

Need for thyroidectomy in patients treated with radioactive iodide for benign thyroid disease

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ABSTRACT

INTRODUCTION: Nodular toxic and non-toxic goitres are seen in approximately 15% of Danish women, and the pros and cons of thyroidectomy versus radioiodine (RI) therapy are often discussed. The purpose of this study was to evaluate the type and number of patients treated on the indication of hyperthyroidism or benign goitre who did not achieve a sufficient effect of RI therapy and therefore needed thyroidectomy.

MATERIAL AND METHODS: Between 1 January 2003 and 1 January 2008, a total of 873 patients were treated with RI on the indication of benign thyroid disease at Herlev Hospital (Denmark). Data concerning these patients were listed consecutively in a database. The data were subsequently cross-checked with the Danish Thyroid Surgery Quality Register (THYKIR) which contains data on all patients treated with thyroid surgery at Danish departments of ear, nose and throat and head and neck surgery since 1 January 2001. Patient data were also cross-checked with the National Patient Register data. The unique Danish social security numbers were used to compare data.

RESULTS: Among the 873 patients treated with RI, 36 were listed in the THYKIR database. Eleven of these had primary thyroid surgery and subsequently underwent RI treatment due to goitre recurrence. Twenty-five patients first received RI therapy and subsequently thyroidectomy due to persisting symptoms (17 had non-toxic goitre and compression symptoms (among these eight had a large goitre with a thyroid volume of > 100 ml (range 100-389 ml)), five had nodular toxic goitre and three had diffuse toxic goitre and continuing hyperthyroidism despite RI treatment. Thyroid surgery revealed a small (2-3 mm) cancer in two patients, both from the group of patients with nodular toxic goitre.

CONCLUSION: The effect of RI therapy sufficiently solved the problem (hyperthyroidism or goitre) and surgery was hence avoided in 848 of 873 (97%) patients. However, within the group of patients with nontoxic goitre, a subgroup of patients with large goitres seems to be resistant to RI treatment and does not achieve sufficient effect under the current RI therapy regime.

FUNDING: not relevant.

TRIAL REGISTRATION: Danish Data Protection Agency (Datatilsynet) HEH.afd.O.750.86-7 and 2010-231-0068.

to moderate iodine deficiency previously present in Denmark [1]. To redress this deficiency, a Danish iodine programme was initiated in 2000, the effect of which is expected to manifest itself during the coming decades. The increase in iodine intake will not reverse nodules already present, but it is expected to reduce the development of new nodules. Therefore, the current, high incidence of thyroid nodules is expected to persist for another 20-30 years [1].

In benign goitre or hyperthyroidism, thyroidectomy or radioiodine (RI) treatment is used if medical treatment proves insufficient. In large goitres, surgery is the gold standard [2, 3]. Surgery allows removal of the whole thyroid gland, but carries a risk of complications such as postoperative haemorrhage, recurrent laryngeal nerve palsy, hypoparathyroidism and hypothyroidism [4-6]. On the other hand, RI therapy is becoming increasingly popular in the treatment of small to moderately sized goitre, toxic as well as non-toxic [7-9]. RI treatment can be performed in an out-patient clinic where small doses of RI are applied which results in a minor and more individualized reduction of the thyroid volume. An effect is expected after 12 (24) months. Treatment with thyroxineLT4 for nodular non-toxic goitre is used in some European countries, but previous studies have demonstrated that such treatment has only limited effect [10] and it is not standard in Denmark.

The purpose of this study was to estimate the need for surgical intervention after RI treatment in patients with benign goitre or hyperthyroidism.

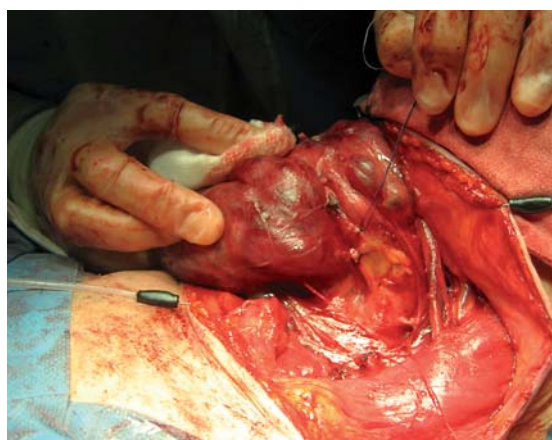
ORIGINAL ARTICLE

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Dan Med Bul 2011;58(12):A4343



Surgery of a large nodular goitre.

