Surgery versus pharmacotherapy of benign thyroid diseases

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ABSTRACT

Surgical management of benign thyroid diseases (BTDs) has been a topic of interest and confusion for many years. Almost 80% of thyroidectomies at an average endocrine surgical unit are carried out for BTDs. Resistance to surgical intervention in BTDs has been based on the belief that increased complication rate is inherent in its use, this is despite the potential advantages in terms of confirming the benign nature of the lesion, controlling the disease, and relieving local symptoms of large neck mass. Benign thyroid diseases are more likely to occur in middle-aged women living in iodine deficient areas, or have a family history of goiter, or in patients taking iodine-containing drugs, like amoidarone, or in patients with previous history of x-ray exposure. However, the physician must be careful in making the diagnosis of BTDs in patients at the extremes of age or in the presence of positive history of radiation, or in patients with family history of thyroid or colon cancer. In this article we will review the etiology, epidemiology, diagnostic methodologies and the recent trends in the surgical and medical management of BTDs.

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Disorders of the thyroid gland occur in 3-5% of the population and are the second most common endocrine disorder, next to diabetes mellitus.[1-3] Autopsy studies have shown that thyroid nodules are present in approximately 37% of general population, and they have been shown to be benign in 70-90% of cases depending on the selectivity of surgical indication.[4,5] Until the late 1800s, surgical treatment of thyroid disorders was reserved for patients with impending death from suffocation due to fears of surgical complications, such as hemorrhage and infection.[6,7] With the introduction of anesthesia, antisepsis, and fine surgical instruments, and the development of new thyroidectomy techniques, surgery became a safer alternative, offering the chance of cure to many patients.[3-6] Today thyroidectomy is a routine procedure performed for thyroid cancer, and many cases of BTDs.[7] Overall, death from thyroid surgery is rare, and the incidence of recurrent laryngeal nerve injury, neck hematoma, thyroid storm, and hypoparathyroidism is low.[7] These reported complication rates vary dramatically, ranging from 0-14% for permanent recurrent laryngeal nerve injury and from 1.2-11% for permanent hypoparathyroidism.[8-10] Several advances have been made in the field of diagnosis, medical management and the molecular biology of BTDs. The surgical treatment, however, remains a matter of controversy. A major reason is differences in experience and attitudes towards surgical resection of benign thyroid lesions and the possibility of complications.[11-13]

Predisposing factors. Several studies have shown that living in iodine deficient or endemic goiter areas is the most frequent predisposing factor for the development of BTDs such as multinodular goiter (MNG) or diffuse goiter.[14-17] According to the WHO iodine deficiency disorders (IDD) are significant health problem in 118 countries around the globe. An estimated 1.58 billion people worldwide live in iodine deficient environment and therefore are at risk of IDD.[18,19] The Eastern Mediterranean region has one of the highest goiter prevalence rates, with more than 42% of the population at risk for iodine deficiency.[18,19] In Jordan,

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and in spite of the iodisation program, which was launched in the early 1990s, Jordan still has high prevalence of goiter rate that is close to 34%.[20] High levels of circulating immunoglobulins such as long acting-thyroid stimulator and thyroid-stimulating immunoglobulins increase the risk of Graves Disease.[21] Patients with defined inherited metabolic defects in thyroid hormone synthesis will develop hyperplastic goiter, which could lead to MNG. Drugs particularly the anti thyroid, pyocynate, perchlorate, sulfonamide, lithium and amiodarone are known goiterogens.[22] Previous radiation exposure has been shown to increase thyroid nodularity.[23-26]

Evaluation of benign thyroid diseases. (a) Clinical examination. It is very important to ask the patient with thyroid swelling about local pressure symptoms such as dyspnoea, dysphagia, neck discomfort and risk factors that might give important clues towards diagnosis and the need for surgical intervention. Patients at the extremes of age (younger than 14 years and older than 60) particularly in males and presenting with thyroid nodules are more likely to have malignant nodules. Past history of radiation exposure increases the frequency of both benign and malignant thyroid nodules. The presence of family history of medullary thyroid carcinoma or papillary thyroid carcinoma or familial polyposis or vocal cord paralysis also increases the risk of cancer. The presence of a very hard, irregular mass or enlarged pathological cervical lymph nodes can also increase the risk of cancer. The risk of thyroid cancer in a dominant nodule of a MNG is as high as in a true single nodule in euthyroid or hypothyroid or toxic goiters approximately 10-30%.[1,3,7]

(b) Investigations. Serum concentration of sensitive TSH is necessary to evaluate the functional status of the thyroid gland in BTDs. Normal TSH level negates the need for further testing of thyroid hormones. The levels of free triiodothyronine (FT_3) and free thyroxine (FT_4) should be determined in patients with clinical evidence of hypo or hyperthyroidism or patients with abnormal TSH results.[7] Patients with Graves disease and solitary toxic nodules usually have marked elevation in thyroid hormones in contrast to patients with toxic MNG (plummers disease) which have only marginally raised levels. Serum thyroglobulin level (measured by RIA) together with antithyroglobulins and antimicrosomal antibodies need to be measured routinely in patients suspected to have thyroiditis.[1,7,24]

(c) Chest roentgenogram. Chest radiographs with special thoracic enlet radiographs are helpful in BTDs to identify and evaluate the extent of tracheal compression or deviation and in patients with retrosternal goiter.

