

NON SURGICAL TREATMENT OF THYROID GOITRE

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OUTLINE AND SCOPE OF THE PRESENTATION

- Present argument for non surgical treatment of thyroid goitre
- The scale of problem of thyroid goitre
- The most serious or dangerous cause is cancer
- That most thyroid goitres are benign
- Treatment of benign goitre should be non surgical



Introduction

- Thyroid Goitre is the most commonly diagnosed endocrine disease \pm 3% to 7% clinically palpable.
- Increased use of ultrasonography and other imaging modalities uncover many asymptomatic thyroid nodules \pm 20% to 76%.
- Estimated that there are 300,000 new cases p.a. in USA.
- More common in women and incidence increases with age
- Although rare, the most feared cause of thyroid goitre is malignancy.
- Male goitre more likely to have malignancy than female.
- Upto 40% of people at age 40yrs have asymptomatic micronodular papillary cancer.

TABLE 7. Incidence of Clinical Thyroid Cancer per 100,000 Population^b (Age-Standardized Rates—World)

Country	Male	Female
Canada (6 provinces)	0.5–1.7	2.3–5.2
Japan (Miyagi prefecture)	0.8	2.0
Poland (south)	0.4–1.1	0.8–2.2
Colombia (Cali)	3.5	5.5
Hawaiian Japanese	1.7	6.5

TABLE 2. Distribution of Cases by Age and Sex

Age groups (yrs)	No. of OPC/ no. of thyroids examined			Prevalence (%) Both sexes
	Males	Females	All	
<1	—/10	—/5	—/15	0
1-10	—/10	—/11	—/21	0
11-20	3/17	—/5	3/22	13.6
21-30	2/12	2/6	4/18	22.2
31-40	6/14	—/3	6/17	35.3
All cases	11/63	2/30	13/93	14.0

OPC: occult papillary carcinoma.

THYROID MALIGNANCIES

- Thyroid cancer is present in upto 17% SNG and 13% MNG.
- TC prevalence is 0.1% of adults \geq 50yrs and forms 0.3% of all cancer deaths in USA.
- Well differentiated thyroid follicular cell cancer viz papillary and follicular are TSH dependant have a very good prognosis if treated early .
- Therefore management of nodular goitre is driven by the fear of missing early cancers.

McCall A et al. Surgery 1986

Castro MR, Gharib H. Ann Intern Med 2005

Table 1 Malignancy in multinodular goitre (MNG) and solitary nodule (SN)

		Total	Cancer <i>n</i> (%)	Carcinoma	Lymphoma
MNG	Males	23	3 (13)	1	2
	Females	149	11 (7.3)	6	5
	Total	172	14 (8)	7 (50)	7 (50)
SN	Males	20	2 (10)	2	0
	Females	85	14 (16.5)	12	2
	Total	105	16 (15.2)	14 (87.5)	2 (12.5)

Table III. Comparison of the incidence of carcinoma in patients with solitary cold nodules and multinodular goiter

	<i>Solitary cold nodule (%)</i>	<i>Multinodular goiter (%)</i>
Men	13	29
Women	17	9

Table I. Incidence of Thyroid Cancer in Nodular and Toxic Thyroid Goitre

Reference	Country	Sample Size			Incidence %			Comment
		SNG*	MNG**	Combined	SNG	MNG	Combined	
McCall A et al 1986 ¹⁰	USA	96	69		17	13		Note men more
Smith JJ et al 2013 ¹¹	USA			1523			15.6	Includes toxic MNG
Cole W 1991 ¹²	USA			663			8	Includes toxic SNG & MNG
Botrugno I et al 2011 ¹³	Italy			462			8.9	
Miccoli P et al 2006 ¹⁴	Italy			998			10.4	Includes toxic MNG
Cakir M et al 2007 ¹⁵	Turkey			375			6.9	Toxic Goitre
Cerci CC et al 2007 ¹⁶	Turkey			294			9.9	Includes toxic MNG
Anwar G et al 2012 ¹⁷	Pakistan			204			16.2	
Mermon W et al 2010 ¹⁸	Pakistan		105			7.6		
Abu-Eshy et al 1995 ¹⁹	Saudi Arabia			105			15.2	Includes lymphoma
Pang H-N et al 2007 ²⁰	Singapore			268			21.2	
Koh KBH et al ²¹	Malaysia		107			7.5		
Hanuma -thappa MB et al 2012 ²²	India		100			10		
Bombil I et al 2014 ²³	South Africa		107				3.7	Includes toxic MNG

* SNG = solitary nodular goitre. ** MNG = multinodular goitre.

