Thyroid-Associated Ophthalmopathy; Quality-of-Life Follow Up of Patients Randomized to Treatment with Antithyroid Drugs or Radioiodine

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Abstract

**Objective:** To investigate Quality of Life (QoL) in patients with Graves’ disease treated with radiiodine or antithyroid drugs.

**Design and Methods:** Open, prospective, randomized multicenter trial between radiiodine or medical treatment. A total of 308 were included in the study group: 145 in the medical group, and 163 in the radiiodine group. QoL was measured with a 36-item Short Form Health Status Survey questionnaire (SF36) at 6 time points during the 48 month study period.

**Results:** Patient who developed or got worse of thyroid associated opthalmopathy (TAO) at any timepoint during the four 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 radiiodine 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’ opthalmopathy 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.
Introduction

Hyperthyroidism is a common disease which affects 32.7 – 41.6 cases/100 000/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 (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 randomised study, “Thyrotoxicosis 1983 (TT83)” (9). In that study patients in the radioiodine group received L-Thyroxine 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 or medical treatment of Graves’ hyperthyroidism in which both study groups recived L-thyroxin early after administration of radioactive iodine (I131) and after antithyroid drugs (ATD) to prevent hypothyroidism. The increased risk of TAO associated with I131 treatment was reconfirmed (14). When the TT96 study was planned in 1994-1996 we designed the study to also address Quality of Life aspects (QoL) and added the SF-36 questionnaire to the follow-up parameters. The reason for that was that we in our original study (9) 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 yr; symptomatic Graves’ hyperthyroidism; confirmation of the diagnosis by serum TSH (\leq 0.1\text{mIU/liter}) and elevated T3 and/or free T4, thyroid uptake of iodine-131, and radionuclide scans compatible with Graves’ disease, i.e. an even distribution of radionuclide. Furthermore, the activity of an orally administered dose of iodine-131 (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 Iodine-131 section). This implied that patients with large goitres were excluded. Patients with a previous history of treatment with antithyroid drugs, iodine-131, 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 full 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, twenty patients were excluded: one patient had an incorrect diagnosis (Hashimoto thyroiditis), 17 had no ophthalmological assessment at randomization, and two had no follow-up visits. These excluded patients had an average age of 50.1 yr, the male/female ratio was 5/15, five of 18 were smokers, and two 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.

All together 313 were included in the study group: 150 in the medical therapy group, and 163 in the radioiodine group. 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 developed de novo ophthalmopathy (eye problem developed in patients which at inclusion did not have eye problems), together thus 42 patients. Out of those 2 patients are excluded in the present report due to lack of SF-36 score at baseline. Additional three patients without TAO in the medical treated groups are excluded due to lack of SF-36 questionnaire. Taken together, this report therefore comprises 308 patients (Fig 1)

The differences between the medical and radioiodine group were non-significant (for details please see Table 1, in Traisk et al 2009). The cumulative dropout (last observation carried forward) from the ophthalmological follow-up in group I and group M, respectively, was as follows: at 1 yr, 3 and 1%; at 2 yr, 6 and 3%; and at 3 yr, 10 and 9%, respectively. At 4 yr (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-thyroxine was added, and it was increased to 100 µg daily 2 weeks later.

At 6 weeks, the dose of L-thyroxine was adjusted to normalize the levels of serum T3 and free T4 and to bring TSH to less than 0.4 mIU/liter. 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.

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

**Iodine-131**

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):

\[
\text{Activity (MBq)} = \frac{[23.4 \times \text{thyroid mass (grams)} \times 120 \text{ (Gy)}]/[\text{estimated uptake (0 h; %)}] \times \text{effective half-life (days)}}
\]

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 iodine-131 and the estimated thyroid uptake at zero hours were calculated from the initial 24-h thyroid iodine uptake and a new uptake test 4 to 9 d later, i.e. the same day the radioiodine therapy was given. L-Thyroxine 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 4 times the first year and then 1-2 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) 36-item 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 Traisk et al 2009).

**Follow-up by ophthalmologist and SF-36**

Within the first 2 weeks after 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 Traisk 2009).