(d) A computed tomography chest and neck with enhancement. A computed tomograhy (CT) scan is useful when retrosternal goiter is suspected clinically. Also it is recommended in patients with recurrent goiter or patients referred for completion thyroidectomy to assess thyroid remnant.[27-29]

(e) Radioisotope scanning (^{123}I or ^{99m}Tc). These studies have a limited value in the initial evaluation of BTDs thyroid disease. However, these studies are indicated in patients with thyrotoxicosis in whom a thyroid nodule is present clinically raising the possibility of a solitary toxic nodule. Scanning may help determine whether a nodule is 'hot' or 'cold'.[30]

(f) Ultrasound. Not useful in the initial assessment of patients with BTDs. However, ultrasound (U/S) may sometimes help provide assistance for needle biopsy of nodules that are difficult to localize by simple palpation,[1-3] or in evaluating thyroid nodularity during pregnancy and occasionally in Graves' disease patients with questionable nodules. The presence of background multinodularity on U/S does not decrease the risk of malignancy nor does the presence of cystic lesions on the U/S.[31,32]

(g) Fine needle aspiration biopsy. The single best test to predict the need for surgery in BTDs is fine needle aspiration biopsy (FNAB). This procedure is safe, reliable and cost effective diagnostic method for thyroid abnormalities. Fine needle aspiration biopsy is quick, simple and easily performed at an outpatient clinic. A thin gauge needle (number 21-23) is passed through the nodule and the specimen is collected on a glass slide then some slides are left to air-dry and some preserved in 95% alcohol. The result of FNAB is most reliable for the diagnosis of papillary carcinoma, medullary carcinoma and anaplastic carcinoma. The presence of (malignant cytology) consistent with these cancers is a clear indication for surgery. On the other hand, FNAB is least reliable in distinguishing benign from malignant follicular and Hurthel cell neoplasms (suspicious cytology); in this case the patient will require surgical resection of the involved lobe to establish a clear diagnosis. The presence of normal follicular cells with plenty of colloid (benign cytology) commonly seen in colloid goiter or thyroid cysts require no further treatment and the patient can be followed clinically. Complications of this technique are extremely rare, hematomas seldom develop and no seeding of the needle tract has been reported in collective experience of many investigators dealing with this procedure.[32-38] Fine needle aspiration biopsy has 96% sensitivity rate and 99% specificity rate in diagnosing thyroid cancer.

Management of benign thyroid diseases. A. Multinodular goiter. Multinodular goiter is the most common of all the disorders of the thyroid gland. It is thought that genetic heterogeneity of follicular cells with regard to function and growth in the presence of stimulatory factors may lead to irregular proliferation of thyroid tissue resulting in MNG. These stimulatory factors may be TSH or local tissue growth factors released as a result of iodine deficiency, inborn errors of thyroid hormone synthesis, goitrogens or immunogenic growth factors. If an euthyroid MNG is small and is producing no symptoms and the FNAB is benign, there is no need for treatment. Surgery is indicated in patients with pressure symptoms, cosmetic reasons or in patients suspected to have cancer. Total thyroidectomy is

recommended for patients with bilateral nodularity. Hemithyroidectomy might be a good alternative if the disease is localized to one lobe.[2,7,39,40] The aim is to remove all of abnormal thyroid tissue, which, reduces the risk of persistent symptoms and removes the risk of future recurrence. Surgery for recurrent goiter carries much higher risk of complications. The only potential disadvantage to total thyroidectomy compared to subtotal thyroidectomy is a higher risk of complications such as recurrent, laryngeal nerve injury or permanent hypoparathyroidism. However, these possible complications will not be increased when total thyroidectomy is performed by skilled surgeons. Another advantage for total thyroidectomy is the use of thyroxine as a replacement therapy instead of suppression.[7,39,41]

B. Solitary thyroid nodules. Adenomas of the thyroid gland usually arise from follicular epithelium, usually single with a uniform histologic structure.[42,43] They are classified according to the size or presence of follicles and degree of cellularity. Macrofollicular adenomas are the most common and they closely resemble the thyroid tissue. Other variants of adenomas include microfollicular, embryonal and Hurthle cell adenoma. Architectural features of follicular adenomas are similar to follicular carcinoma; the only difference, however, is greater tendency for invasion to the capsule, lymphatic channels or blood vessels in follicular carcinomas. Typically macrofollicular adenomas or colloid nodules will demonstrate a benign cytology on FNA, and will not require surgery. Microfollicular adenoma will demonstrate an atypical pattern (suspicious cytology), which requires diagnostic thyroid lobectomy. The minimum operation for a single thyroid adenoma is complete lobectomy, except for true midline lesions in the isthmus, which can be managed by ismethectomy or large nodules >4cm, which requires total thyroidectomy. It has been argued that frozen section at the time of surgery might help in these cases, however, in our experience and the experience of others frozen section diagnosis of follicular lesions was not helpful and in some cases misleading.[44-46]

C. Substernal goiter. Substernal goiters are considered if more than 50% of the thyroid is located behind the sternum. These goiters can cause local compression of mediastinal structures.[47,48] Dyspnea and dysphagia are common symptoms that are often exacerbated by recumbency. Occasionally patients with substernal goiter might present with chest pain or superior venacava obstruction. The optimal treatment for substernal goiters is surgical removal[49,50] which can be managed through a cervical thyroidectomy in the majority of patients. However, ectopic intra thoracic goiters that have no cervical extension require a median sternotomy.

