenesis. Further studies in a randomized-control fashion are needed to determine the standalone impact of ablation of thyroid remnants.

Conflicts of interest

M. Oeverhaus, J. Koenen, N. Bechrakis, M. Stöhr, K. Hermann, A. Eckstein, W. Fendler, M. Weber state that there is no conflict of interest.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

ACKNOWLEDGEMENTS

We would like to pay tribute to our colleague Ina Binse, who contributed to the study design and supervised data collection and analysis, but who sadly died before the study was finished.

KEY POINTS

QUESTION

How does thyroid remnant ablation by use of radioactive iodine impact the course of disease in patients with persistent/worsening Graves Orbitopathy after prior thyroidectomy?

PERTINENT FINDINGS

Ophthalmological assessment revealed clinical improvement 3 and 12 months after thyroid remnant ablation in 29/30 patients. Furthermore, ultrasound, thyroid scintigraphy and TRAb indicated successful ablation.

IMPLICATIONS FOR PATIENT CARE

Thyroid remnant ablation is well tolerated and may improve treatment outcome in GO patients.

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Table 1: Characteristics of study population

Subjects (n=30)	
Age (years)	52.1±9.9
Females	90% (27)
Duration of thyroid disease (years)	2,7 [1-16]
Duration from primary thyroid treatment to ATR (in months)	17.5 [1-256]
TcTU (%)	0.2 [0,01-1.7]
Lobus pyramidalis present at baseline	50% (15)
ATR	
Oral steroids during ATR	83% (25)
Intravenous steroids during ATR	17% (5)
GO status at baseline	
Mild	13% (4)
Moderate-to-severe	83% (25)
Very severe	3% (1)
Previous steroid therapy	83% (25)
Subsequent steroid therapy	20% (6)

Unless otherwise stated data are means ±SD or proportions (%) or median ($\tilde{x}$) [range]

Table 2: Thyroid status

Subjects (n=30)	Baseline	3 months after TTA	12 months after TTA
LT4 dose (µg)	81.5±42.5	101±26.9	108±25.8
TRAb (IU/l)	18.4 [1.4- >40]	13.4 [0.58- >40]	
Thyroid volume (ml)	0.95 [0-5.5]	0.05 [0-2]	

Unless otherwise stated data are means ±SD or proportions (%) or median ($\tilde{x}$) [range]

Table 3: Radioactive iodine therapy parameter

Subjects (n=30)	
Target volume (ml)	0.95 [0-5.5]
Activity (MBq ^{131}I)	411 [100-1036]
Thyroid remnant dose (Gy)	488 [63-2153]
24h-Radioiodine-Uptake (%)	13.4±7
Effective half-Life $t_{1/2eff}$ (days)	2.8±1.5

Unless otherwise stated data are means ±SD or proportions (%) or median ($\tilde{x}$) [range]

Table 4: Ophthalmic status

Subjects (n=30)	Baseline	3 months after TTA	12 months after TTA
CAS	3.4±1.8	1.9±1.6	1.3±1.2
NOSPECS	5.9±1.9	5.1±2.6	4.9±2
Soft Tissue Score	4.7±2.6	3.4±2.9	2.1±2.1
Proptosis (mm)	18.4 [13-24.5]	18.1 [13-24]	17.9 [14-22]
Motility (°)	296.8 [157-350]	302.2 [215-350]	298.6 [180-350]

Unless otherwise stated data are means ±SD or proportions (%) or median ($\tilde{x}$) [range]

FIGURES

Figure 1: Patient example for remaining active thyroid tissue (left) and the same patient 3 months after ablation of thyroid remnant showing no uptake anymore

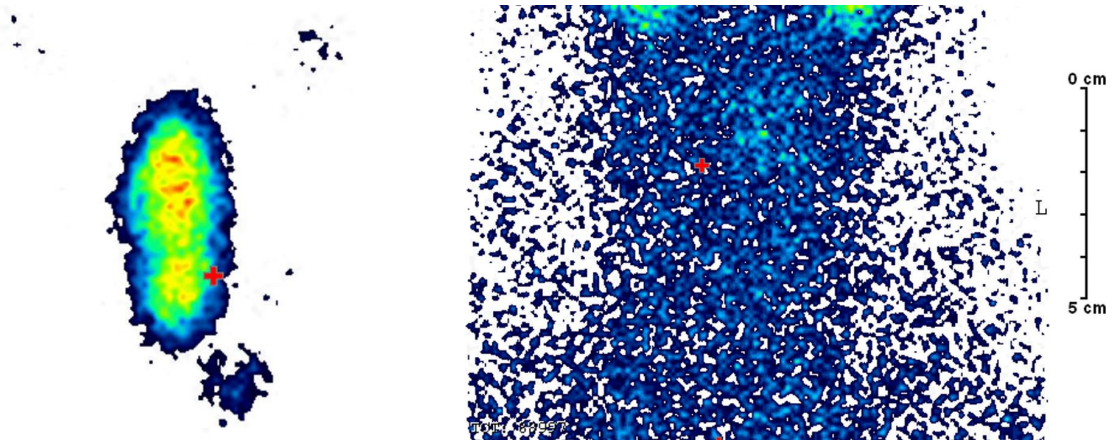


Figure 2: Patients showed a significant decrease of TRAb Levels, Thyroid volume and Technetium-Uptake in scintigraphy at 3 months follow-up compared to baseline indicating a successful ablation of thyroid remnants. **** = $p \leq 0.0001$, * = $p \leq 0.05$.