DIAGNOSIS OF THYROID CANCER

- Fine needle aspiration cytology (FNAC) is the mainstay of TC diagnosis
 - has reduced number of thyroidectomies by 50%
 - reduced cost of management of nodules by 25%
- In expert hands it has high sensitivity (83%) and specificity (92%).
- This increases with the use of ultrasound guidance
- Positive predictive value 75%
- Negative predictive value 97-100%

Table 6
Summary Characteristics for Thyroid Fine-Needle Aspiration: Results of Literature Survey

Feature	Mean (%)	Range (%)	Definition
Sensitivity	83	65-98	Likelihood that patient with disease has positive test results
Specificity	92	72-100	Likelihood that patient without disease has negative test results
Positive predictive value	75	50-96	Fraction of patients with positive test results who have disease
False-negative rate	5	1-11	Fine-needle aspiration negative; histology positive for cancer
False-positive rate	5	0-7	Fine-needle aspiration positive; histology negative for cancer

Data from Gharib (10), Castro and Gharib (30), Gharib and Goellner (33), and Jeffrey and Miller (39).

ULTRASOUND DIAGNOSIS OF THYROID CANCER

Thyroid ultrasound (TUS) features of suspicion for malignancy

- solid or hypoechogenicity
- microcalcification
- irregular mass outline or contour
- increased vascularity / blood flow
- extraglandular extension

Value of ultrasonography features predicting thyroid malignancy

US feature	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Relative risk
Microcalcifications	26.1–59.1	85.8–95.0	24.3–70.7	41.8–94.2	4.97
Hypoechoogenicity	26.5–87.1	43.4–94.3	11.4–68.4	73.5–93.8	1.92
Irregular margins or no halo	17.4–77.5	38.9–85.0	9.3–60.0	38.9–97.8	16.83
Solid	69.0–75.0	52.5–55.9	15.6–27.0	88.0–92.1	4.2 ^a
Intranodule vascularity	54.3–74.2	78.6–80.8	24.0–41.9	85.7–97.4	14.29
More tall than wide	32.7	92.5	66.7	74.8	10.5 ^a

ACCURACY OF PRE-OPERATIVE DIAGNOSIS OF THYROID CANCER

- TUS Guided FNAC plus ultrasonography are accurate for diagnosis of TC except Follicular Cancer (FC).
 - FC and Follicular Adenoma (FA) have similar cytological features.
 - Otherwise TUG FNAC and TUS have very high negative predictive value.
 - FC diagnosed by capsular vascular infiltration only possible by formal histology.
 - To exclude FC at least lobectomy is minimum diagnostic procedure.
 - This might be sufficient treatment depending on the Mayo (AGES) or Lahey (AMES) Criteria or TNM staging.
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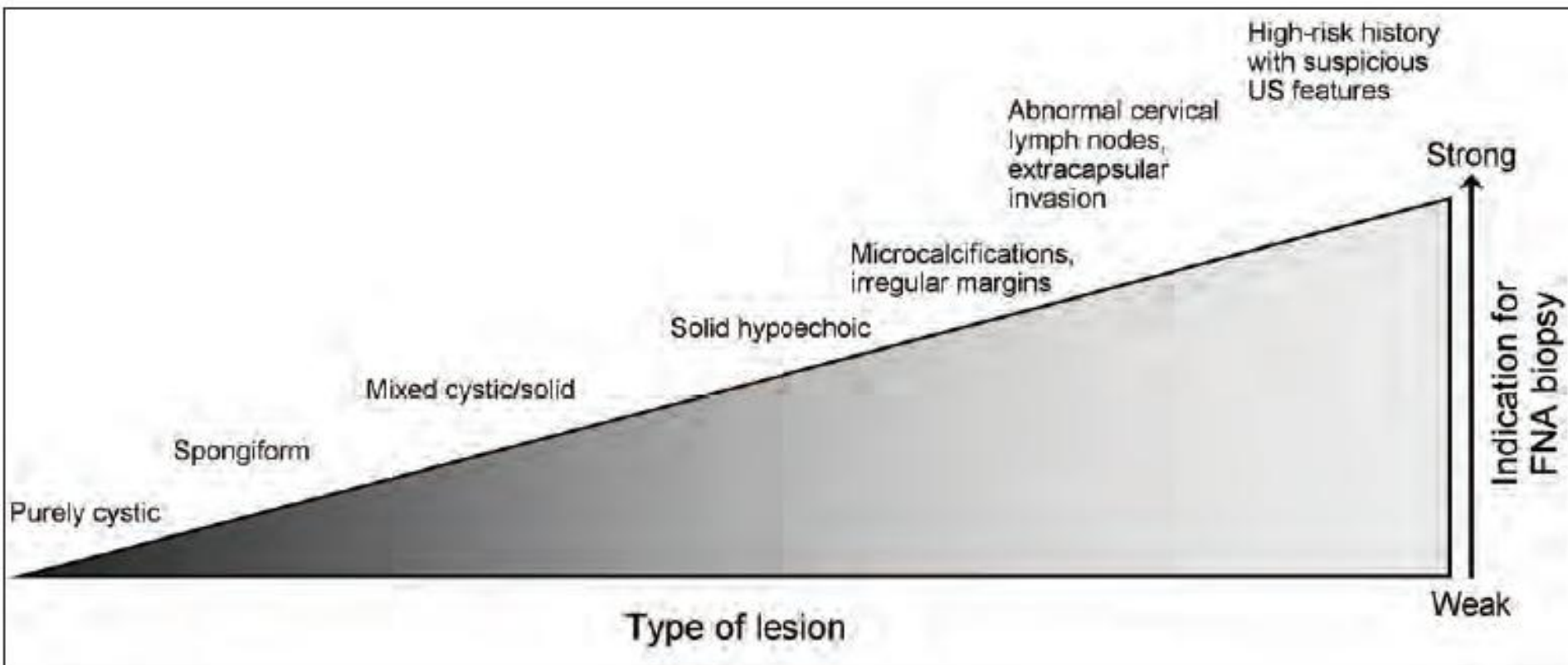


Fig. 2. Strength of indication for fine-needle aspiration (FNA) biopsy of thyroid nodules on the basis of ultrasonography (US) findings.