D. Thyroid cysts. Thyroid cysts constitute 10-15% of all thyroid nodules.[51] Fine needle aspiration will cure most of thyroid cysts after one or more aspiration. However, some cysts will rapidly recur and refill, if it recurs more than 3-4 times, the cyst should be surgically removed. Large cysts (4 cm or more) should also be removed surgically as they have a higher risk of malignancy. Diagnostic lobectomy is recommended for solitary cysts and total thyroidectomy for bilateral lesions.[7,38]

E. Recurrent goiter. Recurrent goiter is the usual sequale of suboptimal surgery for multinodular goiter.[52] Surgery for recurrent goiter caries a much higher risk of complications to the recurrent laryngeal nerve and the parathyroid glands. The risk varies from 9.5-25% and 5-15%.[7,52,53] Surgery for recurrent goiter is recommended only if the patient has significant mechanical compression or suspected malignancy. It is recommended in these cases to identify the recurrent laryngeal nerves and the parathyroid glands during surgery. We also recommend a lateral approach to the thyroid proceeding form the carotid sheath towards the midline making use of the vergin planes not touched in previous surgery,

F. Thyrotoxicosis. Thyrotoxicosis is a general term reflecting that the tissues are exposed to excessive level of thyroid hormones T4, T3, or both. It can be caused by several BTDs including: Graves' disease, toxic multinodular goiter, or a solitary toxic nodule, and occasionally, it can be drug induced secondary to amiodarone administration.

Graves disease. Is an autoimmune syndrome in which thyroid stimulating antibodies act in the same way as thyroid stimulating hormones, the patient manifestations may include hyperthyroidism, diffuse thyroid enlargement, exophthalmos, periorpital myxedema and thyroid acropachy. The prevalence of Graves disease in the United States of America population has been estimated to be 0.3%.[54,55]

Toxic multinodular goiter. The existence of follicles with a very high degree of autonomisty with normal or even non-functioning thyroid follicles. A patient with toxic MNG develops hyperthyroidism if the production of thyroid hormones by these nodules exceeds the normal needs. This hyperthyroidism usually takes several years to develop.

Toxic adenoma. A discrete thyroid mass (nodule) whose function is independent of pituitary control. The prevalence of toxic adenoma depends on iodine availability and geographical location; it ranges from 2-9% in thyrotoxic patients.[56]

Amiodarone induced thyrotoxicosis. Amiodarone contains 37% iodine by weight. Patients with pre-existing thyroid abnormalities develop iodide induced thyroid hormone synthesis and hyperthyroidism. Management of this condition is by withdrawal of the drug if possible, administration of antithyroid drugs including potassium perchlorate if necessary and the use of prednisolone. Another effect of this drug might be destructive thyroiditis due to the excess iodide exposure. The management of this effect is by steroids similar to that used to manage thyroiditis.[57,58]

Hashimotos thyroiditis. A chronic thyroiditis,

affecting women more than men. The patient present with firm or hard goiter with or without hypothyroidism. If the goiter is asymmetrical or the patient has developed solitary thyroid nodule during the course of the disease, malignancy should be suspected and surgery is indicated to rule out malignancy.

Subacute (granulomatous) thyroiditis. A viral infection in the thyroid that can be caused by a wide range of viruses including mumps, measles, Epstein-Barr, influenza, and Coxsackievirus. It is 3 times more common in women and incidence peaks in the age 30-50 years. Viral infection with fever, malaise and painful goiter followed by patient going through 3 phases in this disease: in the first phase he suffers thyrotoxicosis (release of preformed thyroxine), followed by a phase of hypothyroidism, and then recover which might take 1-3 months. Surgery has no role in subacute thyroiditis except if the patient has coexistent thyroid nodule, surgery is indicated in this case to rule out malignancy.[59]

Management of thyrotoxicosis. Three main options are available for the management of thyrotoxicosis, namely: antithyroid medications, radioactive iodine ^{131}I, and surgery. Which option is best is decided on the following basis: the etiology of thyrotoxicosis; concomitant diseases or pregnancy, presence of ophthalmopathy; goiter's size; response to previous therapy; advantages and disadvantages of each management option as it relates to specific patient's need.[60,61]