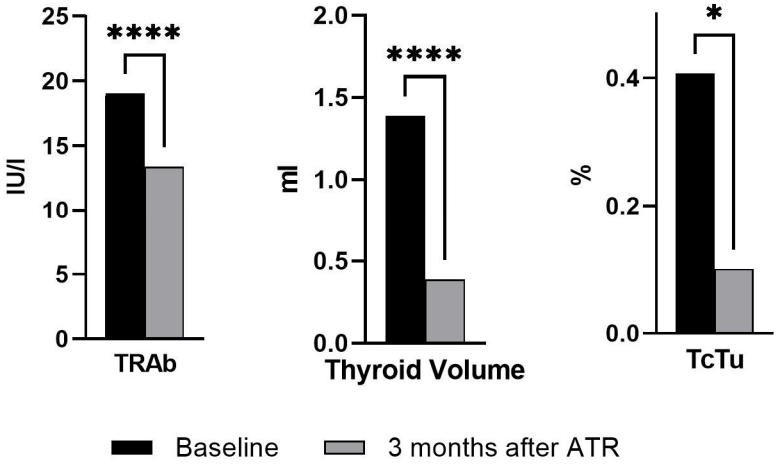
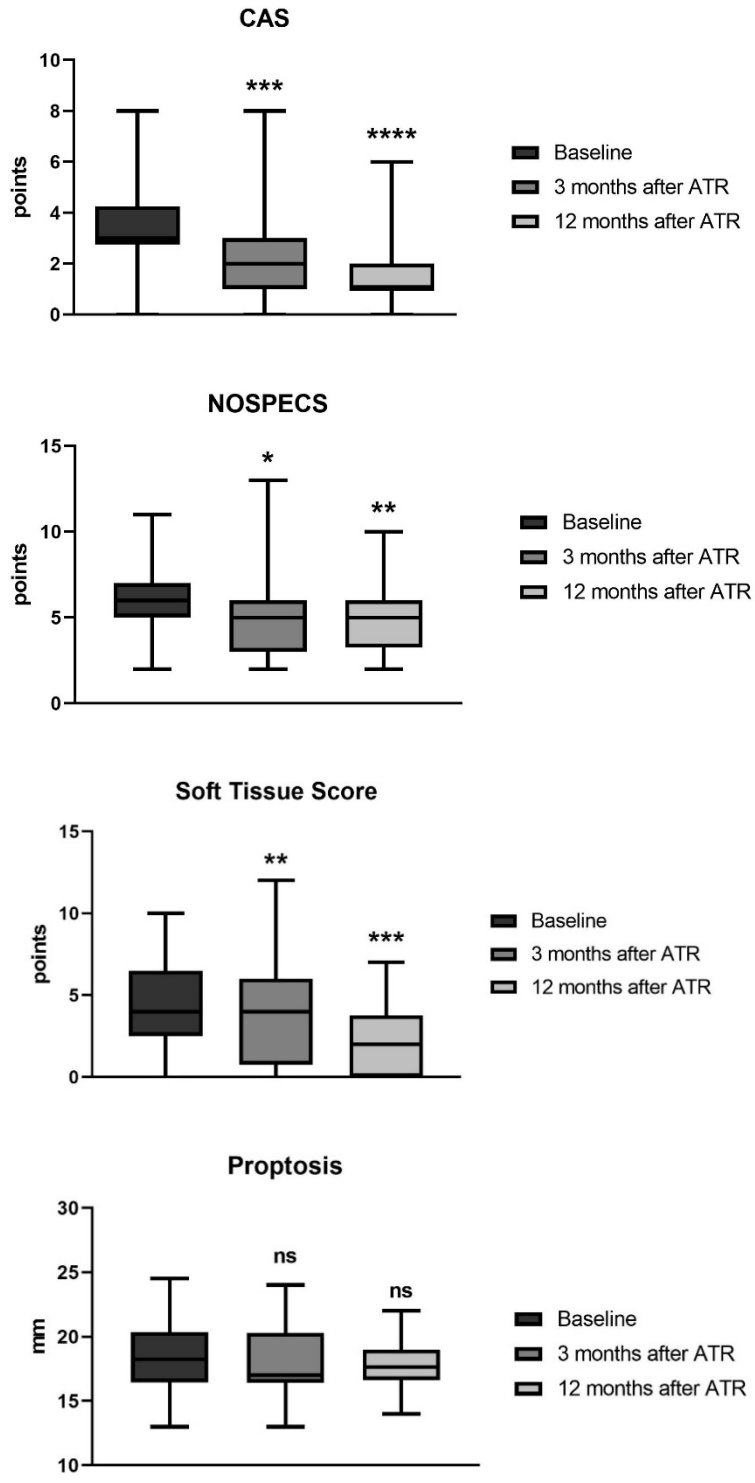


Figure 3: Patients showed a significant decrease of disease activity assessed with the soft tissue score and clinical activity score (CAS) 3 months and 12 months after ATR compared to baseline (p=0.002 and p=0.0003, respectively). NOSPECS showed also a significant decrease (p=0.013) at both time points. Proptosis was mostly stable showing no significant improvement.



Graphical Abstract