Nodular toxic and nontoxic goitres are seen in approximately 15% of Danish women and are related to a mild

MATERIAL AND METHODS

In the period from 1 January 2003 to 31 December 2007, a total of 873 patients received RI treatment for benign goitre or hyperthyroidism at Herlev Hospital (Denmark). Patient- and disease-related data were registered in a database (Danish Data Protection Agency journal no. HEH.afd.O.750.86-7). Patients who had received thyroid surgery after RI treatment were identified through comparison of data in the Danish Thyroid Surgery Quality Register (THYKIR) with data in the National Patient Register (NPR). This cross analysis was performed in May 2010. The unique Danish social security number was

used to identify register data. Permission was granted by the Danish Data Protection Agency (j. no. 2010-231-0068).

The indications for RI therapy were:

- Definitive therapy for nodular toxic goitre.
- Definitive therapy for diffuse toxic goitre when recurrence or difficulties with the primary medical treatment of hyperthyroidism were encountered.
- Induction of volume reduction in patients with a small to moderately sized non-toxic goitre and compression symptoms, sufficient iodine uptake and *no* suspicion of malignancy.
- Induction of volume reduction in patients with large goitre and contraindications to surgery (prior subtotal thyroidectomy was considered a relative contraindication), or if the patient refused surgery.

The choice between primary surgery and RI therapy was given to all patients; however, RI was recommended by the clinicians in cases in which they expected RI therapy would have sufficient effect.

The indication of therapy and estimation of dose were supervised by a team of three specialized endocrinologists. The dose was given as a standard dose of 197, 407 or 592 MBq as estimated from the size of the thyroid and in patient with a non-toxic goitre a 24-hour iodine uptake. A maximum single dose of 592 MBq was given in accordance with to the Danish radiation guideline for RI therapy given in outpatient clinics (one patient received a dose of 1,200 MBq as a single dose in 2003). In general, an iodine uptake of more than 20% was required in patients with a non-toxic goitre.

The indications for surgery following RI therapy were: Inadequate stabilization of thyroid function or inadequate volume reduction and continuing goitre-related discomfort.

The decision to use another RI therapy or thyroidectomy was supervised by the same three specialists and no changes were made in the local recommendations during the period. In general, the effect of nontoxic goitre was evaluated 12 months after RI therapy. Another RI dose was given if *some but not sufficient* effect was seen. In hyperthyroid patients, evaluations were made after 6-12 months.

Data concerning time to event were analyzed using the Kaplan-Meier method and differences between groups were tested with a Log Rank test.

Trial registration: Danish Data Protection Agency (Datatilsynet) HEH.afd.O.750.86-7 and 2010-231-0068.

RESULTS

A total of 873 patients were included in the database

TABLE 1

Characteristics of radioiodine-treated patients according to the most predominant goitre types^a.

	Nodular goitre		Diffuse goitre	
	non-toxic	toxic	non-toxic	toxic
n	182	496	7	186
Age, median (range), years	57 (27-91)	67 (25-94)	46 (35-57)	48 (18-87)
Cumulative activity, median (range), MBq	407 (197-1776)	407 (197-1,221)	407 (197-592)	407 (197-2,368)
<i>Treatment, n (%)</i>				
× 1 RI	166 (91)	461 (93)	7 (100)	167 (89)
× 2 RI	15 (8)	32 (6)	0 (0)	16 (9)
× 3 RI	1 (1)	3 (1)	0 (0)	2 (1)
× 4 RI	0 (0)	0	0 (0)	1 (1)
Thyroidectomy, n (%)	16 (9)	5 (1)	1 (14)	3 (2)
Thyroid cancer, n	0	2	0	0

RI = radioiodine therapy.

a) Two patients with unknown type of goitre have been excluded from the table.