1. Antithyroid drugs. Antithyroid drugs are indicated for the thyrotoxicosis caused by hyperfunction of the thyroid gland. They are also indicated in patients presenting with subclinical thyroiditis (normal thyroid hormones and low TSH value) of the following groups: Women in post-menopause; patient with osteoporosis; patient with cardiac disease; patient with multinodular goiter. Antithyroid drugs are not effective if thyrotoxicosis is due to follicular damage, disruption, and leakage of preformed thyroid hormones or due to thyrotoxicosis factitia (exogenous administrations of thyroid hormones). Three antithyroid drugs are available: propylthiouracil (PTU), methimazole (US) and its precursor carbimazole (United Kingdom). Propylthiouracil can be initiated in a dose of 300-600 mg in a divided or single dose daily. While carbimazole is initially given at doses of 15-40 mg daily (methimazole started at 30-60 mg in 3 divided doses or single dose daily). Response to treatment with antithyroid drugs is monitored with T_4 concentration, which should be measured at 4-8 weeks intervals. Once euthyroid function is achieved, tapering of the dose should be carried out on a monthly bases. The maintenance daily doses for PTU, carbimazole and methimazole are 50-300 mg, 5-15 mg, and 5-30 mg. During the maintenance phase, which could last from 6-18 months, the levels of T_4 and thyrotropin should be measured every 3 months. Patients failing to respond to therapy are either non-complaint or have another underlying disorder and have been initially misdiagnosed. Less than 50% of patients receiving antithyroid drug, remain in permanent remission. When the patient has not been responsive to medications, 2 other alternatives are available: surgery or radioactive iodine ^{131}I administration.

2. Iodides. They are often used as adjunctive therapy to prepare patients for surgery, to attain quick euthyroid states in severely thyrotoxic patients with compromised cardiac function. When used to prepare a patient for surgery they should be administered 7- 14 days before surgery. The usual dose range is 120-400 mg/day in water or juice. If iodide is to be used as an adjunct in radioactive iodine (RAI) treatment it should be given 3-7 days after the administration of RAI so as it would not compete with the RAI concentrating in the thyroid gland.[62]

3. Beta-blockers for hyperthyroidism. Beta-blockers are essential drugs for controlling the undesirable cardiovascular effects in hyperthyroidism. They can be the sole treatment in the management of thyroiditis or iodine induced hyperthyroidism. Not all β-blocker are the same. The selection of the appropriate β-blocker depends on the patient's condition. Selective β1 blockers are better for patients with following diseases: peripheral vascular disease; obstructive airway disease; hyperlipidemia, and diabetic patients receiving oral hypoglycemics. Nonselective β-blockers may be better for patients suffering from migraine, anxiety, or essential tremor. Both selective and non-selective drugs have withdrawal syndrome, which is absent in β-blocker with partial agonist activity.[63,64]

3. Radioactive iodine. Radioiodide therapy is easy to administer and effective. It is contraindicated in children, in pregnancy and in women who are breast-feeding. Thyroelimination with the administration of radioiodide ^{131}I is recommended without previous medicaments preparation. Up to 25-30 mCie can be administered in the out patient department. The patient should receive subsequent immediate treatment with thyrostatics and β-blockers until remission of thyrotoxicosis is achieved (6-12 weeks).[65,66] A dose of ^{131}I that results in accumulation of 8 mCie (296 MBq) in the thyroid gland 24 hour after administration is an effective treatment for the majority of patients with Graves hyperthyroidism. Young patients with larger thyroid glands, higher serum T4 concentrations, and higher 24-hour thyroid ^{123}I uptake values, and those pre-treated with antithyroid medications for greater than 4 months are at higher risk for treatment failure. A higher does of ^{131}I may be advisable in such patients.[67-70]

Surgical management of thyrotoxicosis. Surgery is generally indicated for solitary toxic nodules, toxic multinodular goiter, and amiodarone-induced thyrotoxicosis. Surgery is appropriate for Graves disease patients presenting with large goiter, during pregnancy, breast-feeding and in women, and children where there is a pre-existing nodule. Surgery offers the advantage of being rapid and consistent method to control the disease process, at the same time it provides tissue for histologic

examination and avoids the risk of radioactive iodine. After surgery the patient might become euthyroid on no medication, although the incidence of this varies greatly depending on the extent of residual thyroid tissue.[70]

Preoperative preparation. All patients must be rendered euthyroid prior to surgery using antithyroid drugs. Occasionally the patient may require the addition of perchlorate therapy, or iodine in difficult cases. For patients with Graves disease, iodine is added (Lugol's solution 5 drops daily), 7-14 days before surgery to help bring a toxic gland under control and reduce blood flow to the gland.[41] Propranolol can be used to control the sympathetic over activity caused by elevated thyroxine such as tachycardia, arrhythmias, or anxiety. Depending on the size of the gland and the presence of significant ophthalmopathy, 3 surgical options are available for patients with Graves' disease; the standard treatment is bilateral subtotal thyroidectomy. The aim being to leave 6 gm of residual thyroid tissue (approximately 3 gm on each side). The second option is to do unilateral lobectomy and to leave 6 gm on the contralateral side, but this has not been shown to affect the outcome or the risks of complications. Following this approach, 50% of the patients will become permanently hypothyroid, the majority within 6-12 months and recurrence is less than 1%.[7] The third option is to do total thyroidectomy for patients with severe Graves' ophthalmopathy, large toxic multinodular goiter and for patients with amiodarone-induced thyrotoxicosis. Patients with single toxic adenoma are best treated with unilateral lobectomy.[3,5,7]