Table 17
Indications for Ultrasonography-Guided
Fine-Needle Aspiration of Thyroid Nodule*

Nondiagnostic palpation-guided FNA
Impalpable nodule
Thyroid nodule <1 cm
Neck node
Ablative therapy

*FNA = fine-needle aspiration.

NON SURGICAL TREATMENT OF THYROID GOITRE

Several options for non-surgical treatment of goitre

- * Simple Iodine supplementation
- * L-thyroxine supplementation
- * Alcohol sclerosis of cystic lesions
- * Medical drug therapy
- * Radio-active Iodine ablation (RAIA)
- * Laser photocoagulation
- * Radiofrequency ablation
- * Microwave ablation

These options open only after excluding possibility of malignancy

IODINE AND L-THYROXINE SUPPLEMENTATION

- Iodine supplementation in the diet of iodine deficient environment has reduced incidence of goitre.
- Iodine supplementation is indicated for prepubital goitre and pregnancy associated goitre.
- L-thyroxine given to “small” goitres reduces volume by upto 40%.
- Withdrawal of L-thyroxine may result in relapse .
- L-thyroxine not without side effects and complication especially in the elderly
 - decrease bone density
 - cardiac dysrhythmias

ALCOHOL SCLEROTHERAPY OF NODULAR THYROID GOITRE

- Alcohol sclerosis of cystic nodular goitre has been described.
- Largely reserved for elderly with serious co-morbidities.
- This can be repeated several times if recurrence occurs.
- It has not enjoyed much adoption by many thyroidologists for fear of missing cystic papillary TC.

TABLE 3: Comparison of result, complication, and total procedure time of Alcohol Sclerotherapy; Group A = Alc not aspirated ; Group B = Alc aspirated

	Group A (%)	Group B (%)	<i>P</i>
Success result	29/30 (96.7)	28/30 (93.3)	>.05
Complication			
Mild pain	8/30 (26.7)	9/30 (30)	>.05
Moderate pain	1/30 (3.3)	1/30 (3.3)	>.05
Facial flushing	2/30 (6.6)	1/30 (3.3)	>.05
Drunken sense	2/30 (6.6)	1/30 (3.3)	>.05
Headache	1/30 (3.3)	0/30 (0)	>.05
Mild dizziness	1/30 (3.3)	1/30 (3.3)	>.05
Perithyroidal ethanol leakage	1/30 (3.3)	1/30 (3.3)	>.05
Intracystic hemorrhage	1/30 (3.3)	7/30 (23.3)	<.05
Complaint: double puncture	–	+	<.001
Total procedure (min)	16.8	30.6	<.001

RADIOACTIVE-IODINE ABLATION FOR TOXIC THYROID GOITRE

- RAIA has been used as standard treatment for toxic goitre for over 50 yrs, especially in USA
- Low dose RAIA is the preferred treatment for Graves' disease.
- Many thyroidologists use RAIA for toxic nodules as the risk of malignancy is very low.
- Only absolute contraindication for RAIA is pregnancy.
- Surgery for Graves' disease is associated with
 - recurrence after subtotal thyroidectomy
 - hypothyroidism after total thyroidectomy

Bahn RS et al. Endocrine Practice 2011; Shapiro B. J Nucl Med 1993; Kendall-Taylor P, Keir MJ, Ross WM. BMJ 1984; Hedley AJ et al. BJS 1983

RADIOACTIVE-IODINE ABLATION FOR NON-TOXIC THYROID GOITRE

- “High” dose RAIA is being used increasingly for non-toxic goitres including MNG.
- To achieve ablation at “lower” doses use human recombinant TSH as primer has been advocated.