After 36 months, additional assessments were performed at the eye clinic upon referral by the thyroidologists or if the patients were followed because of established TAO. Also, during the 4-yr follow-up, patients with active TAO had eye assessments by ophthalmologists every 6 wk 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 (Appendix I, published as supplemental data on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). 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): 1) change in exophthalmometry readings of 2 mm or more; 2) improvement or deterioration of the patient’s eye movements between the four scoring levels (Appendix I: no impairment, clearly
impaired, diplopia in the primary position, fixation of the globe); 3) changes of visual acuity caused by optic neuropathy; and 4) 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. Quality of life was measured with the Swedish version of the Medical Outcome Study 36-item Short Form Health Status Survey (SF36) \(^{(17-20)}\).

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 and a standardized Mental Component Score were calculated \(^{(20)}\). In SF-36, eight subscales are summary scales transformed to range 0–100 while the Physical Component Summary and the Mental Component Summary are weighted scores, constructed to mean = 50 and SD = 10 \(^{(17-20)}\).

**Statistics**

The result from The SF-36 scores comprises eight subscales, which are summary scales transformed to range 0–100 and Physical Component Summary and Mental Component Summary are weighted scores, constructed to mean = 50 and SD =10.

The statistic analyses that were used were the Mann-Whitney U-test and the Pearson Chi-square test. The SAS System was used for analysis.

**Results**
Patient who had experienced development or worsening of eye problems at any timepoint during the four 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 already at baseline had a somewhat lower mental component summary score (MCS), although not statistically significant. Throughout the whole study period the TAO-group had lower MCS and PCS the first three years (fig 2 a, 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 point during the study period as compared with the 40 medically treated patients (p < 0.0009, Table 1).

There were no differences in the results on the SF-36 scores between the two treatment groups. Figure 3 shows the Mental and Physical Component Summary score. It is evident from figure 3 that at diagnosis (month 0) of Graves’ disease both groups had decreased QoL SF36 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 month) (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 three years or at least until month 48 (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 antithyroid drugs.
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 (SF36) 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 opthalmopathy was highest at one year after enrolment, (11, 2 percent) compared with 6, 1 percent at baseline. Severe opthalmopathy was here denoted as increase of proptosis of 3 mm or more and/or deterioration of eye motility compared to baseline data.

At one 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-score above 3 or below 3 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-thyroxine 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 quality of life for a considerably time after treatment (fig 2a, 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 considerably 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 medical treated group to reach the average of 50 points for the Swedish reference population. The patients were substituted to have a TSH value less than 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-problem occurred or the clinical course of TAO. This could potentially have equalled 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 SF36 scores independent of the mode of treatment.
It is important to keep in mind that the material was analysed 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 one-year follow-up where the TAO-patients had the highest eye-scores. This was done in an attempt to explore whether the SF36 questionnaire at all reflected the influence of eye-problems on quality of life. 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 in itself. The one year follow up was selected since previous studies have shown that the majority of patients felt rather well at one 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 Graves’ disease. 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 has approached this issue with respect to long-term complaints. We decided to use the SF-36 however, 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’ opthalmopathy since patients with the most severe TAO, who at inclusion required steroid treatment, were not included.

Conclusions
The QoL in patients with Graves’s 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 seem to be independent of mode of treatment.

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The authors have no conflicts of interest to disclose.

Appendix:

The Thyroid Study Group of the TT 96 trial is represented by the authors listed above and the following collaborators: L Tallstedt from Department of Clinical Neurosciences, St. Erik Eye Hospital, V Ponjavic from Departments of Endocrinology and Ophthalmology, Lund University Hospital A Taube from Department of Information Science, University of Uppsala, T Andersson from Department of Ophthalmology, Sahlgrenska University G. Lindstedt from the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg; A. Michanek from the Department of Oncology, Sahlgrenska University Hospital, Gothenburg; K. Norrsell from the Department of Ophthalmology, Sahlgrenska University Hospital, Gothenburg; S. Valdemarsson from the Department of Endocrinology, Lund University Hospital; M. Garkavij, J. Tennvall, and H. Widmark from the Department of Oncology, Lund University Hospital; G. Stigmar from the Department of Ophthalmology, Lund University Hospital; Å. Arwidi and G. Bjelkengren from the Department of Oncology, Malmoe University Hospital; B. Hemdahl and H. Jönsson from the Department of Radiophysics,
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References