Complications of thyroidectomy. Specific complications associated with thyroidectomy are: (1) bleeding and hematoma formation, (2) recurrent laryngeal nerve injury, (3) hypoparathyoidism, (4) injury to the external branch of the superior laryngeal nerve injury, (5) thyroid storm. Mortality on the other hand is extremely rare. As a result of the advances in surgical techniques and preoperative preparation.[7,12,71]

1) Bleeding. It is an early post-operative problem, usually occurs within the first 12 hours. The usual cause is bleeding from branches of the inferior or superior thyroid artery presenting as a swelling of the neck or respiratory obstruction. Actual compression of the trachea is unlikely but laryngeal and subglottic edema can occur by the expanding hematoma obstructing venous drainage. Urgent treatment is necessary, the wound must be opened and the clot evacuated at the bedside. Later the patient can be brought to the theatre to secure the bleeding vessel under general anasthesia.[7,71-74]

2) Recurrent laryngeal nerve injury. Permanent recurrent laryngeal nerve injury has been reported in the order of 0.1-4.5%. The incidence, however, is less than 0.1% in many specialized endocrine centers around the world.[7,71-76] The best way to protect and preserve the nerve during surgery is to visualize it and protect it through its course towards the cricothyroid membrane.[70] If nerve injury is identified postoperatively, it should be observed for at least 6-9 months before being labeled as permanent as recovery can occur up to 18 months after surgery. Temporary recurrent laryngeal nerve pulsy is common it occurs in 5%-15% of cases. It occurs as a result of minor trauma to the nerve during dissection resulting in a huskiness of the speaking voice, which takes several weeks before it improves.[7,71-76]

3) Injury to the external branch of the superior laryngeal nerve. The external branch of the superior laryngeal nerve is related to the superior thyroid pole during its course towards the cricothyroid muscle. Approximately, in 10-15% of the cases, the nerve hooks around the superior thyroid vessels on the surface of the thyroid gland. It is in this situation where the nerve becomes vulnerable to injury resulting in low-pitched voice. This problem improves during the 3-6 months after thyroidectomy.[7,77]

4) Hypocalcemia. Transient postoperative hypocalcemia may result from bruising or damage to one or more parathyroid glands or "hungry bone disease" in thyrotoxic patients. The reported incidence of permanent hypoparathyroidism ranges from 0.1-13.5%. The incidence is much less if the surgery was performed by an experienced thyroid surgeon. It is a serious complication requires lifetime calcium therapy and thus should be avoided. Following the technique of capsular thyroidectomy and the meticulous parathyroid dissection in addition to routine parathyroid autotransplantation in doubtful cases of parathyroid injury, the incidence of this complication has been brought down to zero level.[78,79]

5. Thyroid storm. This is a serious complication of thyroidectomy, which occurs, in the postoperative period as a result of thyroid manipulation in inadequately prepared patient. Thyroid storm can have mortality rates 20-30% and is characterized by fever, hypotension, congestive heart failure and circulatory collapse. Treatment involves initial resuscitation with intravenous fluids, potassium iodine to suppress thyroid synthesis and steroids to treat adrenal insufficiency. Propranolol is helpful in managing cardiac manifestations.[80,81]

Minimally invasive thyroid surgery. With the rapid development of laparoscopic surgery in the last decade, endoscopic neck surgery has evolved starting with parathyroidectomy. The early cases of endoscopic parathyroidectomy were performed using conventional laparoscpic instruments that were not suited for neck surgery. Following the advances in endoscopic instrumentation and the introduction of the miniscops and miniature instruments, many cases of parathyroid adenomas were removed and endoscopic procedures for other cervical structures were tried.[82-86] Multiple endoscopic approaches for thyroid excision have been developed, ranging from gasless video-assisted approach to complete endoscopic approach. There are, however, very few prospective randomized studies for these new techniques. Careful selection of patients is the key for good outcome from this kind of surgery; small thyroid nodules, small thyroid volume and no history of thyroiditis or previous neck explorations are required.

These techniques are minimally invasive and provide an excellent cosmetic result but still they are long procedures and require good experience with endoscopic surgery.[86-92] At the present time, these procedures will be offered to a minority of patients who undergo thyroid surgery and at very specialized centers in the world.

