CLINICAL STUDY

Thyroid-associated ophthalmopathy; quality of life follow-up of patients randomized to treatment with antithyroid drugs or radioiodine

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Abstract

Objective: The objective of this study was to investigate quality of life (QoL) in patients with Graves' disease treated with radioiodine or antithyroid drugs.

Design and methods: The design of the study consists of an open, prospective, randomized multicenter trial between radioiodine and medical treatment. A total of 308 patients were included in the study group: 145 patients in the medical group and 163 patients in the radioiodine group. QoL was measured with a 36-item Short Form Health Status Survey questionnaire (SF-36) at six time points during the 48-month study period.

Results: Patient who developed or got worse of thyroid-associated ophthalmopathy (TAO) at any time point during the 4-year study period (TAO group) had lower QoL when no respect was paid to the mode of treatment.

TAO occurred in 75 patients who had radioiodine treatment at some time point during the study period as compared with TAO in 40 medically treated patients ($P < 0.0009$).

Comparisons between the group of patients who have had TAO versus the group without TAO, in relation to treatments and time, showed significantly decreased QoL scores for the TAO groups at several time points during the study.

In patients without TAO, there were no differences in QoL related to mode of treatment.

Conclusions: The QoL in patients with Graves' ophthalmopathy was similar in radioiodine and medically treated patients, but patients who developed or had worsening of TAO had decreased QoL independent of mode of treatment. Furthermore, patients with TAO recovered physically within 1 year but it took twice as long for them to recover mentally.

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Introduction

Hyperthyroidism is a common disease which affects 32.7–41.6 cases/100 000 per year in Sweden (1, 2). In the majority of patients, Graves' disease is the cause, and thyroid-associated ophthalmopathy (TAO) is one of the main complications (3, 4).

Several studies have shown that TAO is the main reason for discomfort and decreased quality of life (QoL) (5–8).

We have previously observed an increased risk of TAO associated with radioiodine treatment of Graves' hyperthyroidism in comparison to medical or surgical treatment in a randomized study, 'Thyrotoxicosis 1983 (TT83)' (9). In that study, patients in the radioiodine group received L-thyroxine (T₄) only when biochemical hypothyroidism occurred, which may have affected the outcome (10–13). Therefore, we designed a new randomized study 'Thyrotoxicosis 1996 (TT96)'

between radioiodine and medical treatment of Graves' hyperthyroidism, in which both study groups received L-T₄ early after administration of radioactive iodine (¹³¹I) and after antithyroid drugs (ATDs) to prevent hypothyroidism. The increased risk of TAO associated with ¹³¹I treatment was reconfirmed (14). When the TT96 study was planned in 1994–1996, we designed the study to also address QoL aspects and added the 36-item Short Form Health Status Survey (SF-36) questionnaire to the follow-up parameters. The reason for that was in our original study (9), we had observed a decreased mental score and vitality for all three treatment modalities on a follow-up 2 years later (15).

We have also shown that all three treatment groups had a lower QoL compared to an age-matched Swedish reference population group at long-term follow-up at 17 years (16). However, a possible impact of TAO on the QoL scores was not taken into account. In the present study, we report the QoL results from our large randomized study, TT96, in Graves' patients treated with radioiodine or ATD (14).

Materials and methods

Study design

The study was designed as an open, randomized, prospective multicenter trial. Patients were randomized to radioiodine (group I) or medical treatment (group M) within each center (stratified randomization). Randomization was made in blocks over time and was performed by the Oncological Centre at the Karolinska University Hospital in Stockholm. (For more details, see Traisk *et al.* 2009.)

The study was approved by the ethics committee of the Karolinska Institute (Ref.: KI 96-096).

Patients

Inclusion criteria were as follows: age, 35–69 years; symptomatic Graves' hyperthyroidism; confirmation of the diagnosis by serum TSH (≤ 0.1 mIU/l) and elevated tri-iodothyronine (T₃) and/or free T₄; thyroid uptake of ¹³¹I; and radionuclide scans compatible with Graves' disease, i.e. an even distribution of radionuclide. Furthermore, the activity of an orally administered dose of ¹³¹I (as calculated to give the patient an absorbed radiation dose of 120 Gy to the thyroid gland) should not exceed 600 MBq, enabling the therapy to be given on an outpatient basis (see formula in ¹³¹I section). This implied that patients with large goiters were excluded. Patients with a previous history of treatment with ATDs, ¹³¹I, or thyroid surgery were excluded as well as patients with severe TAO requiring treatment with corticosteroids at the time of inclusion. This was done because concomitant steroid treatment would limit the possibility to evaluate the effect of the