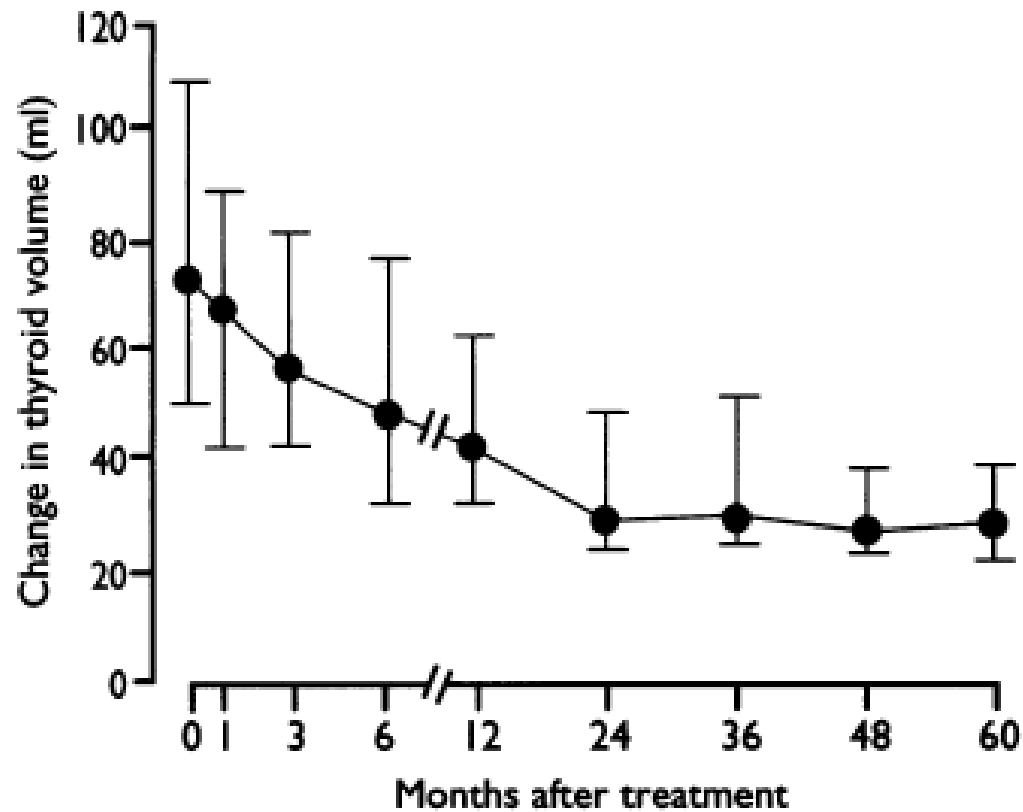


FIG 1—Median changes in thyroid volume alterations after iodine-131 treatment in 39 patients with non-toxic multinodular goitre who remained euthyroid after a single dose. Bars are quartiles

