Management of Thyroid Cancer and Related Nodular Disease

I. Ross McDougall

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With 114 Figures

With contribution by

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This book is dedicated to
Liz, Shona, Stewart, Alison, and Hudson,
the greater McDougall family

Preface

After my early training in medicine, I was invited to join Professor Edward McGirr at the Royal Infirmary in Glasgow Scotland. Two of the main interests in his department were thyroid and isotopic medicine. At that time, 1969, the term isotopic medicine had been changed to Nuclear Medicine in the United States; thus, I embarked on a career in thyroidology and nuclear medicine. From 1972 to 1974, I had the opportunity to spend two years with Professor Joseph Kriss at Stanford University School of Medicine. He was an established investigator in the same subspecialities and provided inspiration, guidance, and resources for me. Both of these chiefs were role models in every regard. Although of different background and personality, they were generous, modest, insightful, ethical, innovative, and productive. Both were excellent clinicians who kept up to date with medicine in general as well as their specialities. Unfortunately, neither is alive. From 1974 to 1976, I returned to the Royal Infirmary and continued working in thyroid, nuclear medicine, and internal medicine. Since 1976, I have been at Stanford. Thus most of my experience has been in two centers with brief sabbatical leaves to a few centers in the United States and Europe. This text is a distillation of my efforts over this time.

Contents

Chapter 1

Thyroid Cancer: Epidemiology and Overview

The purpose of this textbook is to provide a single author text that covers all aspects of thyroid cancer. I requested and acknowledge the assistance of Dr Gerald Berry, a professor in Pathology at Stanford University, who adds expertise and outstanding figures to Chapter 3 on pathology of the thyroid. I hope, the text is easy to read, clinically valuable, authoritative, and enjoyable. Both or all sides of controversial issues are discussed. The final interpretation of data and their management could reflect my personal experience, but I hope not bias. The book is designed for physicians, including internal medicine and primary care doctors, endocrinologists, nuclear medicine physicians, general and head and neck surgeons, and oncologists including radiation oncologists. It is expected that a patient with a thyroid nodule or thyroid cancer would use the information as a resource. Others groups who will find an interest in the book would be trainees, including residents, medical students, and nurse practitioners, when they research a patient related problem.

In this chapter the epidemiology of thyroid cancer is presented followed by a synopsis of the educational goals of the subsequent chapters. Terminology, the use of words, abbreviations, and units of measurements are defined. The interpretation of results and statistics are discussed briefly along with evidence-based medicine and the importance of controlled studies and meta-analysis. The topics of alternative and traditional treatments are introduced briefly and are not included in the remainder of the book.

Epidemiology

In 2004 the American Cancer Society predicts there will be approximately 22,500 new cases of thyroid cancer in the United States. There is a 3:1 ratio of women to men, with estimated numbers of 16,875 cases in women versus 5,625 cases in men. Thyroid cancer accounts for about 1.1% of all cancers, and approximately 1.7% of cancers in women arise in the thyroid, compared with 0.5% of cancers in men. The prognosis is generally good, and overall 6% of patients die from the cancer, but the genders are more equally represented, with about 800 women and 600 men expected to die in the United States due to their thyroid cancers in 2004. This means that less than 0.5% of all cancer deaths are from carcinomas of the thyroid. There has been a progressive increase in the number of new cases in the United States and these have tripled over three decades. Although the total mortality numbers have also increased, they have done so only slightly, so the relative risk of dying has fallen over the same time. Figure 1.1 shows the overall number of cases and deaths in the United States over eight time periods from 1970–2003. Table 1.1 shows the number of new patients (women and men) per 100,000 people from 1973–2000. The increasing number of patients with thyroid cancer is not easily explained but could be due to a true increase that might be in part caused by radioactive fallout from atomic bomb testing, which is discussed in Chapter 5, Etiol-

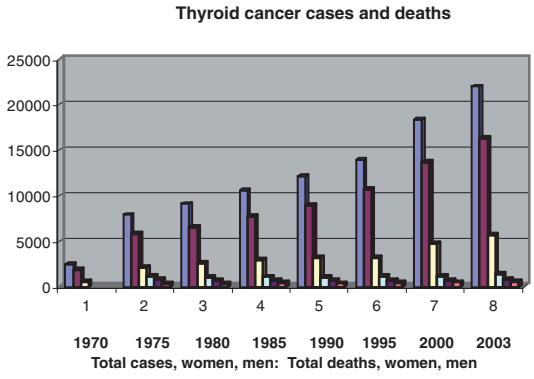

Figure 1.1. Graph shows increases in cases of thyroid cancer between 1976 and 2003 in the United States. The increases in mortality are less marked.

ogy of Thyroid Cancer. Alternatively physicians might be identifying small cancers that would have been overlooked in earlier decades, and the almost stable death rate supports this point of view. As stated above, women are more likely to develop thyroid cancer and the usual ratio is about 3:1 women to men; the only situation where the number of thyroid cancers is similar between the genders is in prepubertal children (1). Because the large majority of patients who are diagnosed with thyroid cancer have an excellent prognosis, each year there are approximately an additional 21,000 patients with this diagnosis who are expected to live for several decades. Therefore, there are several hundred thousand people in the United States who have a diagnosis of thyroid cancer.

Substantial differences in the prevalence of thyroid cancer between ethnic groups are recognized and these are hard to explain. In the United States, African Americans have a low incidence of 3.3 thyroid cancers per 100,000 women, Hawaiian women have 9.1 thyroid cancers per 100,000, Vietnamese women have 10.5 thyroid cancers per 100,000, and Filipino women have the highest incidence of thyroid cancer at 14.6 per 100,000 (1). Caucasian and Hispanic populations have similar incidences in women of 6.5 and 6.2 cancer of the thyroid per 100,000. When age is also considered Filipino women between 55 and 69 years have an incidence of 32.5 cancers per 100,000. Filipino men also have a higher incidence of thyroid cancer with 4.1 per 100,000 compared to 1.4 per 100,000 for African Americans. There would appear to be value in determining whether African Americans have a low incidence based on some protective factor or whether those populations at higher risk are exposed to an environmental or genetic factor that is hazardous. The same applies to the gender difference. Does being a man actually decrease the risk, or do female sex hormones increase it? A multi-ethnic study in the San Francisco Bay area tried to answer the environmental question, but no compelling factor was identified (2).

The incidence of thyroid cancer peaks at age 30–45 years and then levels off making this different from most malignancies, which become more common with advancing age. Hispanic men are the exception to this, having their highest incidence over the age of 70 years (9.2 per 100,000) (1).

In contrast in the United Kingdom there are 1,000 new cases annually yet the population is

Table 1.1. Incidence of thyroid cancer per 100,000 population in the United States.

	Male and female	Male	Female
1973	4.2075	2.3368	5.9243
1974	4.6620	2.9790	6.2627
1975	4.8461	3.1378	6.4344
1976	4.7977	2.9462	6.5740
1977	5.4350	3.4899	7.3072
1978	5.0885	3.1350	6.9367
1979	4.4772	2.6708	6.1617
1980	4.3205	2.3806	6.1296
1981	4.4076	2.5152	6.2171
1982	4.6203	3.0049	6.1329
1983	4.6913	2.7905	6.4705
1984	4.8407	2.6481	6.9154
1985	5.1211	3.0825	7.0859
1986	5.3105	3.0502	7.4816
1987	5.0476	2.8014	7.1354
1988	4.9462	2.9534	6.8944
1989	5.3396	2.9682	7.6179
1990	5.4602	2.8964	7.9208
1991	5.4496	3.1878	7.6181
1992	5.8518	3.5127	8.0698
1993	5.6075	3.5754	7.5896
1994	6.0576	3.3729	8.7112
1995	6.1947	3.3648	8.9393
1996	6.4426	3.4427	9.3737
1997	6.7250	3.6282	9.7197
1998	6.9075	3.6903	9.9821
1999	7.2800	3.8570	10.5671
2000	7.5069	4.0104	10.9165
2001	8.0131	4.2004	11.7265

about one fifth of that of the United States. The incidence is 2.3 thyroid cancers per 100,000 women and 0.9 per 100,000 men, which is substantially less than in the United States (3). Also in contrast 250 (25%) die annually of this cancer in the UK and the five-year survival is only 75% for women and 64% for men compared to ten-year survival rates in the United States that are better by an additional 20% (4). The basic therapies are similar in the United States and UK. The lower incidence and higher mortality in the UK might be due to delayed diagnosis until the cancer is larger and invasive, and small non-lethal lesions are not identified. The use of a staging system such as Tumor, Node, Metastasis (TNM), or a Prognostic Index (see Chapter 6) of every new case would allow this point to be proven or disproved. The survival is also dependant on race. The five-year survival for Caucasians in the United States has been 92% (1974–1976), 94% (1980–1982) and 95% (1989–1995), and over the same time intervals, the outcomes for African Americans were 88%, 94%, and 89%.

Contents of Chapters

Chapter 2 discusses clinically relevant aspects of thyroid anatomy and physiology. The fundamentals of testing thyroid function are included. These are important for understanding the results of thyroid function tests in a patient with a thyroid nodule or cancer and how to proceed with additional testing when patients are treated for these abnormalities. The anatomy of the thyroid and its lymphatics illustrate how the cancer can spread. Knowledge of the physiology of the iodide cycle and the formation of thyroid hormones illustrates how testing and treatment with radioiodine works. It also explains why false positive scans can occur due to trapping of radioiodine in non-thyroidal organs. The embryology allows an understanding of thyroid cancers in ectopic sites, such as ligual thyroid and thyroglossal duct cysts.