treatment for Graves' disease on worsening or development of TAO. Additional exclusion criteria were incipient toxic crisis, coronary heart disease, pregnancy, breast-feeding, or pregnancy planned within the following 2 years. The total number of patients that met the inclusion criteria is not known, but the reported cases were 482. A total of 333 patients gave their informed consent to participate and were enrolled in the study. For ethical reasons, clinical data were not documented for the patients who did not wish to participate or did not meet the inclusion criteria. Of the 333 patients enrolled in the study, 20 patients were excluded, 1 patient had an incorrect diagnosis (Hashimoto thyroiditis), 17 had no ophthalmological assessment at randomization, and 2 had no follow-up visits. These excluded patients had an average age of 50.1 years, the male/female ratio was 5/15; of 18 patients, 5 were smokers, and 2 were missing data. The number of patients belonging to each center was as follows: Gothenburg, 58; Lund, 40; Malmoe, 73; and Stockholm, 142 patients respectively.

Altogether, 313 patients were included in the study group: 150 patients in the medical therapy group (group M) and 163 patients in the radioiodine group (group I). Twenty-two patients in the radioiodine-treated group had TAO at the time of randomization, and 53 patients developed *de novo* ophthalmopathy. The radioiodine group thus comprises 75 patients with TAO. In the medical group, 19 patients had TAO at entry, and 23 patients developed *de novo* ophthalmopathy (eye problem developed in patients which at inclusion did not have eye problems), together thus 42 patients. Out of those, two patients were excluded from the present report due to lack of SF-36 score at baseline. Three more patients without TAO in the medically treated groups were excluded due to lack of SF-36 questionnaire. Taken together, this report therefore comprises of 308 patients (Fig. 1).

The differences between the medical and radioiodine groups were non-significant (for details, see Table 1 in Traisk *et al.* 2009). The cumulative dropout (last observation carried forward) from the ophthalmological

Figure 1 Patients in which both eye score and SF-36 questionnaire were available at baseline according to treatment (¹³¹I and medical therapy) and presence of TAO at baseline or developed *de novo* during the study.

Table 1 The presence or absence of thyroid-associated ophthalmopathy (TAO) at baseline or following treatment in the two treatment groups.

Treatment	No. of patients (%)		Total
	Without TAO	With TAO	
Medical	105 (72.4%)	40 (27.6%)	145
Radioiodine	88 (54.0%)	75* (46.0%)	163
All groups	193	115	308

* $P=0.0009$, Pearson χ^2 test.

follow-up in group I and group M respectively was as follows: at 1 year, 3 and 1%; at 2 years, 6 and 3%; and at 3 years, 10 and 9% respectively. At 4 years (i.e. after protocol for ophthalmological follow-up), 20% of the patients in both groups were still followed by ophthalmologists.

Treatment for Graves' hyperthyroidism

Medical Methimazole was given 15 mg twice daily, and at day 14, 50 μg of L-T₄ was added, and it was increased to 100 μg daily 2 weeks later.

At 6 weeks, the dose of L-T₄ was adjusted to normalize the levels of serum T₃ and free T₄ and to bring TSH to <0.4 mIU/l. A slightly elevated serum-free T₄ was accepted up to 20% above the upper normal limit. Beta-blockers were used for symptomatic treatment. Patients showing serious adverse reactions to methimazole received alternative treatment. Methimazole was replaced by 150 mg propylthiouracil three times daily in patients with minor adverse reactions.

ATD therapy was discontinued after 18 months with an additional month of L-T₄ substitution of 100 μg daily, which thereafter was discontinued.

¹³¹I Beta-blockers were used as pretreatment to the radioiodine therapy. The intention was to give one dose of radioactive iodine, aiming for an estimated absorbed radiation dose in the thyroid gland of 120 Gy. The administered activity was calculated using the following formula (10): Activity (MBq) = $(23.4 \times \text{thyroid mass (g)} \times 120 \text{ (Gy)}) / (\text{estimated uptake (0 h; \%)} \times \text{effective half-life (days)})$. The thyroid mass was assessed by thyroid scintigraphy and by palpation. Reference models of a thyroid gland were used to aid the assessment (30, 40, 50, and 60 ml). The effective half-life of ¹³¹I and the estimated thyroid uptake at 0 h were calculated from the initial 24 h thyroid iodine uptake and a new uptake test 4–9 days later, i.e. the same day the radioiodine therapy was given. L-T₄ substitution was administered with the same type of regimen as used in group M.