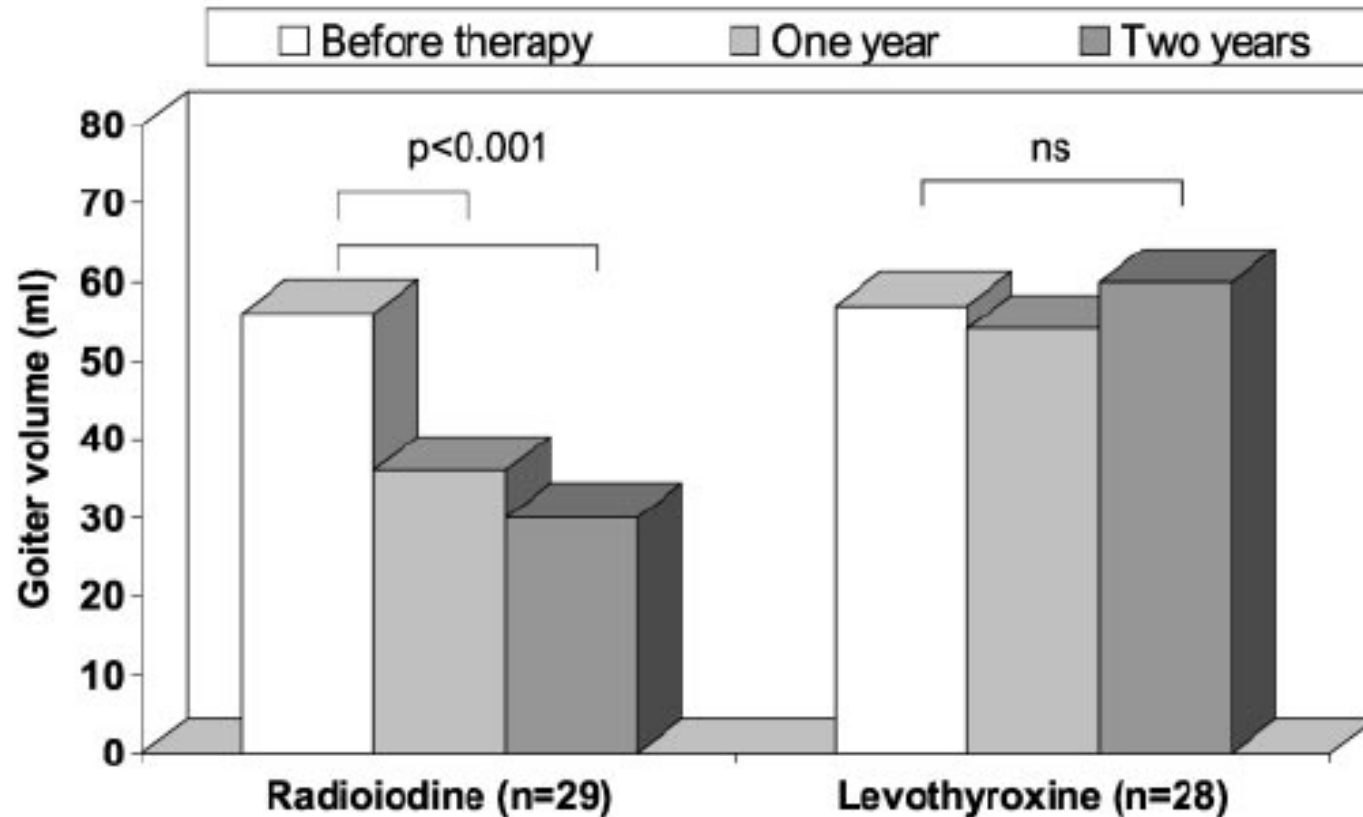


FIG. 5. Comparison of ^{131}I therapy and L-T_4 in the treatment of non-toxic multinodular goiter. Bars represent median goiter volumes. Adapted from Wesche *et al.* (224).

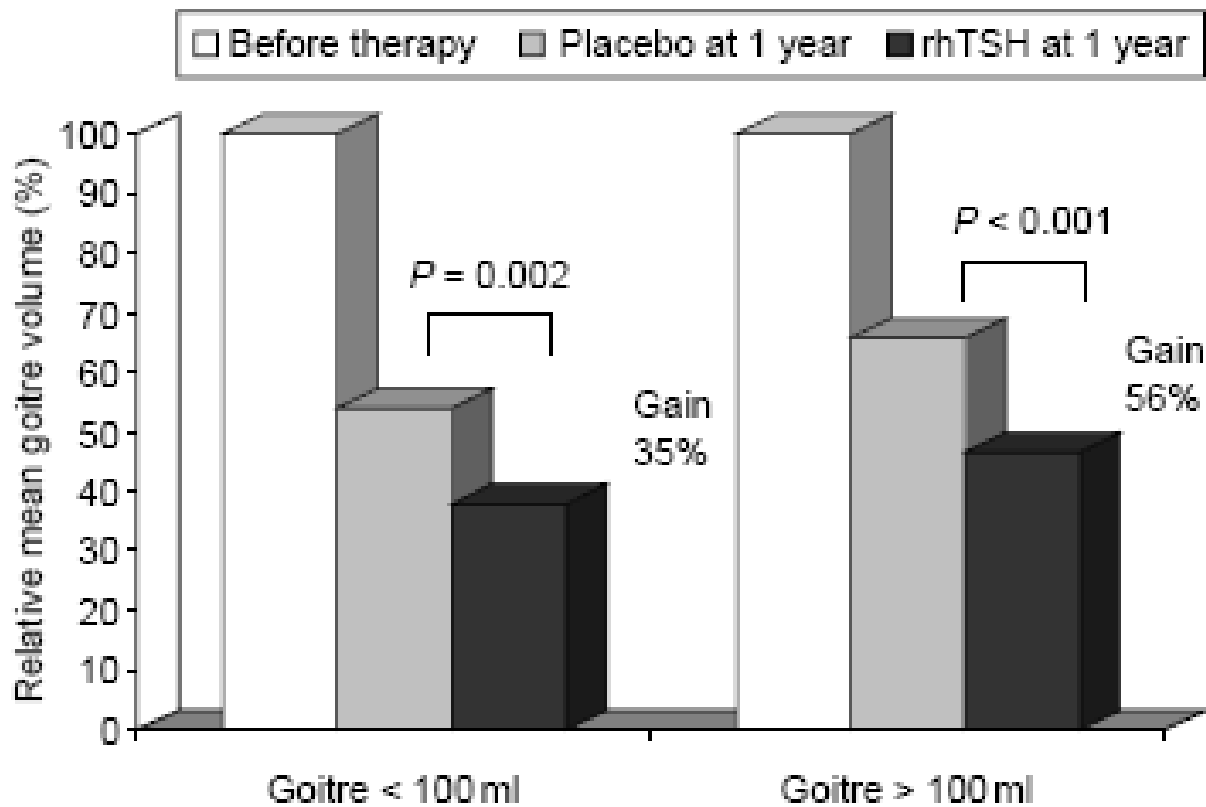


Figure 2 Comparison of the relative goitre volume 1 year after conventional (placebo) and rhTSH augmented ^{131}I therapy for non-toxic multinodular goitre, smaller and larger than 100 ml. Bars represent the relative mean goitre volume before therapy and 1 year after therapy. Adapted from Nielsen *et al.* (18) and Bonnema *et al.* (17).

MEDICAL TREATMENT OF TOXIC THYROID GOITRE

- Medical treatment is the standard alternative treatment to RAIA for toxic goitre.
- Carbimazole or propylthiouracil are used with caution in pregnancy where RAIA is absolutely contraindicated.
- Foregut atresias viz choanal and oesophageal atresias, and congenital aplasia-cutis in the foetus are occasional complications of methimazole (carbimazole) when used during early pregnancy.
- The serious but very rare complications in the mother include agranulocytosis and pancytopenia.