References

1. Lawrence W Jr, Kaplan BJ. Diagnosis and management of patients with thyroid nodules. ***J Surg Oncol*** 2002; 8: 157-170.
2. Shaha AR. Controversies in the management of thyroid nodule. ***Laryngoscope*** 2000; 110: 183-193.
3. Gharib H. Changing concepts in the diagnosis and management of thyroid nodules. ***Endocrinol Metab Clin North Am*** 1997; 26: 777-800.
4. Mazzaferri EL. Management of the solitary thyroid nodule. ***N Engl J Med*** 1993; 328: 553-559.
5. Burguera B, Gharib H. Thyroid incidentalomas. Prevalence, diagnosis, significance, and management. ***Endocrinol Metab Clin North Am*** 2000; 29: 187-203.
6. Praes JM, Dumollard JM, Timoshenko A, Chelikh L, Michel F, Estour B et al. Multinodular goiter: surgical management and histopathological findings. ***Eur Arch Otorhinolaryngol*** 2002; 259: 217-221.
7. Younes N, Robinson B, Delbridge L. The aetiology, investigation and management of surgical disorders of the thyroid gland. ***Aust N Z J Surg*** 1996; 66: 481-490
8. Clark OH. Total Thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer. ***Ann Surg*** 1982: 196: 361-370.
9. Reeve TS, Delbridge L, Crumer P. Total thyroidectomy in the management of differentiated thyroid cancer. A reveiw of 258 cases. ***Aust N Z J Surg*** 1986; 56: 829-833.
10. Siragusa G, Lanzara P, Di Pace G. Subtotal thyroidectomy in the treatment of benign thyroid disease. Our experience. ***Minerva Chir*** 1998; 53: 233-238.
11. Harness JK, Fung L, Thompson NW. Total thyroidectomy: complications and techniques. ***World J Surg*** 1986; 10: 781-786.
12. Lennquist S. Thyroidectomyin. In: Clarck OH, Duh QY, editors. Textbook of Endocrine Surgery. Philadelphia (PA): WB Saunders; 1997. p. 147-154.
13. Castro MR, Gharib H. Thyroid nodules and cancer. When to wait and watch, when to refer. ***Postgrad Med*** 2000; 107: 113-116, 119-120, 123-124.
14. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F et al. The spectrum of thyroid disease in a community: the Whickham Survey. ***Clin Endocrinol (Oxf)*** 1977; 7: 481-493.
15. Delange F. The disorders induced by iodine deficiency. ***Thyroid*** 1994; 4: 107-128.
16. Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. ***Endocrinol Metab Clin North Am*** 1997; 26: 189-218.
17. Ibbertson HK. Endemic goiter and critinism. ***J Clin Endocrinol Metab*** 1979; 8: 97-128.
18. World Health Organization (WHO). UNICEF/ICCID. Global prevalence of iodine deficiency disorders. Geneva; 1993.
19. Gaitan E, Nelson NC, Poole GV. Endemic goiter and endemic thyroid disorders. ***World J Surg*** 1991; 15: 205.
20. World Health Organization (WHO). Khrabsheh SH, Belbesi A, Qarquash W. Assessement of iodine deficiency status in growing Jordanian children after introduction of iodized salt. Amman; 2000.
21. Dumont JE, Roger PP, Lydgate M. Assays for thyroid growth immunoglobulins and clinical implications: methods, concepts, and misconceptions. ***Endocrin Rev*** 1987; 8: 448.
22. Shopsin B, Shenkman L, Blum M, Hollander CS. Iodide and lithium-induced hypothyroidism. ***Am J Med*** 1973; 55: 695-699.
23. Schneider AB, Shore-Freedman E, Weinstein RA. Radiation-induced thyroid and other head and neck tumors: occurrence of multiple tumors and analysis of risk factors. ***J Clin Endocrinol Metab*** 1986; 63: 107-112.