Follow-up by thyroidologist (endocrinologist or oncologist)

The patients were followed up by a thyroidologist four times in the first year and then one to two times yearly (endocrinologist or oncologist) where the treatment for hyperthyroidism was monitored by clinical assessment and laboratory evaluations. At the first visit and after 3, 12, 24, 36, and 48 months, they answered the Swedish version of the validated generic Medical Outcome Study (MOS) SF-36 questionnaire. If at any time TAO developed or deteriorated, the patients were referred to the ophthalmologist for additional eye examinations. (For details, see (14)).

Follow-up by ophthalmologist and SF-36

Within the first 2 weeks following enrollment, all patients were seen by an ophthalmologist and thereafter at 3, 12, 24, and 36 months as part of the study protocol and additionally if TAO developed. (For details, see (14)).

After 36 months, additional assessments were performed at the eye clinic upon referral by the thyroidologists or if the patients were followed up because of established TAO. Also, during the 4-year follow-up, patients with active TAO had eye assessments by ophthalmologists every 6 weeks until the condition had markedly improved. At each visit at the eye clinic, visual acuity, proptosis, eyelid retraction, eyelid swelling, chemosis, conjunctival redness, impairment of the eye movements, corneal ulceration, and optic nerve involvement were documented (see supplemental data of (14)). Eyelid retraction alone was not classified as TAO. Within each center, the majority of patients were followed by the same ophthalmologist throughout the study.

For the set criteria (worsening or development and improvement of TAO), two of the following four decisive factors were required (compared with baseline data): i) change in exophthalmometry readings of 2 mm or more; ii) improvement or deterioration of the patient's eye movements between the four scoring levels (no impairment, clearly impaired, diplopia in the primary position, and fixation of the globe); iii) changes of visual acuity caused by optic neuropathy; and iv) changes in two of the three TAO activity measures (chemosis, eyelid edema, and conjunctival redness). The patients who did not meet the criteria of improvement or worsening or development of TAO were referred to as having no change of TAO.

SF-36

SF-36 QoL was measured with the Swedish version of the MOS SF-36 (17–20).

Figure 2 (a and b) The results of the combined mental component score in SF-36 questionnaire for the group where the patients had TAO anytime during the study period and the group where the patients never had TAO independent of mode of treatment (Mann–Whitney *U* test). (a); a, $P=0.022$; b, $P=0.008$; c, $P=0.046$. (b); a, $P=0.033$; b, $P=0.007$; c, $P=0.051$.

The questionnaire includes 36 items that can be classified into the following eight health status subscales: physical functioning, physical role limitations, bodily pain, general health perception, vitality, social functioning, emotional role limitations, and mental health. A standardized physical component summary (PCS) and a standardized mental component score were calculated (20). In SF-36, eight subscales are summary scales transformed to range 0–100, while the PCS and the mental component summary (MCS) are weighted scores, constructed to mean = 50 and s.d. = 10 (17–20).

Statistical analysis

The result from the SF-36 scores comprises of eight subscales, which are summary scales transformed to range 0–100, while PCS and MCS are weighted scores, constructed to mean = 50 and s.d. = 10.

The statistical analyses that were used were the Mann–Whitney *U* test and the Pearson χ^2 test. The SAS System was used for analysis.

Results

Patients who had experienced development or worsening of eye problems at any time point during the 4-year study period (TAO group) had lower QoL estimated by the SF-36 questionnaire when no attention was paid to the mode of treatment. The TAO group at baseline already had a somewhat lower MCS score, although not

statistically significant. Throughout the whole study period, the TAO group had lower MCS and PCS for the first 3 years (Fig. 2a and b).

To study the possible influence of treatment modality on the occurrence of TAO, we thus found that more patients ($n=75$) who had radioiodine treatment had experienced TAO at entry or at some time points during the study period as compared with the 40 medically treated patients ($P<0.0009$, Table 1).