Foulds N et al. Am J Med Genetics 2004; Stagnaro-Green A et al. Thyroid 2011
Koren G, Solden O. Ther Drug Monit 2006

THE FEAR OF MISSING THYROID CANCER

- Most microcarcinoma are papillary and
- Papillary is indolent and “benign” cancer
 - many people die of unrelated causes
 - new studies shows that observation of microcarcinomas is without danger
- Fear of TC is over rated

Fate of Untreated Benign Thyroid Nodules: Results of Long-Term Follow-up

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Abstract: The fate of benign thyroid nodules has been unknown because there has been no study in this regard. We re-examined 134 patients with thyroid nodules who had had benign aspiration biopsy cytology 9 to 11 years ago. The thyroid gland was palpated by the same two thyroidologists throughout the study. Ultrasonography, fine-needle aspiration biopsy (FNAB), and ultrasound-guided FNAB were employed to examine the nature of nodules of 9 to 11 years' duration. Patients ($n = 61$) who had nodules difficult to palpate (small nodules), multiple nodules, or cystic nodules with papillomatous proliferation underwent ultrasound-guided FNAB; patients ($n = 55$) having a distinctly palpable single nodule underwent usual FNAB. None of the patients received any medical or surgical treatment. There were 86 single nodules, 14 multiple nodules, and 34 cystic nodules on the first examination. These benign nodules were reexamined for changes in size and cytology 9 to 11 years later. The most striking finding was a decrease in size or disappearance of the nodule in 42% to 79% of benign nodules. About 92% of nodules remained benign without changing cytologic classification. Only one case (0.9%) previously regarded as benign turned out to be malignant; this nodule grew in size compared with the previous examination. Among single and multiple nodules, 21% to 23% of the nodules increased in size; however, most patients with enlarged nodules (86%) showed the same class 2 cytology as before. Our present study indicates that biopsy-proved benign thyroid nodules remain benign over a prolonged period. Thus no medical or surgical treatment is required so long as the nodules do not grow.



TABLE 2. CHANGE IN SIZE OF MICROCARCINOMA DURING FOLLOW-UP

<i>Time of follow-up</i>	<i>Total</i>	<i>Number of patients (%)</i>			
		<i>Size (mm)</i>	<i>Increased^a</i>	<i>Unchanged</i>	<i>Decreased</i>
0 (beginning of follow-up)	162	6.9 ± 1.8 ^{*,**}			
One year	130	7.0 ± 2.3	20 (15.3%)	92 (70.8%)	18 (13.8%)
Two years	145	6.8 ± 3.0	31 (21.4%)	90 (62.1%)	24 (16.6%)
Three years	90	7.8 ± 2.4 [*]	19 (21.1%)	61 (67.8%)	10 (11.1%)
Four years	72	7.8 ± 2.2 ^{**}	21 (29.2%)	48 (66.7%)	3 (4.2%)
Five years or more ^b	58	7.0 ± 2.4	16 (27.5%)	35 (60.3%)	7 (12.1%)

^aThe size was compared with that at the beginning of follow-up in each case. Increased: 2 mm or more increase in maximum diameter on ultrasonography. Decreased: 2 mm or more decrease in maximum diameter on ultrasonography.

^bTen years in the longest patients.

p* = 0.0133, *p* = 0.0001

Table II. Cancer Incidence After Radioiodine Treatment

Reference	Country	Sample Size	Excess Relative Risk	Comment
Shore RE 1992 ²⁴	USA	31000	up to 20 times	highest for high dose I ¹³¹ among juveniles
Metso et al 2007 ²⁵	Finland	2793	5/3 = 1.89	increased cancer in many extrathyroid sites
Hall P et al 1996 ²⁶	Sweden	34104	up to 4.3	
Holm LE et al 1991 ²⁷	Sweden	10552	1.3	increased cancer also in many extrathyroid sites
Hoffman DA et al 1982 ²⁸	USA	1005	9.1	

SUMMARY

- Thyroid goitre is most common endocrine disease.
- Goitre increases with age
- Many asymptomatic goitres especially nodules are discovered incidentally by physical or imaging especially US examination of the neck.
- Majority of thyroid nodules are benign and do not need surgery.
- Most benign thyroid nodules are asymptomatic, non-toxic and slow growing and require only simple follow up.
- Although much feared, thyroid cancer is rare and relatively benign.
- Post-mortem examination of people from unrelated deaths uncover up to 40% otherwise asymptomatic papillary TC.
- Number of non surgical options available and effective for goitre treatment if TC has been excluded by TUG-FNAC and TUS.

Conclusion

- Thyroid goitres are largely benign *circa* 90%.
- Ultrasound guided FNAC and ultrasonography are very reliable in diagnosis of cancer.
- Incidence of cancer is very low thus fear of missing TC is grossly exaggerated.
- When thyroid cancer has been excluded, goitre should be treated non-surgically .
- Surgery is attended by significant morbidity even in expert hands therefore it should be reserved for malignant goitre.

**THANK YOU
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References are available on request and
will be posted on the Surgery Dept website

-<http://web.up.ac.za/default.asp?ipkCategoryID=4101>

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Box 2 Therapeutic options and main indications for treatment of benign thyroid nodules.