Chapter 3, which is on pathology, includes cytology and histology, and should aid the clinician working with a pathologist on reaching a correct decision about management. The prognosis varies depending on the type of cancer and in some cases the classification of the cancer. This is based on subtle pathological changes. Because thyroid cancer usually is diagnosed when a nodule is found in the thyroid, Chapter 4 is on management of thyroid nodules. Nodules are very common and are present in 4% to 6% of normal adults. This has to be contrasted with the 22,500 new cancers diagnosed annually in the United States. Since there are potentially 12 million to 18 million ($[4-6]/100 \times 300{,}000{,}000$ people in the United States) patients in the United States with a palpable thyroid nodule, this is a significant clinical problem. The numbers should not be interpreted as meaning that a nodule has about a one in 1,000 chance of being cancer (22,500/18,000,000), since each year there are 22,500 additional cancers and an unknown additional number of benign nodules. The numeric importance of thyroid nodules is significantly greater when it is recognized that 30% to 50% of adults have a nodule, or nodules, that can be identified by imaging, such as an ultrasound scan. Chapter 5 is devoted to the causes of thyroid nodules and more importantly of thyroid cancer. The role of radiation and genetic mutations are reviewed. The sources of radiation are medical, both diagnostic and therapeutic; occupational such as working in radiology or nuclear medicine, or a nuclear power plant and accidental release of radiation from atomic power stations; and radioactive fall-out from atomic bombs both intentional and from nuclear testing. The reader should obtain an understanding of the physics of radioactivity and the interaction of radioactive emissions with biological compounds such as deoxyribonucleic acid (DNA), plus knowledge of how mutations cause or predispose to malignant transformation.

Chapter 6 covers all aspects of differentiated thyroid cancer, which numerically is the most important cancer accounting for approximately 80% to 85% of the cases. The majority of differentiated cancers are classified as papillary cancer based on pathologic features and these along with the less common follicular cancer retain many of the functional characteristics of thyroid cells, hence the designation of differentiated thyroid cancer. All treatments in the management of differentiated thyroid cancer are addressed, including surgery, the role and logistics of radioactive iodine therapy, and long-term prescription of thyroid hormone. The methods for follow-up including scintigraphy and measurement of thyroglobulin (Tg) are presented.

Problems such as complications of thyroidectomy and radioiodine testing and treatment are described. Methods of determining the dose of iodine-131 (^{131}I) to be administered are demonstrated. Radiation safety planning for the release of radioactive patients from the hospital and the documents that can be used by medical personnel to advise and educate patients and families are provided. Controversial areas such as the need for whole-body diagnostic scans, stunning of the thyroid attributed to diagnostic ^{131}I, the role of whole-body scintigraphy with iodine-123 (^{123}I) versus ^{131}I, and the management of scan negative and Tg positive patients are debated. For each of these topics, arguments for and against are analyzed and advice of how to proceed given. The role of Positron Emission Tomography (PET and PET/CT) is included. There are several variants of differentiated cancer, such as tall cell and columnar, for which prognosis is worse, and these are discussed individually. Also included are differentiated cancers in ectopic sites such as the thyroglossal duct and the struma ovarii. Familial differentiated thyroid cancer, also called familial non-medullary cancer, is presented as a topic of increasing importance.

Chapter 7 is devoted to differentiated thyroid cancer in children. There are specific features of the disease and added emotional factors in these patients. Because thyroid cancer is predominantly a disease of women, in particular in the 20-year to 50-year age group, thyroid cancer in pregnancy, the effects of the disease and its treatment on fertility, offspring, and nursing are included in Chapter 8. The importance of not treating a pregnant patient with radioiodine is stressed, and the medical and legal literature is reviewed.

Anaplastic cancer affects the same cell as differentiated thyroid cancer and, in fact, often arises from or occurs in a pre-existing differentiated thyroid cancer. Because of its clinical course, treatment and prognosis is very different; it is discussed separately in Chapter 9. Medullary cancer and the familial syndromes of multiple endocrine neoplasia 2A and B (MEN 2A and 2B) pose different management problems and are reviewed independently. The importance of early diagnosis of familial cases by genetic screening is stressed. Lymphoma of the thyroid is also presented separately, since the treatment is very different from all other types of thyroid cancer. Most often this cancer is under the management of a medical or radiation oncologist. Finally, Chapter 12 is a brief chapter about cancers that metastasize to the thyroid. Each chapter should stand alone; therefore, there is some overlap but not excessive repetition. For example thyroid function testing is discussed in the second chapter on physiology and again in the follow-up of adult patients, children and pregnant women in Chapters 6, 7 and 8 respectively. Pathology is discussed in Chapter 3 and only the hallmarks of lesions are repeated along with each specific cancer. Genetic mutations as a cause of cancer are presented in Chapter 5 and clinically important issues reviewed in particular in Chapter 6 in the discussion of familial differentiated thyroid cancer and Chapter 10 on medullary cancer.

Words and Abbreviations

The main thyroid hormone, **thyroxine** (3,5,3′,5′ tetra-iodothyronine), can be written in many forms in addition to the two already mentioned. These include levo-thyroxine, l-thyroxine, T_4 and L-T_4. Throughout the text when thyroxine is the medication the term levo-thyroxine is used and when thyroxine, the serum level of thyroid hormone is discussed it is written as T_4 or in the case of the free hormone, FT_4.

There appears to have been the development of new languages in which only abbreviations are used. Each specialist group has its lexicon so that non-card-carrying members are left in the dark. When I read some scientific papers, the importance of the findings is lost in an alphabet soup of meaningless letters. In the book 1984, George Orwell describes a C vocabulary from which "any scientific worker or technician could find all the words he needed in the list devoted to his own speciality, but he seldom had more than a smattering of words occurring in the other lists" (5). I accept that some abbreviations are in common usage such as DNA and RNA. With regard to the thyroid there are also several in common and universal use and recognized by physicians and patients alike as shown in Table 1.2. Throughout the text when a commonly used name or term is presented the full title is given on the first occasion, followed by the shortened form and from then on the abbreviation is employed. In contrast there are enormous numbers of abbreviations that are not in common use. Table 1.3 provides a random list

Table 1.2. Abbreviations used commonly in relation to the thyroid.

Abbreviation	Full name	Possible source of confusion
T_4	Thyroxine	Thymus derived lymphocytes
	Levo-thyroxine	
	L-thyroxine	
	3,5,3′,5′ tetraiodothyronine	
FT_4	Free-Thyroxine	
	Free-Levo-thyroxine	
	Free-L-thyroxine	
	Free-3,5,3′,5′ tetraiodothyronine	
T_3	Triiodothyronine	
	3,5,3′ triiodothyronine	
FT_3	Free-Triiodothyronine	
	Free-3,5,3′triiodothyronine	
TSH	Thyroid stimulating hormone	
	Thyrotropin	
TRH	Thyrotropin releasing hormone	
	TSH releasing hormone	
Tg	Thyroglobulin	
TPO	Thyroid peroxidase	
Anti-Tg	Anti-thyroglobulin	
Anti-TPO	Anti-thyroperoxidase	
NIS	Sodium iodide symporter	
SUV	Standardized uptake value	Sports utility vehicle
CT	Computed tomography	
MRI	Magnetic resonance imaging	

Table 1.3. Examples of abbreviations not in common use.

Abbreviation	Meaning	Alternative meaning
ACZ	Acetazolamide	
ATF	Anatomic tissue fraction	
BAT	Brown adipose tissue	A flying nocturnal mammal A tool for striking a ball
BBN	Bombesin	
BETIT	Biological event targeting imaging	
BMPR 2	Bone mineral protein receptor	
Cactus	Clinical application of cellular trafficking for understanding stem cells	Desert plant
CASTLE	Carcinoma showing thymus-like differentiation	The home of a king or knight
CEA	Carcino embryonic antigen	Carotid endarterectomy
CGRP	Calcitonin gene related peptide	
DA	Diagnostic	District attorney
DCM	Dilated cardiomyopathy	
DLBCL	Diffuse lymphocytic B cell lymphoma	
EPC	Endothelial progenitor cells	
FDCS	Follicular dendritic cell sarcoma	
GBM	Glioblastoma multiforme	
GRPR	Gastrin releasing peptide receptor	
HCM	Hypercalcemia of malignancy	
IGMA	Image guided microassay analysis	
ITET	Intrathyroidal epithelial tumor	
MZBL	Marginal zone B cell lymphoma	
NAC	Non attenuation corrected	
PACAP	Pituitary adenylate cyclase activated peptide	
PDA	Poorly differentiated adenocarcinoma	Patent ductus arteriosus
PSMA	Prostate specific membrane antigen	
PTI	Perfusable tissue index	
SETTLE	Spindle epithelial tumor with thymus like differentiation	
SKA	Simplified kinetic analysis	
SMECE	Sclerosing mucoepidermoid carcinoma with eosinophilia	
VEGF	Vascular endothelial growth factor	

generated in one day from scientific papers that I was reading and a lecture I attended. The authors and speaker are not identified to protect the not so innocent. Not only are these abbreviations difficult to keep track of but also some have alternative meanings that can lead to additional confusion. In situations like those listed in Table 1.3, the full designation and not the abbreviation is repeated each time the term is used.

The word tumor is interpreted by most patients to mean cancer. In fact it is an indeterminate term that should be qualified by benign or malignant. I have tried to avoid the word and use "nodule" in place of "benign tumor" and "cancer" or "carcinoma" in place of "malignant tumor."

Units of Measurement

In many parts of the text there are descriptions and discussions of radioactivity used for diagnostic testing and for therapy. The definition of these units is presented in Chapters 5 and 6. Their use cover a very large numerical range from very small fractions to numbers that are many orders of magnitude greater. Table 1.4 provides prefixes and symbols for the range 10^{-15} (femto, f) to 10^{12} (tera, T). There are two systems for expressing the units of radiation and radioactivity. These are the *Système International* (SI) units and the standard system. There are different units for quantities of radioactivity that are administered and for radiation that is absorbed by tissues of the body. In SI the units of radioactivity that are administered are the Becquerel (Bq) or multiples of Becquerels (Megabecquerel [MBq] or Gigabecquerel [GBq]). In the standard system the Curie (Ci) is the basic unit, and usually microcuries or millicuries are administered (μCi or mCi). Absorbed radiation is expressed in units of the Gray (Gy) and the Sievert (Sv) in the SI and rad and roentgen equivalent in man (rem) in the standard system. For most forms of medical radiation Gy and Sv are equivalent as are rad and rem. These units are defined fully in Chapters 5 and 6 and how to convert from one to the other system.