There were no differences in the results of the SF-36 scores between the two treatment groups. Figure 3 shows the MCS and PCS scores. It is evident from Fig. 3 that at diagnosis (month 0) of Graves' disease, both groups had decreased QoL SF-36 score as compared with the Swedish reference population. The QoL scores increased in both treatment groups during the study. Already after 3 months, the physical component score reached the average for the Swedish reference population (score 50) and remained at this level throughout the study period (48 months; Fig. 3a). The mental component score showed some delay in both the radioiodine and medically treated groups to reach the average score of 50 not until 12 months. Thereafter, the mental component score remained rather constant for 3 years or at least until 48 months (Fig. 3b).

Comparisons between the two groups of patients without TAO showed no significant differences in QoL regardless whether they had been treated with radioiodine or ATDs.

Comparisons between the group of patients who have had TAO versus the group without TAO, in relation to

Figure 3 (a and b) The results of the SF-36 questionnaire for the two treatment groups show that there were no differences between them (Mann–Whitney *U* test).

Table 2 Patients with thyroid-associated ophthalmopathy (TAO) and 36-item short form health status survey in relation to treatment group. The table shows, for both treatment groups, all time points during the study when patients with TAO as a group had a significantly decreased QoL compared with patients without TAO. Analyses were done for all time points, but only significant results are shown (Mann–Whitney *U* test).

Treatment/time point	0 months	3 months	12 months	24 months	36 months	48 months
PCS						
Radioiodine						
Medical				<i>n</i> =33, <i>P</i> =0.0323		
MCS						
Radioiodine		<i>n</i> =62, <i>P</i> =0.0187	<i>n</i> =66, <i>P</i> =0.0056			
Medical						
Physical functioning						
Radioiodine						
Medical				<i>n</i> =33, <i>P</i> =0.0035		
Physical role						
Radioiodine						
Medical				<i>n</i> =33, <i>P</i> =0.0111		<i>n</i> =19, <i>P</i> =0.0202
Bodily pain						
Radioiodine						
Medical		<i>n</i> =30, <i>P</i> =0.0174		<i>n</i> =34, <i>P</i> =0.0080		
General health						
Radioiodine				<i>n</i> =64, <i>P</i> =0.0220		
Medical		<i>n</i> =29, <i>P</i> =0.0363	<i>n</i> =35, <i>P</i> =0.0348	<i>n</i> =34, <i>P</i> =0.0345	<i>n</i> =27, <i>P</i> =0.0324	
Vitality						
Radioiodine		<i>n</i> =62, <i>P</i> =0.0382				
Medical						<i>n</i> =19, <i>P</i> =0.0312
Social functioning						
Radioiodine		<i>n</i> =62, <i>P</i> =0.0072	<i>n</i> =67, <i>P</i> =0.0326			
Medical				<i>n</i> =34, <i>P</i> =0.0032		
Emotional role						
Radioiodine			<i>n</i> =67, <i>P</i> =0.0248			
Medical				<i>n</i> =33, <i>P</i> =0.0046		
Mental health						
Radioiodine		<i>n</i> =62, <i>P</i> =0.0454				
Medical			<i>n</i> =35, <i>P</i> =0.0142	<i>n</i> =34, <i>P</i> =0.0190	<i>n</i> =27, <i>P</i> =0.0411	

treatments and time, showed significantly decreased QoL (SF-36) scores for the TAO groups at several time points during the study (Table 2).

In the whole study group, the frequency of patients with more severe ophthalmopathy was highest at 1 year after enrollment, 11.2%) compared with 6.1% at baseline. Severe ophthalmopathy was denoted here as increase of proptosis of 3 mm or more and/or deterioration of eye motility compared to baseline data.

At the 1-year time point, there was no clear correlation association between the objective eye score and PCS and MCS. Neither were there any significant differences between those with eye scores above 3 or below 3 time points with respect to PCS and MCS.

Discussion

The patients were thoroughly and equally controlled in both treatment groups throughout the follow-up period. In addition, hypothyroidism was avoided by early addition of L-T₄ in both treatment groups.

When no consideration of the mode of treatment was taken into account, it was clear that patients with TAO had a significantly decreased QoL for a considerable amount of time after treatment (Fig. 2a and b). This observation corroborated earlier finding by others when an eye-specific questionnaire had been used (6–8).