TABLE 2

Characteristics of thyroidectomized patients according to the most predominant goitre types.

	Nodular goitre		Diffuse goitre	
	non-toxic	toxic	non-toxic	toxic
N	16	5	1	3
Total/hemi-thyroidectomy, n	9/7	2/3 (isthmus resection 5 ml in 1)	0/1	3/0
Volume of removed thyroid tissue, median (range), ml	208 (15-514)	25 (5-247)	20	(22-157)
Previous thyroid surgery, n	2	0	0	0
Indication of thyroidectomy	Compression symptoms in all	Compression (1 had a non-functioning benign adenoma) Continuous hyperthyroidism: 1	Compression symptoms: 1	Continuous hyperthyroidism: 3
24-hours iodine uptake	Measured in 13 patients Median: 29% Range: 18-47%	–	–	–
Complications	1 patient who was previously partially thyroidectomized developed bilateral recurrence palsy	0	0	0

(730 females and 143 males). The characteristics of the patients according to predominant goitre type are shown in **Table 1**.

A cross-check with the THYKIR database and the NPR showed that 36 of the patients had received thyroid surgery (4%). In 11 of these cases, the surgery had been performed prior to the RI treatment, which left 25 (2.7%) patients who needed thyroid surgery after RI treatment. The 11 patients who had thyroid surgery before the RI treatment were omitted from the time-to-event-related analyses.

In 803 patients only one RI treatment was given (92%). However, in 70 patients (8%), two or more treatments were necessary to obtain a sufficient treatment effect. The median initial RI dose was 407 MBq (range 197-1,200) and the median cumulated dose was 407 MBq (range 197-4,434).

Data of patients needing surgery are shown in **Table 2**.

Kaplan-Meier estimates were calculated for the time from initial RI treatment to the time of surgery or supplementary RI treatment. The overall five-year probability of avoiding surgery was estimated to 97.1% (confidence interval (CI): 96.0-98.2%) and the overall five-year probability of avoiding supplementary treatment with RI was 91.5% (CI: 89.6-93.4%). The overall five-year probability of avoiding surgery and/or supplementary RI treatment was 89.0% (CI: 86.9-91.2%). **Figure 1** shows the correlated Kaplan-Meier plots.

Figure 2 shows the probability of avoiding thyroid surgery according to the most predominant goitre types. The group of diffuse nontoxic goitres consisted of only seven patients of whom only one needed surgery. The difference between the nodular non-toxic goitres and the group of toxic diffuse and toxic nodular was highly significant, which indicates a lower efficacy of RI in non-toxic nodular goitres.

DISCUSSION

It is often discussed which treatment modality should be preferred in the therapy of goitre, toxic as well as non-toxic [3]. A randomized controlled trial (RCT) would give us some answers. However, the treatment modalities (surgery or RI) are very different, and patients often have their own preference; some patients will do almost anything to avoid surgery. On the other hand, other patients want the problem solved as soon as possible and they want to be sure that no cancer has been missed. Also, some patients are afraid of a treatment modality involving radioactivity. Consequently, an RCT will be difficult to carry out, which justifies a retrospective set-up.

This study enjoys the advantage of making prospective use of a database that describes a consecutive group of patients from a single department where no

changes in treatment regimens were made during the study period. The evaluation was done more than two years after RI therapy at which time the full effect of the RI therapy had presumably occurred. However, observation time is crucial in studies of this type and may have great impact on results. We therefore used survival statistics.

Previous surgery on the thyroid gland is considered a relative contraindication for another surgical thyroid procedure due to an increased risk of complications related to surgery in the same region [8, 9]. Previously, partial lobar resection of the thyroid gland was used routinely and a Danish study has shown goitre recurrence in approximately 25% during a 25-years follow-up [11]. Current recommendations are that surgery be more complete to avoid recurrence [5] and hence reduce the need for reoperation. In the present study, one patient who previously had a bilateral partial resection developed recurrence of a large goitre that proved resistant to RI therapy. A second thyroidectomy was necessary in this case and unfortunately the patient got

FIGURE 1

Kaplan-Meier plot showing the probability of avoiding surgery or supplementary radioiodine treatment for 860 patients eligible for time-related analysis. RI = radioiodine therapy.