Interpretation of Test Results and Statistics

A recent study found that 38% of the statistics in articles in Nature and 25% of the statistics in articles in the British Medical Journal were wrong (6). Therefore when reading an article (and this text) it is important to check the numbers and make an approximation to determine whether the conclusions of investigators are reasonable. In the interpretation of data, it is helpful to calculate sensitivity and specificity of the procedure under analysis. Sensitivity is defined as the proportion of patients with the disease who have a positive test result (7). The specificity of the test is the proportion of patients who have no disease and whose test is negative. The perfect test would have a sensitivity of 100% and a specificity of 100%, but there is no such test. Figure 1.2 provides a template for calculating these numbers.

Table 1.4. Names and numbers and their symbols.

Factor	Prefix	Symbol
10^{12}	Tera	T
10^{9}	Giga	G
10^{6}	Mega	M
10^{3}	Kilo	K
10^{-1}	Deci	d
10^{-2}	Centi	c
10^{-3}	Milli	m
10^{-6}	Micro	μ
10^{-9}	Nano	n
10^{-12}	Pico	P
10^{-15}	Femto	f

Test	Patient with disease	Patient without disease	Total
Abnormal	**True positive A**	**False positive B**	**A + B**
Normal	**False negative C**	**True negative D**	**C + D**
Total	**A + C**	**B + D**	**A + B + C + D**

Sensitivity $\frac{A}{A+C}$ Specificity $\frac{D}{B+D}$

Figure 1.2. Chart shows how to calculate sensitivity and specificity.

The equations for calculating sensitivity and specificity are:

$$\text{Sensitivity} = \frac{\text{Number of patients with disease who have a positive test [A]}}{\left(\begin{array}{c}\text{Number with disease and positive test [A]} + \\ \text{Number with disease and negative test [C]}\end{array}\right)}$$

$$\text{Specificity} = \frac{\text{Number of patients with no disease who have a negative}}{\left(\begin{array}{c}\text{Number with no disease and negative test [D]} + \text{Number with} \\ \text{no disease and positive test [B]}\end{array}\right)}$$

There is usually a reciprocal relationship between sensitivity and specificity. As the sensitivity of a test increases the specificity decreases and vice versa. When a test has a high specificity a positive result is more likely to be a true positive. Conversely a negative result from a test that has a high sensitivity has a high probability of being a true negative, which rules out disease. Although the calculation of sensitivity and specificity does not depend on the prevalence of disease, their use in managing a patient does. For example, let us assume in an investigation the sensitivity of fine needle aspiration (FNA) of a thyroid nodule for diagnosing cancer in a nodule is 80% and the specificity is 90% and we study two new and different groups of patients. The first group consists of 100 healthy, asymptomatic women with a small nodule. The second is made up of 100 patients with a thyroid nodule who had been exposed to radiation in childhood from the release of radioactive nuclides at Chernobyl. For purpose of calculation, the a priori risk of cancer in the first group is accepted to be 5% and in the second group 30%. Using the sensitivity and specificity as shown in Figures 1.3 and 1.4 the post priori risks of cancer when the FNA is positive are 31% and 77% respectively.

An additional and more useful method of handling the data is to determine the likelihood ratio (8). This is the ratio of the probability of an abnormal test in patients with the disease to the probability of an abnormal test in those who

Use of FNA in 100 patients with a thyroid nodule and 5% chance of malignancy. Sensitivity of the test is 80% and the Specificity is 90%

Test FNA	Thyroid cancer	Benign nodule	
Positive	4 A	9 B	13
Negative	1 C	86 D	87
Totals	5	95	100

Positive FNA is likely to be cancer in 4/5 (80%) [A/A + C] and there are 9 false positive results giving the specificity of 90% (86/95) [B/B + D]

Use of FNA in 100 patients with a thyroid nodule and 30% chance of malignancy Sensitivity 80%, Specificity 90%

Test FNA	Thyroid cancer	Benign nodule	
Positive	24 A	7 B	31
Negative	6 C	63 D	69
	30	70	100

Positive FNA is due to cancer in 24/30 (80%) [A/A + C]
and there are 7 false positive results and the specificity is 63/70 (90%) [B/B + D]

Figures 1.3 and 1.4. Charts demonstrate how the probability of a positive test result being a true positive depends not only on the sensitivity of a test but the prevalence of the disease in the population under investigation. Similarly the probability of a negative test being a true negative also depends on the prevalence of the disease or rather the prevalence of those who do not have the disease. These concepts are presented with a test (fine needle aspiration [FNA] of a solitary thyroid nodule) that has a sensitivity of 80% and a specificity of 90% for two populations, one with a 5% chance of disease the other with a 30% chance.

are free of the disease. When the likelihood ratio is one the result of the test is neutral and of little value. The larger the likelihood ratio is above one the more likely disease is present and conversely the lower the ratio is below one the less likely the disease. Let us return to the two groups with thyroid nodules. From the five patients in group A with thyroid cancer, four had an abnormal test (FNA), which is 80%. Nine patients without cancer had an abnormal test, 9/95 = 9.5%. The positive likelihood ratio is 80%/9.5% = 8.4. In this case the calculation can be made using the formula:

$$\text{Positive Likelihood ratio} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{The pretest possibility of cancer} = 0.05 (5 \text{ out of } 100)$$

$$\text{The pretest odds} = 0.05/0.95 = 0.053$$

$$\text{The post test odds} = \text{pretest odds} \times \text{likelihood ratio} = 0.053 \times 8.4 = 0.445$$

$$\text{The post test probability} = \text{post test odds}/(1 + \text{post test odds}) = 0.445/1.445 = 0.308(31\%).$$

Of the thirty patients in group B with thyroid cancer, twenty-four had an abnormal test (FNA), which is also 80%. Seven patients (10%) without cancer had an abnormal test. The positive likelihood ratio is 80%/10% = 8. In this case the calculation can be made using the same formula:

$$\text{Likelihood ratio} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{The pretest possibility} = 0.3$$

$$\text{The pretest odds} = 0.3/0.7 = 0.433$$

$$\text{The post test odds} = \text{pretest odds} \times \text{likelihood ratio} = 0.433 \times 8 = 3.46$$

$$\text{The post test probability} = \text{post test odds}/(1 + \text{post test odds}) = 3.46/4.46 = 0.77(77\%).$$

For people who are educated on the nuances of betting on horse or dog races the use of odds is second nature. Fagan developed a nomogram that can be used to find the post test probability when the pre test probability and likelihood ratio are known.

The negative likelihood ratio is obtained from the equation

$$\frac{1 - \text{sensitivity}}{\text{specificity}}$$

Confidence Intervals

Sensitivity and specificity are calculated from a group of patients or tests however the results might not be representative for the entire population. One method to determine the precision is the Confidence Interval. Usually this is expressed as a range that lies within random samples. The most common in practice is the 95% confidence interval, meaning that only 5% of the true answer for the population would lie outside that range. For more precision the 99% confidence intervals could be employed. When the sensitivity has been calculated the 95% confidence interval is obtained from the equation:

$$\text{Sensitivity expressed as a proportion } (p) \pm 1.96 \times \sqrt{(p[1-p])}\Big/(\text{the number of subjects}).$$

Using the second group of patients with thyroid nodules described above the 95% confidence intervals are

$$0.8 \pm 1.96\sqrt{0.8(1-0.8)\Big/100} = 0.722, 0.878.$$

Factors that are not incorporated into these calculations are the reliability of the test and the reliability of the interpreter of the test. There are very few studies addressing this point with regard to imaging tests of the thyroid. How reliable are the technical aspects of the test when a patient has the test repeated under the same conditions within a short time? To answer this is difficult to justify in the case of a patient undergoing a nuclear medicine procedure, especially when thyroid hormone has to be withdrawn and the patient is symptomatically hypothyroid. However, in the case of nuclear cardiac studies a difference of up to 5% is accepted as normal. The reader can infer that the same test in different institutes using different instruments is likely to show even less reproducibility. With regard to the interpreter, the reliability can be calculated by reading the same images on two or more occasions. All identifying features have to be removed from the images to ensure a "blinded" reading. This is called intraobserver reliability. An experienced reader can usually recall that he/she is looking at the same images and might reach a concordance by recognition. Since in many departments more than one person is responsible for the interpretation of images interobserver reliability can be measured by having a set of images read by two or more people and the concordance calculated. This is not as simple as determining how many cases the observers agree on, in other words whether both interpretations are negative or positive, since concordance can occur by chance. If two readers review 100 scans and the concordance is as shown in Figure 1.5 this appears impressive at 80 out of 100 (80%). The true agreement is called the Kappa score (K) and is calculated as follows, first using the formula:

Results of double reading of 100 thyroid scans

	Observer 2 Positive	Observer 2 Negative
Observer 1 Positive	40 (A)	10 (B)
Observer 1 Negative	10 (C)	40 (D)

This would appear to result in an 80% agreement
However there could be agreement in 50% by chance

Figure 1.5. Chart illustrates the use of the double reading of studies to determine the agreement between interpreters.

$$\frac{(A+B)\times(A+C)}{n}+\frac{(B+D)\times(C+D)}{n}$$

The result of this is 0.5 or 50% and is the chance agreement. K is then obtained from a second equation:

$$K=\frac{\text{agreement (80)}-\text{chance agreement (50)}}{1-\text{chance agreement (50)}}$$
$$=0.6 \text{ or } 60\%$$

The greater the K value the better the agreement and values below 0.4 are problematic. Our group conducts a double reading of scintiscans monthly looking not only at the interpretation but the quality of the images, clarity of the report and whether the referring physician was contacted with the results. A search of the literature did not identify a single publication addressing intraobserver or interobserver reliability of reading thyroid scans.