Hypothyroidism after radioiodine treatment has been considered to increase the risk of TAO. However, no such

association could be revealed in a *post hoc* analysis of a randomized prospective study (21). Furthermore, in the present study where hypothyroidism was avoided, an increased risk of TAO associated with radioiodine was still observed. The study thus supported the concept of radioiodine as an independent risk factor for development or worsening of TAO as we had proposed earlier (9, 22). The study also showed that QoL was rather equal in both treatment groups when no attention was paid to the possible influence of TAO (Fig. 3a and b). Interestingly, the improvement in mental QoL was somewhat slower to normalize as compared with the physical performance capacity. In previous studies, we have observed that patients with Graves' hyperthyroidism had lower mental QoL scores at follow-up after treatment (16). Most likely, the negative influence on normal brain functions by the hyperthyroid phase before treatment may have taken a considerable amount of time to resolve after start of treatment. According to Fig. 3b, it took 3 months for the radioiodine group and almost a year for the medically treated group to reach the average of 50 points for the Swedish reference population. The patients were substituted to have a TSH value <0.4 mIU/l, and whether this was of importance for the rather slow improvement in mental QoL is open to speculation.

The observation that the QoL scores were rather equal in both treatment groups was a positive outcome of treatment of such a common and serious disease. The finding also corroborates our previous results from TT83 that the mode of treatment did not significantly affect the QoL as estimated by the generic questionnaire SF-36 (16, 23). However, in this analysis, no attention was paid to when in the study period eye problems occurred or the clinical course of TAO. This could potentially have equaled out possible influences of TAO on SF-36 scoring. We therefore performed a subsequent analysis of when during the follow-up period the TAO occurred in each treatment group (Table 2). Patients with TAO generally had significantly lower QoL scores as compared with patients without TAO at several time points, but no consistent treatment- or time-related pattern could be found. However, patients without TAO never had lower QoL compared with TAO patients. Patients with TAO, on the other hand, had lower SF-36 scores independent of the mode of treatment.

It is important to keep in mind that the material was analyzed in the way that once a patient experienced TAO that particular patient was included in the TAO group without regard to the time point during the study the event occurred. Therefore, we have analyzed the relation between the SF-36 score and TAO at the 1-year follow-up where the TAO patients had the highest eye scores (14). This was done in an attempt to explore whether the SF-36 questionnaire at all time points reflected the influence of eye problems on QoL, since it is possible that the patients' response to the questions in SF-36 may have reflected not only the probable eye

problems but also the Graves' disease (GD) in itself. The 1-year follow-up was selected since previous studies have shown that the majority of patients felt rather well at 1 year.

The result of this analysis showed that the SF-36 due to its generic properties is not an optimal instrument for measuring QoL-related issues in this population. A caveat of this study therefore is the possibility that the SF-36 questionnaire does not capture all the appropriate quality-of-life issues that are relevant for patients who have had GD. Although the SF-36 is used extensively, it has not been specifically evaluated in a population of GD patients, but neither have other disease-specific instruments. However, the Hyperthyroidism Complaint Questionnaire developed by Fahrenfort *et al.* (4) has approached this issue with respect to long-term complaints. We however, decided to use the SF-36, for the following important reasons. The SF-36 questionnaire has been extensively evaluated in a large age-matched Swedish reference population, allowing us to make an appropriate comparison with our study group. Another caveat of the study is that it did not cover the whole spectrum of eye problems associated with Graves' ophthalmopathy since patients with the most severe TAO, who at inclusion required steroid treatment, were not included.