24. Wheeler MH. Investigation of the solitary nodule. ***Clin Endocrinol (Oxf)*** 1996; 44: 245-247.
25. Fraker DL. Radiation exposure and other factors that predispose to human thyroid neoplasia. ***Endocr Surg*** 1995; 75: 365-375.
26. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. ***N Engl J Med*** 1991; 325: 599-605.
27. Yousem DM, Huang F, Lourner LA. Clinical and economic impact of incidental thyroid lesions found with CT and MRI. ***Am J Neuroradiol*** 1997; 18: 1423-1428.
28. Ladenson PW. Optimal laboratory testing for diagnosis and monitoring of thyroid nodules, goiter, and thyroid cancer. ***Clin Chem*** 1996; 42: 183-187.
29. Ashcraft MW, Van Herl AJ. Management of thyroid nodule, scanning techniques, thyroid suppression therapy and fine needle aspiration biopsy. ***Head Neck Surg*** 1981; 3: 297-322.
30. Sabel MS, Staren ED, Gianakakis LM, Dwarakanathan S, Prinz RA. Effectiveness of the thyroid scan in evaluation of the solitary thyroid nodule. ***Am Surg*** 1997; 63: 660-664.
31. Giammanco M, Di Gesu G, Massenti MF, Di Trapani B, Vetri G. Role of color flow Doppler sonography in pre-operative diagnostics of the thyroid pathology. ***Minerva Endocrinol*** 2002; 27: 1-10.
32. Kountakis SE, Skoulas IG, Maillard AA. The radiologic work-up in thyroid surgery: fine-needle biopsy versus scintigraphy and ultrasound. ***Ear Nose Throat J*** 2002; 81: 151-154
33. Wang CY, Chang TJ, Chang TC, Hsiao YL, Chen MH, Huang SH. Thyroidectomy or radioiodine? The value of ultrasonography and cytology in the assessment of nodular lesions in Graves' hyperthyroidism. ***Am Surg*** 2001; 67: 721-726.
34. Agrawal S. Diagnostic accuracy and role of fine needle aspiration cytology in management of thyroid nodules. ***J Surg Oncol*** 1995; 58: 168-172.
35. Woeber KA. Cost-effective evaluation of the patient with a thyroid nodule. ***Endocr Surg*** 1995; 75: 357-363.
36. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. ***Thyroid*** 1998; 8: 283-289.
37. McLoughlin MJ, Ho CS, Langer B, McHattie J, Tao LC. Fine needle aspiration of malignant lesions in and around the pancreas. ***Cancer*** 1978; 4: 2413-2419.
38. Jossart GH, Clark OH. Well differentiated thyroid cancer. ***Curr Prob Surg*** 1994; 31: 935-1011.
39. Liu Q, Djuricin G, Prinz RA. Total thyroidectomy for benign thyroid disease. ***Surgery (St Louis)*** 1998; 123: 2-7.
40. Korun N, Asci C, Yilmazlar T, Duman H, Zorluoglu A, Tuncel E et al. Total thyroidectomy or lobectomy in benign nodular disease of the thyroid: changing trends in surgery. ***Int Surg*** 1997; 82: 417-419.
41. Singer PA, Cooper DS, Daniels GH, Ladenson PW, Greenspan FS, Levy EG et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. ***Arch Intern Med*** 1996; 156: 2165-2172.
42. Paphavasit A, Thompson GB, Hay ID, van Heerden JA, Ilstrup DM, Schleck C et al. Follicular and Hurthle cell thyroid neoplasms. Is frozen-section evaluation worthwhile? ***Arch Surg*** 1997; 132: 674-679.
43. DeGroot LJ, Larsen PR, Hennemann G. In the thyroid and its diseases. 6th ed. Thyroid Neoplasia. New (NY): Churchill Livingstone; 1996. p. 635-695.
44. Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid: does frozen section evaluation alter operative management? ***Ann Surg*** 1995; 222: 101-106.
45. McHenry CR, Raeburn C, Strickland T, Marty JJ. The utility of