Received Operator Characteristics

It was stated earlier that there is reciprocity between sensitivity and specificity. The more sensitive a test is the greater the number of true positives but also the number of false positives increases so that the specificity drops. In some situations the cutoff between normal and abnormal is arbitrary, and the level chosen results in variations in sensitivity and specificity. As an example, let us use the uptake of a tracer of radioiodine in the thyroid bed after treatment of thyroid cancer by thyroidectomy and ^{131}I. Some authorities accept a value <0.1% as evidence of successful therapy but others uses values as high as 1%. This is shown graphically in Figure 1.6. The low cut-off value would identify almost all patients with residual functioning tissue (high sensitivity) but could include some where the counts are due to background activity or scattered radiation from salivary activity (low specificity). The higher value would miss patients with residual tissue (low sensitivity), but there would be few false positives (high specificity). The varying relationship between sensitivity can be produced in graphic form by plotting sensitivity (true positive) on

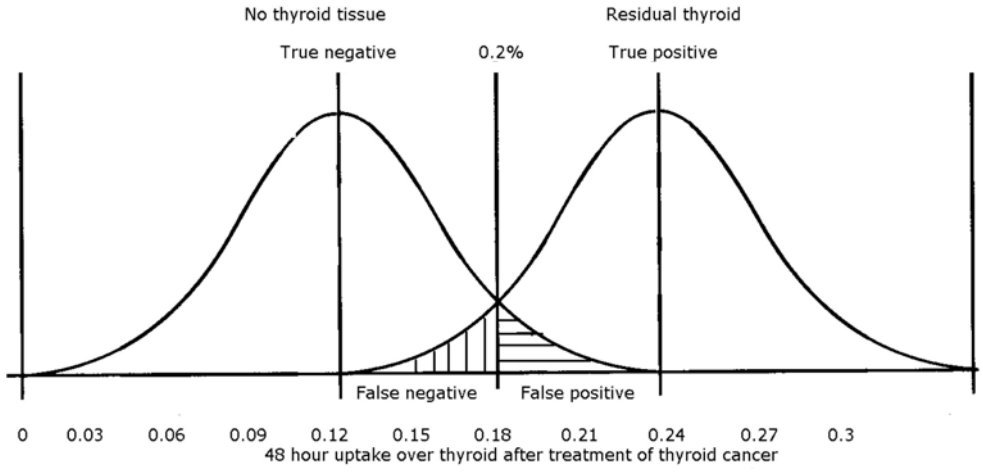

Figure 1.6. Graph demonstrates how an arbitrary decision on where to separate normal from abnormal (percent uptake over the thyroid bed after treatment of thyroid cancer) can result in different sensitivities and specificities.

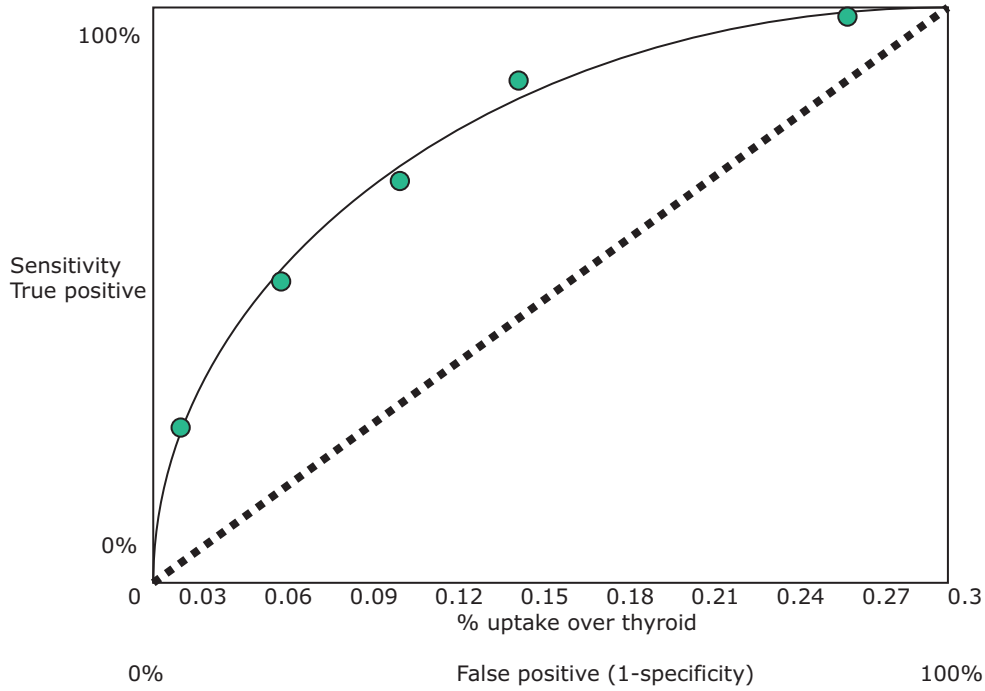

Figure 1.7. Graph shows how a receiver operator characteristic curve (ROC) is developed from pairs of sensitivities and specificities. This allows a choice of cut-off that would give the optimal choice of sensitivity coupled with specificity for the interpretation of a test.

the y-axis and one minus specificity (false positive) on the x-axis. This is the receiver operator characteristic curve (ROC). An example is shown in Figure 1.7. The goal is to identify the optimal cut-off where there is a high sensitivity and an acceptably low specificity.

Evidence-Based Medicine

An excellent definition of evidence-based medicine comes from Sackett and colleagues, who are recognized as leaders in this discipline (9). "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." External clinical evidence is based mostly on the results of randomized controlled studies and meta-analyses. These are discussed below. However, the experience of the physician is important since he or she knows the patient as a person rather than a "case" in a research investigation. There are no double blind controlled studies on any aspects of treatment of thyroid cancer; therefore, advice to use treatment A versus treatment B is not cast in stone. In spite of this limitation, some treatments can be advised with conviction. It is not correct to leave a cancer in the thyroid without any treatment. The cancer will grow and with time invade and metastasize and no controlled study of thyroidectomy versus no thyroidectomy would be justified under any circumstance. In retrospective studies total thyroidectomy appears to be superior to lobectomy, but even this is not accepted by all authorities for all patients (10, 11). Likewise, it is not ethical to compare the outcome in patients treated with thyroid hormone after thyroidectomy with those not given thyroid hormone.

Implicit in the definition of evidence-based medicine is that the treating physician has the "best available clinical evidence." This requires an enormous amount of time to read the appropriate journals, use computer searches, and

attend lectures and conferences. Sackett et al. estimated that a practitioner would need to read about twenty articles every day of the year to achieve this goal. Patients might be despondent on reading this however I am not. It appears this should be an area for potential gain. Physicians do read and make computer searches, they do attend conferences, and they do have a close understanding of the fundamentals and controversies. In addition nowadays, many patients educate themselves on their specific problems and expect to be involved actively in decisions about testing and treatment. The combination of an informed physician and patient adds power to decision making.

Randomized Controlled Studies and Randomized Double Blind Controlled Studies

Cochrane wrote, "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all randomized controlled trials." Several important aspects of the management of thyroid cancer continue to raise questions. Is it better to excise the entire gland or part of it? Is the outcome better in those treated with ^{131}I? For long-term management what is the optimal level for serum thyrotropin (thyroid stimulating hormone, TSH)? Questions such as these can be answered by randomized trials. It is unrealistic to have double blinded trials in some situations, for example the administration of ^{131}I therapy. The patients treated with ^{131}I would have symptoms, such as a change in taste, and evidence of therapy, such as a post therapy scan and measurements of emitted radiation for radiation safety requirements. Nevertheless, there would be important information from an open randomized trial comparing one group treated with ^{131}I to a control group matched for age, gender, and stage of cancer that did not receive ^{131}I. There is no data. Several reasons account for this. First and central is the excellent outcome in most patients with thyroid cancer. Physicians tend to accept that whatever treatment they administer accounts for that success, and they are, therefore, both reluctant to change that regime and also unwilling to randomize patients not to receive their therapies. Related to the overall good outcome is the number of patients and the time necessary to reach a statistically significant answer. The outcome could be recurrence of cancer or death from cancer. Let us use a hypothetical set of numbers. The chance of dying from differentiated thyroid cancer is about 5% at ten years when the disease is treated by operation and thyroid hormone. The mortality over 10 years is 4% for those treated by surgery, thyroid hormone, and ^{131}I. For those treated with ^{131}I the absolute risk reduction is 5–4 = 1%. The number needed to treat to prevent 1 death would be 100 patients followed for 10 years. The relative risk for death when ^{131}I is included is 4/5 = 0.8 or 80%. The absolute risk reduction and number to treat are more valuable than the relative risk since they incorporate the prevalence of the problem. In order to reach statistical significance, several thousand patients would need to be randomized and followed for more than twenty years.

One randomized trial concerned with ^{131}I allocated patients to one of 8 therapy groups, but all patients received ^{131}I treatment (12). Unfortunately, this trial could not answer whether ^{131}I reduced the rate of recurrence or mortality; rather it determined what administered dose would ablate residual thyroid. The lowest dose these investigators administered was 555 MBq or 15 mCi, and they increased this by 185 MBq (5 mCi) increments up to a maximum of 1.85 GBq (50 mCi). They demonstrated that doses of 925 MBq (25 mCi) or greater were superior to smaller doses. There was no difference in outcome between the subgroups treated with 0.925 MBq to 1.85 MBq (25–50 mCi). The paper includes odds ratios and confidence intervals and makes valuable reading.