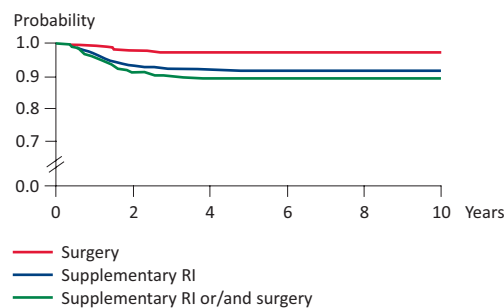
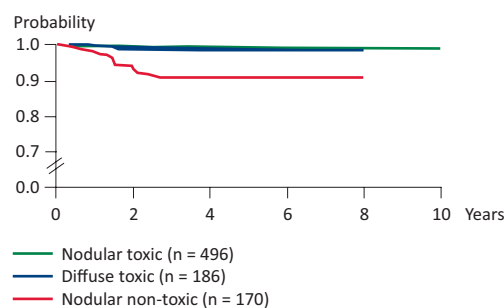


FIGURE 2

Kaplan-Meier plot showing the probability of avoiding surgery according to the most predominant goitre types. The difference between the two toxic types and the nodular non-toxic goitre was significant ($p < 0.01$).



a bilateral palsy of the recurrent laryngeal nerves and therefore needed tracheotomy. This might have been avoided if the primary thyroid surgery had been more complete.

The limitations of this retrospective study are wide-ranging. Firstly, thyroid volume was not measured systematically. We were therefore unable to describe the thyroid volume before RI therapy or to describe the actual volume reduction. However, previous studies from our group and others have shown a reduction of approximately 50% over 1-2 years [12-17].

Secondly, no attempt was made to quantify a possible partial effect of RI therapy in those patients in whom therapy was did not have sufficient effect or who needed surgery or supplementary RI. In this study, ten of 25 patients needing surgery had a large goitre exceeding 100 ml in volume. Previous trials evaluating large goitres have described a decreased effect of RI therapy in large goitres [17], but if RI therapy is combined with injection of recombinant human thyroid-stimulating hormone (TSH), the effect may be improved [18]. In our patients with large goitres, we expect that the RI therapy was insufficient. We therefore suggest that one of the three following options be considered: 1) surgery, 2) a combination of RI therapy and recombinant human TSH (when hopefully soon registered for this use), or 3) a high dose of RI given in-hospital (not in the outpatient clinic) in conformity with prevailing radiation provisions. It might be argued that some of our patients with a very large goitre should not have been offered RI therapy in the first place; however these, patients either had a contraindication or wanted to avoid surgery.

Thirdly, no unambiguous definition determined when RI therapy would be insufficient and surgery had to be done. The choice of therapy was determined for each patient individually and guided by the individual patient's preference. A small goitre with a close relation to the trachea or the oesophagus can induce symptoms, while a large goitre with no such relation can be asymptomatic. This explains the large range in removed thyroid tissue (5-514 ml).

Fourthly, patients who receive thyroid surgery after RI treatment may have been missed in the cross-checking procedure between the RI-database and the THYKIR/NPR. However, the risk of this is considered absolutely minimal.

CONCLUSION

Comparison of data on consecutively RI-treated patients with data on patients needing thyroid surgery shows that RI therapy apparently eliminated the need for surgical treatment in approximately 97% of patients in our study-group with benign goitre and/or hyperthyroidism.

The effect of treatment was significantly better in toxic than in non-toxic patients. The study was unable to evaluate goitre size as an indicator of efficacy. However, it is anticipated that patients with non-toxic, large goitres may be resistant to RI treatment as the effect of the current regime is expected to be insufficient. In patients with large goitres, surgery or a high dose of RI or a combination of RI therapy and recombinant human TSH should be considered.

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ACCEPTED: 15 September 2011

CONFLICTS OF INTEREST: none

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