Surgery

- Large intrathoracic goiter
- Rapidly growing nodules
- No cardiopathy

Iodine supplementation

- In iodine-deficiency areas
- Young patients
- Not for autonomous nodules or TSH-suppressed patients

Levothyroxine

- Men aged <60 years, premenopausal women
- Recently diagnosed nodules
- Small nodule size
- Predominantly solid nodules
- Abundant colloid on fine-needle aspiration
- No cardiopathy

Radioactive ¹³¹I

- Toxic nodules
- Nontoxic nodules in elderly patients
- Nontoxic nodules in cardiopathic patients

Percutaneous ethanol injection

- Symptomatic recurrent cystic nodules

Percutaneous laser ablation

- Currently not recommended

Filetti S, et al. Nat Clin Pract Endocrinol Metab 2006.

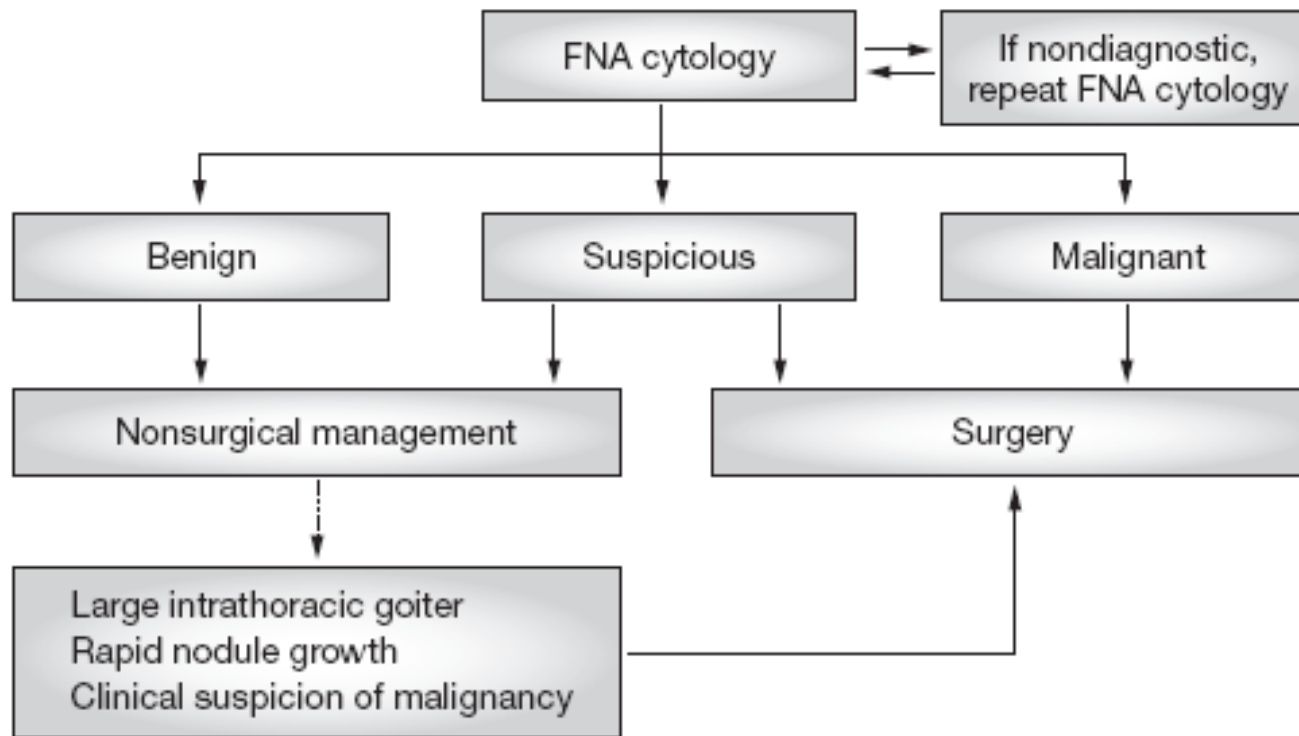


Figure 1 Diagnostic procedure for deciding between surgical and nonsurgical approaches to the management of nonautonomous thyroid nodules. Abbreviation: FNA, fine-needle aspiration.