routine frozen section examination for intraoperative diagnosis of thyroid cancer. ***Am J Surg*** 1996; 172: 658-661.
46. Hamming JF, Vriens MR, Goslings BM, Songun I, Fleuren GJ, VanDeVelde CJH. Role of fine-needle aspiration biopsy and frozen section examination in determining the extent of thyroidectomy. ***World J Surg*** 1998; 22: 575-580.
47. Mack E. Management of patients with substernal goiters. ***Endocr Surg*** 1995; 75: 377-394.
48. Newman E, Shaha AR. Substernal goiter. ***J Surg Oncol*** 1995; 60: 207-212.
49. Allo MD, Thompson NW. Rationale for the operative management of substernal goiters. ***Surgery (St. Louis)*** 1983; 94: 969-977.
50. Torre G, Borgonovo G, Amato A, Arezzo A, Ansaldo G, De Negri A et al. Surgical management of substernal goiter: analysis of 237 patients. ***Am Surg*** 1995; 61: 826-831.
51. Clark OH. Needle aspiration of thyroid cysts. In: Hamburger JI, Miller JM, editors. Controversies in clinical thyroidology, New York (NY): Springer-Verlag Inc; 1981. p. 218.
52. Rojdmark J, Jarhult J. High long term recurrence rate after subtotal thyroidectomy for nodular goitre. ***Eur J Surg*** 1995; 161: 725-727.
53. Wilson DB, Staren ED, Prinz RA. Thyroid reoperations: indications and risks. ***Am Surg*** 1998; 64: 674-678; [discussion] 678-679.
54. Wartofsky L. Radioiodine therapy for Graves disease: case selection and restriction recommended to patients in North America. ***Thyroid*** 1997; 7: 213-216.
55. Kannan CR, Seshadri KG. Thyrotoxicosis. ***Dis Mon*** 1997; 43: 601-677.
56. Seigel RD, Lee SL, Toxic nodular goiter. Toxic adenoma and multinodular goiter. ***Endorinol Metab Clin North Am*** 1998; 27: 151-168.
57. Harjai KJ, Livata AA. Effects of amiodarone on thyroid function. ***Annals of Internal Medicine*** 1997; 126: 63-73.
58. Gittoes NJ, Franklyn JA. Drug-induced thyroid disorders. ***Drug Saf*** 1995; 13: 46-55.
59. Mazzaferri EL. Management of a solitary thyroid nodule. ***N Engl J Med*** 1993; 328: 553-559.
60. Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G et al. Treatment guidelines for patients with hyperthyroidism. Standards of care committee, American
61. Lazarus JH. Hyperthyroidism. ***Lancet*** 1997; 349: 339-343.
62. Cooper DS. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. ***Endocrinol Metab Clin North Am*** 1998; 27: 225-247.
63. Tamarg J, Deplon E. Otimization of beta-blockers' pharmacology. ***J Cadiovasc Pharmacol*** 1990; 16 suppl 5: S10-S18.
64. Hrbciar J. Thyrotoxic heart disease. Part II—aspects of treatment of thyrotoxicosis with cardiac involvement. ***Vnitr Lek*** 2002; 48: 137-141.
65. Wartofsky L. Radioiodine therapy for Graves' disease: Case selection and restrictions recommended to patients in North America. ***Thyroid*** 1997; 7: 213-216.
66. Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. ***J Clin Endocrinol Metab*** 2002; 87: 1073-1077.
67. Kaplan MM, Meier DA, Dworkin HI. Treatment of hyperthyroidism with radioactive iodine. ***Endocrinol Metab Clin North Am*** 1998; 27: 205-223.
68. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. ***N Engl J Med*** 1998; 338: 712-718.
69. David E, Rosen IB, Bain J, James J, Kirsh JC. Management of the hot thyroid nodule. ***Am J Surg*** 1995; 170: 481-483.
70. Weetman AP. Graves' diseases. ***N Engl J Med*** 2000; 26: 1236-1248.
70. Gough IR, Wilkinson D. Total thyroidectomy for management of thyroid disease. [Review] ***World J Surg*** 2000; 24: 962-965.
72. Wheeler MH. Total thyroidectomy for benign thyroid disease. ***Lancet*** 1998; 23: 35: 1526-1527.
73. Steurer M, Passler C, Denk DM, Schneider B, Niederle B, Bigenzahn W. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and postoperative laryngoscopic examination in more than 1000 nerves at risk. ***Laryngoscope*** 2002; 112: 124-133.
74. Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. ***World J Surg*** 2000; 24: 1335-1341.
75. Hermann M, Alk G, Roka R, Glaser K, Freissmuth M. Laryngeal recurrent nerve injury in surgery for benign thyroid diseases: effect of nerve dissection and impact of individual surgeon in more than 27,000 nerves at risk. ***Ann Surg*** 2002; 235: 261-268.
76. Menegaux F, Turpin G, Dahman M, Leenhardt L, Chadarevian R, Aurengo A et al. Secondary thyroidectomy in patients with prior thyroid surgery for benign disease: a study of 203 cases. ***Surgery*** 1999; 126: 479-483.
77. Riedman M, LoSavio P, Ibrahim H. Superior laryngeal nerve identification and preservation in thyroidectomy. ***Arch Otolaryngol Head Neck Surg*** 2002; 12: 296-303.
78. Shaha AR, Jaffe BM. Parathyroid preservation during thyroid surgery. ***Am J Otolaryngol*** 1998; 19: 113-117.
79. Olson JA Jr, DeBenedetti MK, Baumann DS, Wells SA Jr. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. ***Ann Surg*** 1996; 223: 472-478 [discussion] 478-480.
80. Tietgens ST, Leinung MC. Thyroid storm. ***Med Clin North Am*** 1995; 79: 169-184.
81. Yoshida D. Thyroid storm precipitated by trauma. ***J Emerg Med*** 1996; 14: 697-701.
82. Gagner M. Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. ***Br J Surg*** 1996; 83: 875.
83. Miccoli P. Minimally invasive surgery for thyroid and parathyroid diseases. ***Surg Endosc*** 2002; 16: 3-6.
84. Furukawa T, Watanabe M, Ozawa S, Otani Y, Wakabayashi G, Morikawa Y. Development of endoscopic surgery for the minimally invasive treatment of digestive and other diseases. ***Keio J Med*** 2001; 50: 167-174.
85. Huscher CSG, Chiodini S, Napplitano C, Recher A. Endoscopic right thyroid lobectomy. ***Surg Endosc*** 1997; 11: 877.
86. Yeung GHC. Endoscopic surgery of the neck. ***Surg Laparosc Endosc*** 1998; 8: 227-232.
87. Inabnet WG, Gagner M. How I do it: endoscopic thyroidectmy. ***J Otolaryngol*** 2001; 30: 1-2.
88. Gagner M, Inabnet WB. Endoscopic thyroidectomy for solitary thyroid nodules. ***Thyroid*** 2001; 11: 161-163.
89. Miccoli P, Berti P, Conte M, Bendinelli C, Marcocci C. Minimally invasive surgery for thyroid small nodules: prelimmnary report. ***J Endocrinol Invest*** 1999; 177: 849-851.
90. Miccoli P, Berti P, Raffaelli M, Conte M, Materazzi G, Galleri D. Minimally invasive video-assisted thyroidectomy. ***Am J Surg*** 2001; 181: 567-570.
91. Yeh T, Jan Y, Hus BR, Chen KW, Chen MF. Video-assisted endoscopic thyroidectomy. ***Am J Surg*** 2000;180: 82-85.
92. Bellantone R, Lombardi CP, Raffaelli M, Rubino F, Boscherini M. Minimally invasive, totally gasless video-assisted thyroid lobectomy. ***Am J Surg*** 1999; 117: 342-343.