There are randomized cross over placebo studies to determine the effect of levo-thyroxine on the size of thyroid nodules (13). There are randomized trials of injection of ethanol versus levo-thyroxine for thyroid nodules (14). There is no investigation comparing a supraphysiological dose of levo-thyroxine versus a physiological dose in prevention of recurrence of cancer or reduction in mortality.

Meta-Analysis

In recent years there has been a cult in the value of meta-analysis. A meta-analysis is a review combining the results or outcomes of many published studies. When each of the studies demonstrates a trend for example radioiodine therapy reducing the number of recurrences of thyroid cancer, the combined data add strength to the thesis that ^{131}I is beneficial. When the studies used for the meta-analysis show disparate results the outcome of the meta-analysis is neutral. Many meta-analyses have been used to help in development of guidelines for managing medical conditions. They also form a basis for evidence-based medicine. It is important that the basic publications are consistent in the types of patients evaluated and the therapies prescribed. If all of the patients in one study who receive ^{131}I treatment have small cancers that have been totally excised, ^{131}I will appear to be very successful because there was no residual disease to treat. If these data are combined with publications discussing patients who had metastases to distant sites, their response to ^{131}I would be substantially worse and the studies would cancel each other out. Conversely, if all of the publications analyzed contain patients with small cancers and ^{131}I appears to be consistently successful, it would be wrong to conclude that ^{131}I would be useful for metastatic disease. Therefore it is valuable to review the raw information used in a meta-analysis before making a judgement. Higgins et al. have developed a technique for measuring the degree of inconsistency in a meta-analysis (15). This has been designated I^2 and is derived from the formula $I^2 = 100 \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Cochran's Q is calculated by summing the squared deviations of each study's estimate from the overall meta-analytic estimate. The degree of freedom is the number of studies analyzed minus one.

References to Published Articles

The text is extensively referenced and includes personal published work of 35 years managing patients with thyroid disorders including thyroid nodules and thyroid cancer. I have used PUBMED and MEDLINE and on occasion Google and have tried to update each chapter as it was being revised. I had to draw the line at some empiric ending time and used December 1, 2004.

Every effort has been made to refer to key articles and I apologize for any omission. Authors who find one of their important publications has been overlooked should not take this personally; the defect is an oversight not a slight. I would be happy to receive information that has been omitted by regular mail or e-mail.

There are several very useful sources of information apart from the computer links and standard textbooks. These include medical journals and now patients in addition to physicians can usually get access to abstracts and texts through PUBMED. The search engine Google can also find information and references. Several organizations provide help for patients as well as physicians, as seen in Table 1.5. The first is reached through the web site www.thyca.org. This thyroid cancer survivor organization provides solid current information for patients and it has published an excellent

Table 1.5. Web sites of use when researching problems related to thyroid nodules or thyroid cancer.

Web site	Note
http://ebm.bmjjournals.com	Access to journals with original peer reviewed articles
http://www.clinicalevidence.com	–
http://gateway.ut.ovid.com	–
http://md.skolar.com	–
http://Pubmed.com	–
http://www.allthyroid.org/	Thyroid Foundation of America
http://www.thyroid.ca/	Thyroid Foundation of Canada
http://wwwThyCanSurv.org	Thyroid cancer survivors association
http://www.aace.com	American Association of Clinical Endocrinology
http://www.thyroid.com	American Thyroid Association

low iodine diet recipe book. This organization convenes an annual meeting with invited experts to lecture on and discuss treatment options and future developments. Other professional associations include the American Thyroid Association (ATA). The web site is www.thyroid.org. The ATA and the American Association of Clinical Endocrinologists (www.aace.com) provide medical information and can facilitate referral to specialists based on geographic requirement of the patient.

Patient-Physician Relationship

This is a complex topic to condense. The relationship of patient and physician varies greatly between doctors, from country to country. It is based on education, role models, personal characteristics of family upbringing, personal experience, of being a user rather than a giver of care, and other factors that are hard to understand. There are differences that can relate to gender, age, ethnicity, education, and interest. (16) The patient wants "a patient-physician relationship based on understanding, honesty, and trust" (17). In the United States there are two trends that are not compatible. On one hand is an educated public that wants to share in the decision-making. On the other is managed care, where the aim is to make money for shareholders of companies responsible for delivering care. Those in charge of managed care organizations state there are other aims such as providing uniform, high quality medical care and preventative medicine, but in reality these leaders would not be in position if their companies were in the red. Other countries have problems with long waiting lists for testing and therapy. I have been informed that in some European countries a patient who would benefit from ^{131}I treatment frequently has to wait for months for a designated hospital bed to become available. These events can strain the patient physician relationship. In talking to physicians from all parts of the world, there is a consensus that they are working harder and consulting on more patients than in previous years. This also strains the relationship. There are several criticisms cited by patients. First that they do not have enough time to discuss their problems and to digest and understand the protocols for testing and treatment and to ask questions. In addition, they do not have the ability to have input in their management, which is presented to them as gospel and immutable. These issues are not easy to rectify but each clinician should try within their system to provide unhurried, sensitive, empathic, and knowledgeable care and to work with rather than above the patient. Objective evaluation of empathy has demonstrated that women physicians perform better than men, and psychiatrists are significantly superior to anesthesiologists, orthopedic surgeons, neurosurgeons, radiologists, cardiovascular surgeons, obstetricians and gynecologists, and general surgeons (18). Medical schools are investing more time in development of programs to increase the communication skills of young physicians (19). Patients should be advised to bring records such as operative and pathology reports and pathology slides. The slides should be reinterpreted and where possible scintiscans and radiological studies should be reviewed. This is superior to reading the reports. On occasion the volume of information the patient brings is large and it has to be reviewed and discussed separately. I was once faced with a patient who wheeled a large suitcase full of documents into the consulting room. When a patient is referred from your own institute it is beneficial to have all the information available at the time of the consultation. Patients are also advised to develop a list of questions related to their management. Once the relationship is established small pieces of information can be discussed by a short phone call. This could include the result of a recent blood test and whether the dose of a medication should be adjusted. These interactions are usually brief. When the issue turns out to be more substantial, a clinic visit can be organized (20). A study of patients who used scripted simulated problems found that triage by telephone was erratic (21). However, the range of advice sought was diverse and when the patients and their conditions are known and the item to be discussed relates to their illness the advice should be robust. Patients appreciate this since it avoids taking time off work, parking at the hospital, registering, and waiting. All consultations, including phone messages, should be documented. Another frequent complaint is that patients say they love Dr X but he keeps them waiting three or four hours. This should not happen.

Some patients use e-mail to relay symptoms and questions. Some physicians use it to convey information. This could be the way of the future. My preference is for direct communication either in the clinic or by telephone. The new regulations concerning privacy in the United States make the use of the Internet very hazardous. The privacy requirements make it important to talk directly to the patient and only after explicit permission has been given is it acceptable to speak with a designated alternative.

Alternative Therapy

Alternative medicine applies to non-standard or unconventional treatments. Many people place great stock in these. The therapies are supported by testimonies, but usually there are no peer reviewed published data. It is difficult to argue against alternative therapy with two provisos. One, that the alternative treatment is not used in place of conventional treatment. Secondly, that the treatment is known to have no deleterious side effects. There is almost no data on the latter. I sent batches of alternative therapies used by one patient for analysis by scientists in a company that had top chemists working on identifying active ingredients of traditional Chinese and Oriental remedies. They were unable to find any known active ingredient in the patients alternative medications. This suggests the therapies would provide no benefit, but the analysis did not guarantee that the materials were non-toxic. The following are 3 examples of alternative medicines copied directly from their web sites:

If you are reading this page, you or someone you love has cancer. Dr X's goal is to provide hope and an alternative to the unsuccessful common treatments offered by the medical field. TumorX Paste & Proteolytic Enzymes. This is a web site where one can find alternative cancer treatments, using TumorX Paste and TumorX Proteolytic Enzymes. These are used in conjunction to eliminate the cancer from one's body. TumorX Paste contains the apoptotic and antiproliferative ingredient Bloodroot, (i.e., Sanguinarine canadensis.) Bloodroot's anti-cancer compounds have been known historically as Hoxsey salve, Dr. Mohs Chemosurgery salve, escharotic salve, black salve, bloodroot salve, and other names. TumorX Paste is used in conjunction with proteolytic enzymes that can, in most cases, defeat one's cancers.

Ukrain with two cycle Insulin Potentiation Therapy (IPT): We believe Ukrain/IPT is very effective. We have treated all kinds of cancers including Pancreatic, breast, colon, ovarian, thyroid, liver, lymphomas, leukemia, multiple myeloma, prostate, brain, stomach, lungs, mesothelioma, sarcoma, and so forth. Melding this modality with other therapies. Many of the cancers we treated resulted in reduction of tumor markers and shrinkage of tumor mass without any of the horrendous toxic effects we see with traditional chemotherapy.

Here are the products most useful for cancer – the top tier, foundational products:

- EOxygen Elements Plus: Four to six bottles a month are a high therapeutic amount. This would work in tandem with the oxygen utilization effects of Super Quinone.
- Ellagic Formula with Graviola: Three or four bottles is a month high therapeutic amount.
- SSR Super Quinone: A course of fourteen vials will last a month and a half and can be repeated until healthy.
- Five Elements Mineral Catalyst: One bottle lasts three months.
- U-Fn: Three bottles a month is the suggested therapeutic usage.
- MPS Gold and MPS 3X: One to three large bottles of the Gold is the therapeutic to high therapeutic level. Add on an equal amount of MPS 3X bottles to boost the immune system even more.
- Whole Cell Beta Glucan: One to three bottles a month depending on your size. This works well with MPS Gold.
- AFA Blue Green Algae: The highest therapeutic amount is about fifteen grams a

day. Try Blue Manna algae for working on emotions and mental outlook.
- Nature's Biotics: A good fundamental product to get, but you have to work into it slowly using just one bottle the first month. Three or four bottles a month would be a good high therapeutic amount.
- eTag: Several cancer clinics are successfully using the eTag to help fight cancer. Protects you from EMFs and energizes your body for better healing.