Conclusions

The QoL in patients with Graves' ophthalmopathy was similar in radioiodine and medically treated patients, but patients who developed or had worsening of TAO had decreased QoL independent of mode of treatment. Furthermore, patients with TAO recovered physically within 1 year, but it took twice as long for them to recover mentally. The QoL in patients without TAO seemed to be independent of mode of treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Abraham-Nordling M, Torring O, Lantz M, Hallengren B, Ohrling H, Lundell G, Calissendorff J, Jorreskog G & Wallin G. Incidence of hyperthyroidism in Stockholm, Sweden, 2003–2005. *European Journal of Endocrinology* 2008 **158** 823–827. (doi:10.1530/EJE-07-0877)
- 2 Lantz M, Abraham-Nordling M, Svensson J, Wallin G & Hallengren B. Immigration and the incidence of Graves' thyrotoxicosis, thyrotoxic multinodular goiter and solitary toxic adenoma. *European Journal of Endocrinology* 2009 **160** 201–206. (doi:10.1530/EJE-08-0548)
- 3 Bahn RS & Heufelder AE. Pathogenesis of Graves' ophthalmopathy. *New England Journal of Medicine* 1993 **329** 1468–1475. (doi:10.1056/NEJM19931113292007)
- 4 Fahrenfort JJ, Wilterdink AM & van der Veen EA. Long-term residual complaints and psychosocial sequelae after remission of hyperthyroidism. *Psychoneuroendocrinology* 2000 **25** 201–211. (doi:10.1016/S0306-4530(99)00050-5)
- 5 Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF & Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. *Thyroid* 1997 **7** 885–889. (doi:10.1089/thy.1997.7.885)
- 6 Egle UT, Kahaly GJ, Petrak F, Hardt J, Batke J, Best J & Rothenbacher M. The relevance of physical and psychosocial factors for the quality of life in patients with thyroid-associated orbitopathy (TAO). *Experimental and Clinical Endocrinology and Diabetes* 1999 **107** (Suppl 5) S168–S171. (doi:10.1055/s-0029-1212177)
- 7 Kahaly GJ, Hardt J, Petrak F & Egle UT. Psychosocial factors in subjects with thyroid-associated ophthalmopathy. *Thyroid* 2002 **12** 237–239. (doi:10.1089/105072502753600205)
- 8 Terwee C, Wakelkamp I, Tan S, Dekker F, Prummel MF & Wiersinga W. Long-term effects of Graves' ophthalmopathy on health-related quality of life. *European Journal of Endocrinology* 2002 **146** 751–757. (doi:10.1530/eje.0.1460751)
- 9 Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H & Taube A. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *New England Journal of Medicine* 1992 **326** 1733–1738. (doi:10.1056/NEJM199206253262603)
- 10 Almqvist S & Algvare P. Hypothyroidism in progressive ophthalmopathy of Graves' disease. *Acta Ophthalmologica* 1972 **50** 761–770. (doi:10.1111/j.1755-3768.1972.tb06615.x)
- 11 Kung AW, Yau CC & Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 542–546. (doi:10.1210/jc.79.2.542)
- 12 Gorman CA. Therapeutic controversies. Radioiodine therapy does not aggravate Graves' ophthalmopathy. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 340–342.
- 13 Acharya SH, Avenell A, Philip S, Burr J, Bevan JS & Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. *Clinical Endocrinology* 2008 **69** 943–950. (doi:10.1111/j.1365-2265.2008.03279.x)
- 14 Traisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nystrom E, Ponjavic V, Taube A, Torring O, Wallin G, Asman P & Lundell G. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3700–3707. (doi:10.1210/jc.2009-0747)
- 15 Ljunggren JG, Torring O, Wallin G, Taube A, Tallstedt L, Hamberger B & Lundell G. Quality of life aspects and costs in treatment of Graves' hyperthyroidism with antithyroid drugs, surgery, or radioiodine: results from a prospective, randomized study. *Thyroid* 1998 **8** 653–659. (doi:10.1089/thy.1998.8.653)
- 16 Abraham-Nordling M, Torring O, Hamberger B, Lundell G, Tallstedt L, Calissendorff J & Wallin G. Graves' disease: a long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. *Thyroid* 2005 **15** 1279–1286. (doi:10.1089/thy.2005.15.1279)
- 17 Sullivan M, Karlsson J & Ware JE Jr. The Swedish SF-36 Health Survey – I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Social Science & Medicine* 1995 **41** 1349–1358. (doi:10.1016/0277-9536(95)00125-Q)
- 18 Persson LO, Karlsson J, Bengtsson C, Steen B & Sullivan M. The Swedish SF-36 Health Survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenburg. *Journal of Clinical Epidemiology* 1998 **51** 1095–1103. (doi:10.1016/S0895-4356(98)00101-2)
- 19 Sullivan M & Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. *Journal of Clinical Epidemiology* 1998 **51** 1105–1113. (doi:10.1016/S0895-4356(98)00102-4)
- 20 Ware JE Jr & Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992 **30** 473–483. (doi:10.1097/00005650-199206000-00002)
- 21 Torring O, Tallstedt L, Wallin G, Lundell G, Ljunggren JG, Taube A, Saaf M & Hamberger B. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine – a prospective, randomized study. Thyroid Study Group. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 2986–2993. (doi:10.1210/jc.81.8.2986)
- 22 Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E & Pinchera A. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *New England Journal of Medicine* 1998 **338** 73–78. (doi:10.1056/NEJM199801083380201)
- 23 Lundgren E & Borup Christensen S. Decreasing incidence of thyrotoxicosis in an endemic goitre inland area of Sweden. *Clinical Endocrinology* 1990 **33** 133–138. (doi:10.1111/j.1365-2265.1990.tb00473.x)

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