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Table 1. The presence or absence of TAO at baseline or following treatment in the two treatment groups, ***p= 0.0009 Pearson Chi-square test.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Treatment</th>
<th>Without TAO</th>
<th>With TAO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>Medical</td>
<td>105</td>
<td>40</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72.4%</td>
<td>27.6%</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>Radioiodine</td>
<td>88</td>
<td>75***</td>
<td>163</td>
</tr>
<tr>
<td>Percent</td>
<td></td>
<td>54.0%</td>
<td>46.0%</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>All groups</td>
<td>193</td>
<td>115</td>
<td>308</td>
</tr>
</tbody>
</table>
Table 2. Patients with TAO and SF-36 in relation to treatment group. The table shows, for both treatment groups, at all time point during the study when patients with TAO as a group had a significant decreased QoL compared to patients without TAO. Analyses were done for all time points but only significant results are shown (Mann-Whitney U-test).

<table>
<thead>
<tr>
<th>Treatment/ Timepoint</th>
<th>0 months</th>
<th>3 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
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</thead>
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<tr>
<td>PCS- Physical Component Summary</td>
<td>Radioiodine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td></td>
<td></td>
<td></td>
<td>n=33, p=0.0323</td>
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<tr>
<td>MCS- Mental Component Score</td>
<td>Radioiodine</td>
<td>n=62, p=0.0187</td>
<td>n=66, p=0.0056</td>
<td></td>
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<td></td>
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<tr>
<td>PF- Physical Functioning</td>
<td>Radioiodine</td>
<td></td>
<td></td>
<td>n=33, p=0.0035</td>
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<td></td>
</tr>
<tr>
<td>Medical</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RP-</td>
<td>Radioiodine</td>
<td></td>
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<td></td>
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<tr>
<td>Physical Role</td>
<td>Medical</td>
<td>Radioiodine</td>
<td>n=33, p=0.0111</td>
<td>n=19, p=0.0202</td>
<td></td>
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<tr>
<td>BP- Bodily Pain</td>
<td>Medical</td>
<td>n=30, p=0.0174</td>
<td>n=34, p=0.0080</td>
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<td>GH- General Health</td>
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<td></td>
<td>Medical</td>
<td>n=29, p=0.0363</td>
<td>n=35, p=0.0348</td>
<td>n=34, p=0.0345</td>
<td>n=27, p=0.0324</td>
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<td>VT- Vitality</td>
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<td>n=62, p=0.0382</td>
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<tr>
<td></td>
<td>Medical</td>
<td>n=19, p=0.0312</td>
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<td>SF- Social Functioning</td>
<td>Radioiodine</td>
<td>n=62, p=0.0072</td>
<td>n=67, p=0.0326</td>
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<td>n=34, p=0.0032</td>
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<td>Radioiodine</td>
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<tr>
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<td>n=34, p=0.0190</td>
<td>n=27, p=0.0411</td>
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</table>
**Figure legends**

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

**Figure 2a, b**

The results of the combined mental component score in SF36 questionnaire for the group where the patients had TAO anytime during the study period and the group where the patients never had had TAO independent of mode of treatment (Mann-Whitney U-test).

2a; a: p = 0.022; b: p = 0.008; c: p = 0.046 2b; a: p = 0.033; b: p = 0.007; c: p = 0.051

**Figure 3a, b.** The results of the SF36 questionnaire for the two treatment groups show that there were no differences between them (Mann-Whitney U-test).
Study group 308

Iodine-131 (TAO) 75
Iodine-131 (No TAO) 88
Medical therapy (TAO) 40
Medical therapy (No TAO) 105
Figure 2.

(a) PCS

(b) MCS