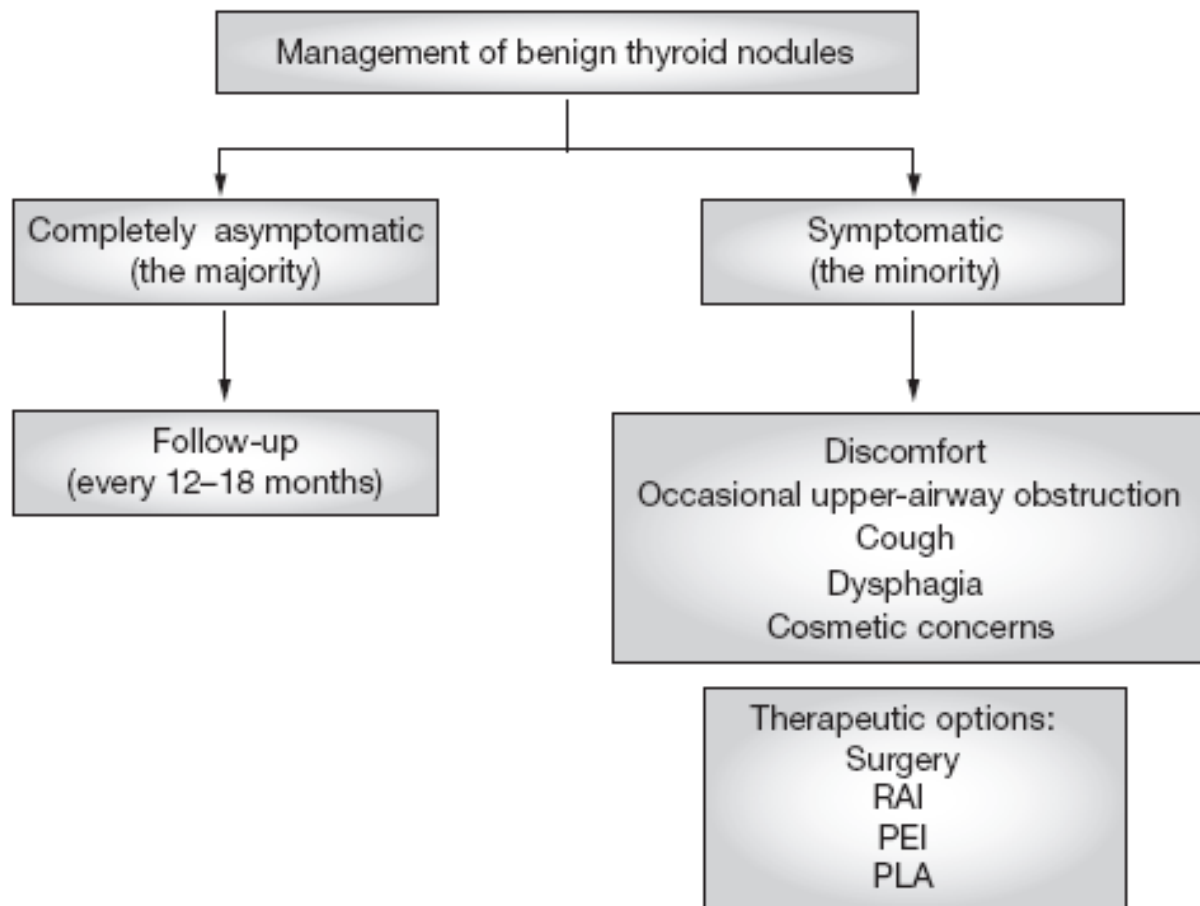


Figure 2 Management of benign, nonautonomous thyroid nodules.
 Abbreviations: PEI, percutaneous ethanol injection; PLA, percutaneous laser ablation; RAI, radioactive ¹³¹I.

Table 22
Key Recommendations Regarding Laser Thermal Ablation
in Patients With Thyroid Nodules*

- LTA is a low-cost, rapid, and effective mini-invasive technique for the treatment of benign thyroid nodules causing pressure symptoms or cosmetic complaints
- The procedure should be performed only in carefully selected cases (high-surgical-risk patients). In most patients, 1 to 3 sessions of LTA or a single treatment with multiple fibers induces a nearly 50% decrease in nodule volume and the amelioration of local symptoms (*grade C*)†
- LTA should be restricted to specialized centers, in light of the need for skilled operators to avoid the risk of major complications (*grade D*)

*LTA = laser thermal ablation.

†See Table 1 for explanation of grades.

Table 4 Ultrasound features suggesting malignancy

Irregular margin

Fine calcifications

Extraglandular extension

Solid or hypoechogenicity

TABLE 5. Prevalence of Occult Thyroid Carcinomas at Autopsy by Age, Sex, and Country

Age	Hawaii		Japan		Canada		Poland		Colombia	
	No.	%	No.	%	No.	%	No.	%	No.	%
Males										
10-39	5(1)	—	6(0)	—	4(1)	—	4(0)	—	253(9)	3.6
40-59	37(12)	32.4	28(6)	21.4	25(2)	8.0	19(0)	0	121(10)	8.3
60-79	66(11)	16.7	25(10)	40.0	29(0)	0	31(2)	6.5	62(4)	6.5
80+	32(5)	15.6	0	—	4(0)	—	2(0)	—	10(0)	0
Females										
10-39	6(0)	—	7(3)	—	5(1)	—	4(2)	—	102(6)	5.9
40-59	25(9)	36.0	18(5)	27.8	12(2)	16.7	21(3)	4.3	41(3)	7.3
60-79	50(16)	32.0	16(5)	31.2	16(0)	0	28(3)	10.7	18(2)	11.1
80+	27(6)	22.2	2(0)	—	5(0)	—	1(0)	—	0	—

Percentages calculated only where 10 or more specimens were examined. Figures in parentheses indicate number of specimens with carcinoma.