You don't have to use everything in high therapeutic amounts, but the worse your cancer is, the more you may want to use.

Readers can recognize the promoters of these are preying on the fears and hopes of patients. It is hoped that sympathetic and sensitive discussions can dissuade patients from investing a lot of hope, money, and time into these.

Traditional Herbal Therapy

The majority of herbal therapies for thyroid disorders come from Chinese sources. Most are used for goiter, thyrotoxicosis and some for hypothyroidism. Figure 1.8 shows the ingredients a patient was advised to ingest for the treatment of thyrotoxicosis. The components were to be boiled and ingested like tea. The concoction did not work. Some plant extracts are purported to have anti-tumor effects but the literature is noted for its brevity (22, 23). Some plants have been identified to have antiproliferative effect on medullary cancer cells in vitro (24). Acupuncture should be included under this heading. Acupuncture applied by experts to the right patient can be used for anesthesia (25). Acupuncture is disappointing for treatment of thyroid nodules and has no role in managing proven thyroid cancer. (26) Search of the literature did not identify an article discussing the role of acupuncture and thyroid cancer. Alternative and traditional therapies are not included further in the text.

Figure 1.8. Picture shows the ingredients for traditional medicine used to treat thyrotoxicosis.

Summary and Key Facts

The incidence of thyroid cancer is increasing in the United States. Three out of four patients are women and the average age is 30 years to 45 years. Although the treatments are established and adhered to vigorously by some authorities, there is a remarkable lack of controlled trials.

- In 2004 there are 22,500 new cases of thyroid cancer in the United States.
- Approximately 16,900 of these are in women
- There are ethnic differences with a low incidence in African Americans and high in people from the Pacific Rim in particular the Philippines.
- There is equality of genders in prepubertal patients with thyroid cancer.
- Interpretation of tests and definitions of sensitivity, specificity, positive, and negative likelihood ratios are presented.
- Methods of obtaining information through web sites are presented
- There is an increasing interest of patients to become educated about their illnesses and for them to be active and have input in discussion about management decisions.

References

1. Miller B, Kolonel LN, Bernstein L, et al. Racial/ethnic patterns of cancer in the United States 1988–1992. *Cancer Institute NIH Pub* 1996;No 96–4104.(Bethesda, MD.).
2. Horn-Ross P, Morris JS, Lee M, et al. Iodine and thyroid cancer risk among women in a multiethnic population. *Cancer Epidemiol Biomarkers Prev*. 2001;10:979–85.

3. Mallick UK, Charalambous H. Current issues in the management of differentiated thyroid cancer. *Nucl Med Commun*. 2004;25(9):873–81.
4. Kendall-Taylor P. Managing differentiated thyroid cancer. *BMJ*. 2002;324(7344):988–9.
5. Orwell G. 1984. New York: Plume, Hardcourt Brace; 1949:276.
6. Garcia-Berthou E, Alcaraz C. Incongruence between test statistics and P values in medical papers. *BMC Med Res Methodol*. 2004;4(1):13.
7. Altman DG, Bland JM. Diagnostic tests. 1: sensitivity and specificity. *BMJ*. 1994;308(6943):1552.
8. Deeks JJ, Altman DG. Diagnostic tests. 4: likelihood ratios. *BMJ*. 2004;329(7458):168–9.
9. Sackett D, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM*. New York: Churchill Livingstone; 2007:2–20.
10. Cady B. Papillary carcinoma of the thyroid gland: treatment based on risk group definition. *Surg Oncol Clin N Am*. 1998;7(4):633–44.
11. Cady B. Presidential address: beyond risk groups – a new look at differentiated thyroid cancer. *Surgery*. 1998; 124(6):947–57.
12. Bal CS, Kumar A, Pant GS. Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. *J Clin Endocrinol Metab*. 2004;89(4):1666–73.
13. Koc M, Ersoz HO, Akpinar I, Gogas-Yavuz D, Deyneli O, Akalin S. Effect of low- and high-dose levo-thyroxine on thyroid nodule volume: a crossover placebo-controlled trial. *Clin Endocrinol (Oxf)*. 2002;57:621–8.
14. Bennedbaek FN, Nielsen LK, Hegedus L. Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. *J Clin Endocrinol Metab*. 1998;83(3):830–5.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557–60.
16. Saha S, Arbelaez JJ, Cooper LA. Patient-physician relationships and racial disparities in the quality of health care. *Am J Public Health*. 2003;93(10):1713–9.
17. Stock Keister MC, Green LA, Kahn NB, Phillips RL, McCann J, Fryer GE. What people want from their family physician. *Am Fam Physician*. 2004;69(10):2310.
18. Hojat M, Gonnella JS, Nasca TJ, Mangione S, Vergare M, Magee M. Physician empathy: definition, components, measurement, and relationship to gender and specialty. *Am J Psychiatry*. 2002;159(9):1563–9.
19. Wagner PJ, Lentz L, Heslop SD. Teaching communication skills: a skills-based approach. *Acad Med*. 2002; 77(11):1164.
20. Shapiro SE, Izumi S, Tanner CA, et al. Telephone advice nursing services in a U.S. health maintenance organization. *J Telemed Telecare*. 2004;10(1):50–4.
21. Moriarty H, McLeod D, Dowell A. Mystery shopping in health service evaluation. *Br J Gen Pract*. 2003; 53(497):942–6.
22. Jiang TL, Yan SC, Wang SF, et al. Effect of "liuwei dihuang decoction" on prevention and treatment of tumor. *J Tradit Chin Med*. 1984;4(1):59–68.
23. Jiang TL, Yan SC, Zhao LF. Preventing effect of "liuwei dihuang decoction" on esophageal carcinoma. *Gan To Kagaku Ryoho*. 1989;16(4 Pt 2–2):1511–8.
24. Rinner B, Siegl V, Purstner P, et al. Activity of novel plant extracts against medullary thyroid carcinoma cells. *Anticancer Res*. 2004;24(2A):495–500.
25. Kho HG, van Egmond J, Zhuang CF, Lin GF, Zhang GL. Acupuncture anaesthesia. Observations on its use for removal of thyroid adenomata and influence on recovery and morbidity in a Chinese hospital. *Anaesthesia*. 1990;45(6):480–5.
26. Guo XZ, Li CJ, Gao BH, Ye MR, Zhao RW. Acupuncture treatment of benign thyroid nodules. Clinical observation of 65 cases. *J Tradit Chin Med*. 1984;4(4):261–4.

Appendix 1.1.

International Codes for Thyroid Diseases. ICD-9-CM Coding System.

The International Classification of Diseases is a system developed collaboratively between the World Health Organization (WHO) and ten international centers. The codes allow comparability of collection, classification, processing and presentation of health statistics.

ICD 9 code	Diagnosis
140–239	Neoplasms
193	Malignant neoplasm of the thyroid: Thyroid cancer
240.0	Simple goiter
240.9	Goiter unspecified
241.0	Non toxic uninodular goiter
241.1	Non toxic multinodular goiter
241.9	Unspecified nodular goiter
242.0	Graves' disease
–	Graves' disease with crisis
242.0	Ophthalmopathy/dermopathy
242.1	Toxic thyroid nodule
242.2	Toxic multinodular goiter
242.3	Toxic nodular goiter
242.4	Thyrotoxicosis ectopic
242.8	Thyrotoxicosis, other origin
243	Congenital hypothyroidism
244.0	Post surgical hypothyroidism
244.1	Other post ablation hypothyroidism
244.2	Iodine hypothyroidism
244.3	Other iatrogenic hypothyroidism
244.8	Specific acquired hypothyroidism
244.9	Unspecified hypothyroidism
245.0	Acute thyroiditis
245.1	Subacute thyroiditis
245.2	Chronic lymphocytic thyroiditis
245.3	Chronic fibrous thyroiditis
245.4	Iatrogenic thyroiditis
245.8	Chronic thyroiditis unspecified
246.2	Cyst of the thyroid
246.3	Hemorrhage into the thyroid

Appendix 1.2.

Articles Related to Thyroid Gland by Author

1. Kalinyak JE, McDougall IR. Whole-body scanning with radionuclides of iodine, and the controversy of "thyroid stunning." *Nucl Med Commun*. 2004;25(9):883–9.
2. Cohen JB, Balzer B, Wapnir I, McDougall IR. Elephantiasic pretibial myxedema. *Thyroid*. 2004;14(3):237–8.
3. Cohen JB, Kalinyak JE, McDougall IR. Clinical implications of the differences between diagnostic 123I and post-therapy 131I scans. *Nucl Med Commun*. 2004; 25(2):129–34.
4. Kalinyak JE, McDougall IR. How should the dose of iodine-131 be determined in the treatment of Graves' hyperthyroidism? *J Clin Endocrinol Metab*. 2003; 88(3):975–7.
5. Cohen JB, Troxell M, Kong CS, McDougall IR. Ectopic intrathyroidal thymoma: a case report and review. *Thyroid*. 2003;13(3):305–8.
6. Cohen JB, Kalinyak JE, McDougall IR. Modern management of differentiated thyroid cancer. *Cancer Biother Radiopharm*. 2003;18(5):689–705.
7. Chan BK, Desser TS, McDougall IR, Weigel RJ, Jeffrey RB Jr. Common and uncommon sonographic features of papillary thyroid carcinoma. *J Ultrasound Med*. 2003; 22(10):1083–90.
8. Carlisle MR, Lu C, McDougall IR. The interpretation of 131I scans in the evaluation of thyroid cancer, with an emphasis on false positive findings. *Nucl Med Commun*. 2003;24(6):715–35.
9. Karwowski JK, Nowels KW, McDougall IR, Weigel RJ. Needle track seeding of papillary thyroid carcinoma from fine needle aspiration biopsy. A case report. *Acta Cytol*. 2002;46(3):591–5.
10. Karwowski JK, Jeffrey RB, McDougall IR, Weigel RJ. Intraoperative ultrasonography improves identification of recurrent thyroid cancer. *Surgery*. 2002;132(6):924–8; discussion 8–9.
11. Verneris M, McDougall IR, Becton D, Link MP. Thyroid carcinoma after successful treatment of osteosarcoma: a report of three patients. *J Pediatr Hematol Oncol*. 2001; 23(5):312–15.
12. McDougall IR, Weigel RJ. Recombinant human thyrotropin in the management of thyroid cancer. *Curr Opin Oncol*. 2001;13(1):39–43.
13. McDougall IR. Management of thyroglobulin positive/whole-body scan negative: is Tg positive/131I therapy useful? *J Endocrinol Invest*. 2001;24(3):194–8.
14. McDougall IR, Donaldson SS. Radiotherapy for Graves' ophthalmopathy: current treatment recommendations. *Front Radiat Ther Oncol*. 2001;35:57–64.
15. McDougall IR, Davidson J, Segall GM. Positron emission tomography of the thyroid, with an emphasis on thyroid cancer. *Nucl Med Commun*. 2001;22(5):485–92.
16. Marquez SD, Lum BL, McDougall IR, et al. Long-term results of irradiation for patients with progressive Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys*. 2001;51(3):766–74.
17. Horn-Ross PL, Morris JS, Lee M, et al. Iodine and thyroid cancer risk among women in a multiethnic population: the Bay Area Thyroid Cancer Study. *Cancer Epidemiol Biomarkers Prev*. 2001;10(9):979–85.
18. Desai D, Jeffrey RB, McDougall IR, Weigel RJ. Intraoperative ultrasonography for localization of recurrent thyroid cancer. *Surgery*. 2001;129(4):498–500.
19. McDougall IR. Systemic radiation therapy with unsealed radionuclides. *Semin Radiat Oncol*. 2000;10(2):94–102.
20. Durski JM, Weigel RJ, McDougall IR. Recombinant human thyrotropin (rhTSH) in the management of differentiated thyroid cancer. *Nucl Med Commun*. 2000;21(6):521–8.
21. Davidson J, McDougall IR. How frequently is the thymus seen on whole-body iodine-131 diagnostic and post-treatment scans? *Eur J Nucl Med*. 2000;27(4): 425–30.
22. Carlisle MR, McDougall IR. Dramatic parotid uptake of I-131 on a diagnostic whole-body scan. *Clin Nucl Med*. 2000;25(11):895–7.
23. McDougall IR. Cancer deaths after 131I therapy for thyrotoxicosis. *Nucl Med Commun*. 1999;20(5):407–9.
24. McDougall IR. Recombinant human thyrotropin (rhTSH) in the management of differentiated thyroid carcinoma. *Nucl Med Commun*. 1999;20(10):871–3.
25. Jadvar H, McDougall IR, Segall GM. Evaluation of suspected recurrent papillary thyroid carcinoma with [18F]fluorodeoxyglucose positron emission tomography. *Nucl Med Commun*. 1998;19(6):547–54.
26. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. *Thyroid*. 1998;8(4):283–9.
27. Carlisle M, Cortes A, McDougall IR. Uptake of I-131 in the biliary tract: a potential cause of a false-positive result of scintiscan. *Clin Nucl Med*. 1998;23(8):524–7.
28. Van Wyngaarden K, McDougall IR. Is serum thyroglobulin a useful marker for thyroid cancer in patients who have not had ablation of residual thyroid tissue? *Thyroid*. 1997;7(3):343–6.
29. McDougall IR. 74 MBq radioiodine 131I does not prevent uptake of therapeutic doses of 131I (i.e. it does not cause stunning) in differentiated thyroid cancer. *Nucl Med Commun*. 1997;18(6):505–12.
30. McDougall IR. 131I treatment of 131I negative whole body scan, and positive thyroglobulin in differentiated thyroid carcinoma: what is being treated? *Thyroid*. 1997;7(4):669–72.
31. Van Wyngaarden M, McDougall IR. What is the role of 1100 MBq (<30 mCi) radioiodine 131I in the treatment of patients with differentiated thyroid cancer? *Nucl Med Commun*. 1996;17(3):199–207.
32. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. *Arch Intern Med*. 1996;156(19):2165–72.
33. Becker D, Charles ND, Dworkin H, et al. Procedure guideline for thyroid scintigraphy: 1.0. Society of Nuclear Medicine. *J Nucl Med*. 1996;37(7):1264–6.
34. Becker D, Charkes ND, Dworkin H, et al. Procedure guideline for thyroid uptake measurement: 1.0. Society of Nuclear Medicine. *J Nucl Med*. 1996;37(7): 1266–8.
35. Becker D, Charkes ND, Dworkin H, et al. Procedure guideline for extended scintigraphy for differentiated thyroid cancer: 1.0. Society of Nuclear Medicine. *J Nucl Med*. 1996;37(7):1269–71.

36. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. *JAMA*. 1995;273(10):808–12.
37. McDougall IR, Maclin N. Hypothyroid women need more thyroxine when pregnant. J Fam Pract 1995; 41(3):238–40.
38. McDougall IR. Whole-body scintigraphy with radioiodine-131. A comprehensive list of false-positives with some examples. *Clin Nucl Med*. 1995;20(10):869–75.
39. Kwok CG, McDougall IR. Familial differentiated carcinoma of the thyroid: report of five pairs of siblings. *Thyroid*. 1995;5(5):395–7.
40. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1165–70.
41. Mello AM, Isaacs R, Petersen J, Kronenberger S, McDougall IR. Management of thyroid papillary carcinoma with radioiodine in a patient with end stage renal disease on hemodialysis. *Clin Nucl Med*. 1994;19(9):776–81.
42. Hays MT, McDougall IR. Circulating 131I thyroxine and thyroid cancer. Thyroid 1994;4(2):195–8.
43. Choe W, McDougall IR. Thyroid cancer in pregnant women: diagnostic and therapeutic management. *Thyroid*. 1994;4(4):433–5.
44. McDougall IR. Does radioiodine cause the ophthalmopathy of Graves' disease? *Nucl Med Commun*. 1993;14(2):79–81.
45. Choe W, McDougall IR. Ablation of thyroid function with radioactive iodine after recurrent episodes of silent thyroiditis. *Thyroid*. 1993;3(4):311–13.
46. Mello AM, McDougall IR. The role of functional imaging in neoplasms of the thyroid. *Crit Rev Clin Lab Sci*. 1992;29(2):117–39.
47. McDougall IR. Radionuclide therapy for thyroid disease. *West J Med*. 1992;157(1):62.
48. Tomlinson C, Nowles KW, McDougall IR. Papillary cancer in a patient treated with radioiodine for Graves' hyperthyroidism. Case report and a review of the risk. *Clin Nucl Med*. 1991;16(10):729–31.
49. McDougall IR. Graves' disease. Current concepts. *Med Clin North Am*. 1991;75(1):79–95.
50. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med*. 1991;325(9):599–605.
51. Petersen MM, McDougall IR. Evaluation and medical management of thyroid cancer. *Cancer Treat Res*. 1990;52:151–70.
52. Petersen IA, Kriss JP, McDougall IR, Donaldson SS. Prognostic factors in the radiotherapy of Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys*. 1990; 19(2):259–64.
53. McDougall IR. The importance of obtaining thyroid uptake measurement in patients with hyperthyroidism. *Nucl Med Commun*. 1990;11(2):73–6.
54. Klonecke A, Petersen MM, McDougall IR. Thyrotoxicosis with low thyroidal uptake of radioiodine. *Semin Nucl Med*. 1990;20(4):364–6.
55. Petersen M, Keeling CA, McDougall IR. Hyperthyroidism with low radioiodine uptake after head and neck irradiation for Hodgkin's disease. *J Nucl Med*. 1989;30(2):255–7.
56. McDougall IR, Krasne D, Hanbery JW, Collins JA. Metastatic malignant struma ovarii presenting as paraparesis from a spinal metastasis. *J Nucl Med*. 1989; 30(3):407–11.
57. Donaldson SS, Link MP, McDougall IR, Parker BR, Shochat SJ. Clinical investigations of children with Hodgkin's disease at Stanford University Medical Center. A preliminary overview using low-dose irradiation and alternating ABVD/MOPP chemotherapy. *Cancer Treat Res*. 1989;41:307–15.
58. Nagai GR, Pitts WC, Basso L, Cisco JA, McDougall IR. Scintigraphic hot nodules and thyroid carcinoma. *Clin Nucl Med*. 1987;12(2):123–7.
59. Macoviak JA, McDougall IR, Bayer MF, Brown M, Tazelaar H, Stinson EB. Significance of thyroid dysfunction in human cardiac allograft procurement. *Transplantation*. 1987;43(6):824–6.
60. Bayer MF, Macoviak JA, McDougall IR. Diagnostic performance of sensitive measurements of serum thyrotropin during severe nonthyroidal illness: their role in the diagnosis of hyperthyroidism. *Clin Chem*. 1987; 33(12):2178–84.
61. Wilson DM, Hopper AO, McDougall IR, et al. Serum free thyroxine values in term, premature, and sick infants. *J Pediatr*. 1982;101(1):113–17.
62. Spratt DI, Pont A, Miller MB, McDougall IR, Bayer MF, McLaughlin WT. Hyperthyroxinemia in patients with acute psychiatric disorders. *Am J Med*. 1982;73(1): 41–8.
63. McDougall IR, Bayer MF, Nierenberg D, Lewis SJ. Disparate effects of heparin on free thyroxine as measured by two radioimmunoassays: concise communication. *J Nucl Med*. 1982;23(6):507–10.
64. Constine LS, McDougall IR. Radiation therapy for Hodgkin's disease followed by hypothyroidism and then Graves' hyperthyroidism. *Clin Nucl Med*. 1982; 7(2):69–70.
65. Bayer MF, McDougall IR. Free thyroxine by solid phase radioimmunoassay: improvement in the laboratory diagnosis of thyroid status in severely ill patients. *Clin Chim Acta*. 1982;118(2–3):209–18.
66. McDougall IR. Treatment of hyper- and hypothyroidism. *J Clin Pharmacol*. 1981;21(8–9):365–84.
67. McDougall IR, Nelsen TS, Kempson RL. Papillary carcinoma of the thyroid seven years after I-131 therapy for Graves' disease. *Clin Nucl Med*. 1981;6(8):368–71.
68. McDougall IR. The thyroid gland and radiation for Hodgkin's disease. *Ann Intern Med*. 1980;92(4):572.
69. McDougall IR, Coleman CN, Burke JS, Saunders W, Kaplan HS. Thyroid carcinoma after high-dose external radiotherapy for Hodgkin's disease: report of three cases. *Cancer*. 1980;45(8):2056–60.
70. McDougall IR, Bayer MF. Follow-up of patients with differentiated thyroid cancer using serum thyroglobulin measured by an immunoradiometric assay. Comparison with I-131 total body scans. *J Nucl Med*. 1980;21(8): 741–4.
71. Donaldson SS, McDougall IR, Egbert PR, Enzmann DR, Kriss JP. Treatment of orbital pseudotumor (idiopathic orbital inflammation) by radiation therapy. *Int J Radiat Oncol Biol Phys*. 1980;6(1):79–86.
72. Bayer MF, McDougall IR. Radioimmunoassay of free thyroxine in serum: comparison with clinical findings and results of conventional thyroid-function tests. *Clin Chem*. 1980;26(8):1186–92.
73. Sung LC, McDougall IR. Graves' hyperthyroidism. Spontaneous occurrence after autoimmune hypothyroidism

with persistent infiltrative ophthalmopathy. *Arch Intern Med*. 1978;138(6):1009–10.
74. McDougall IR. Treatment with radioisotopes. *Internist (Berl)*. 1978;19(7):431–6.
75. Forrester JV, Sutherland GR, McDougall IR. Dysthyroid ophthalmopathy: orbital evaluation with B-scan ultrasonography. *J Clin Endocrinol Metab*. 1977;45(2):221–4.
76. McDougall IR, Greig WR. 125I therapy in Graves' disease. Long-term results in 355 patients. *Ann Intern Med*. 1976;85(6):720–3.
77. McDougall IR, Greig WR. Combined carbimazole-131-I treatment for thyrotoxicosis. *Scott Med J*. 1972; 17(2):57–61.
78. Gray HW, Hooper LA, Greig WR, McDougall IR. A twenty minute perchlorate discharge test. *J Clin Endocrinol Metab*. 1972;34(3):594–7.
79. McDougall IR, Kennedy JS, Thomson JA. Thyroid carcinoma following iodine-131 therapy. Report of a case and review of the literature. *J Clin Endocrinol Metab*. 1971;33(2):287–92.
80. McDougall IR, Greig WR, Gillespie FC. Radioactive iodine (125I) therapy for thyrotoxicosis. *N Engl J Med*. 1971;285(20):1099–104.
81. McDougall IR, Greig WR. Pathogenesis and treatment of thyrotoxicosis. *Scott Med J*. 1971;16(12):519–31.

Book Chapters and Nonpeer-Reviewed Articles

1. Carlisle MR, McDougall IR. Familial differentiated carcinoma of the thyroid. In: *Thyroid Cancer, 2nd ed*. Biersack HJ, Grunwald F, eds. New York: Springer; 2005:57–70.
2. McDougall IR. 2005 positron emission tomography in thyroid and adrenal disease. Positron emission tomography. In: *Principles and Practice*. 2nd ed. Valk P, Bailey DA, Townsend DW, Maisey MN, eds. London: Springer-Verlag; 2005.
3. McDougall IR. 2005 In-vivo radionuclide tests and imaging. *TheTthyroid – A Fundamental and Clinical Text*. 9th ed. Braverman LE, Utiger RD, eds. Philadelphia: Lippincott-Raven; 2005:309–328.
4. McDonald J, Hailer D, McDougall IR, Weigel RJ, 2004 Endocrine system. In: *Clinical Oncology*. Abeloff MD, Armitage JO, Lichter AS, Neiderhuber JE, editors. New York: Churchill Livingstone 2004;1360–97.
5. Cohen J, Franc B, McDougall IR. Thyroid imaging. *Encyclopedia of Endocrinology and Endocrine Diseases*. Luciano Martini, ed. Academic; 2004;4:496–504.
6. McDougall IR. Positron emission tomography in thyroid and adrenal disease. In: *Positron Emission Tomography Principles and Practice*. DA Bailey, DW Townsend, PE Valk, MN Maisey, eds. London: Springer-Verlag; 2003;669–78.
7. McDougall IR. Thyroid imaging. *Oxford Textbook of Endocrinology*. Shalet SM, Wass JAH, eds. Oxford; 2002;3.1.6:324–33.
8. McDougall IR, Donaldson SS. Radiotherapy for Graves' ophthalmopathy: current treatment recommendations. *Frontiers Radiat Ther Oncol*. 2001;35;57–64.
9. Carlisle MR, McDougall IR. Familial differentiated carcinoma of the thyroid. In: *Thyroid Cancer in the Year 2000*. Biersack HJ, Grunwald F, eds. New York: Springer; 2000.
10. McDougall IR. Systemic radiation therapy with unsealed radionuclides. *Seminars Radiation Oncology*. Tepper J, Knox SJ, eds. 2000;10:94–102.
11 McDougall IR. Recombinant human thyrotropin (rhTSH) in the management of differentiated thyroid carcinoma. *Nucl Med Commun*. 1999;20:871–3.
12. McDougall IR, Cancer deaths after I-131 therapy for thyrotoxicosis. *Nucl Med Commun*.1999;20;407–9.
13. McDougall IR, Cavalieri RR. In-vivo radionuclide tests and imaging. *The Thyroid – A Fundamental and Clinical Text*. 8th ed. Braverman LE, Utiger RD, eds. Philadelphia: Lippincott-Raven; 2000;355–75.
14. McDonald J, Hailer D, McDougall IR, Weigel RJ. Endocrine system. In: *Clinical Oncology*. Abeloff MD, Armitage JO, Lichter AS, Neiderhuber JE, eds. New York: Churchill Livingstone; 2000;1360–97.
15. Horn-Ross PL, Whittemore AS, West DW, McDougall IR, Morris JS, Spate VL. Rationale for a study of iodine, selenium, and thyroid cancer. *Sixth International Thyroid Symposium*. Graz, Austria; 1996.
16. Cavalieri RR, McDougall IR. In-vivo isotopic tests and imaging. *Werner and Ingbar's the Thyroid – A Fundamental and Clinical Text*. 7th ed. Braverman LE, Utiger RD, eds. Philadelphia: Lippincott; 1996; 352–76.
17. Blum M, Braverman LE, Holiday RA, et al. The thyroid in principles of nuclear medicine. Wagner HN Jr., Sabo Z, Buchannan JW, eds. Philadelphia: Saunders 1996;595–621
18. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. *Int J Radiat Oncol Biol Phys*. 1995;31:1165–70.
19. McDougall IR, Thyroid: isotopic imaging. *Principles of Nuclear Medicine*. 2nd ed. Wagner H, ed. Philadelphia: Lippincott; 1994.
20. McDougall IR. Does radioiodine cause the ophthalmopathy of Graves' disease? *Nucl Med Commun*. 1993; 14:79–81.
21. Cavalieri R, McDougall IR. Thyroid scintigraphy. *Werner and Ingbar's the thyroid*. 6th ed. Philadelphia: Lippincott; 1993;445–62.
22. McDougall IR. Radionuclide therapy for thyroid disease. *West J Med*. 1992:62.
23. Mello AM, McDougall IR. The role of functional imaging in neoplasms of the thyroid. *Crit Rev Clin Lab Sci*. 1992;29(2):177–39.
24. McDougall IR. Graves' disease: Current concepts. *Med Clin North Am*. 1991;75:79–95.
25. Petersen M, McDougall IR. Evaluation and medical management of thyroid cancer. *Carcinomas in the Head and Neck*. Jacobs C, ed. Boston: Kluwer; 1990;151–70.
26. McDougall IR. Editorial. The importance of obtaining thyroid uptake measurement in patients with hyperthyroidism. *Nucl Med Commun*. 1990;11:73–6.
27. Klonecke A, Petersen MM, McDougall IR. Thyrotoxicosis with low thyroidal uptake of radioiodine. *Semin Nucl Med*. 1990;20:364–66.
28. Petersen M, Keeling C, McDougall IR. To the Editor. Hyperthyroidism after head and neck irradiation. *J Nucl Med*. 1989;30:2063.
29. McDougall IR. Editorial. Which therapy for Graves' hyperthyroidism in children? *Nucl Med Commun*. 1989; 10:855–57.

30. Donaldson SS, McDougall IR, Kriss JP. Orbital tumors, section II, Graves' disease. In: *Radiotherapy of Interorbital and Interocular Tumors*. Alberti W, Sagerman RH, eds. Springer Verlag; 1989.
31. Donaldson SS, Link MP, McDougall IR, Parker BR, Shochat SJ. Clinical investigations of children with Hodgkin's disease at Stanford University Medical Center-a preliminary overview using low dose irradiation and alternating ABVD/MOPP chemotherapy. In: *Hodgkin's Disease in Children*. Kamps WA, ed. Boston: Kluwer; 1989;25:307–15.
32. Bayer MF, McDougall IR, Kriss JP. Retrospective study of serum thyroglobulin measurements performed in patients with differentiated thyroid carcinoma at the Stanford University Thyroid Clinic between 1979 and 1983. In: *International Workshop on Thyroglobulin and Thyroglobulin Antibodies in the Follow-up of Thyroid Cancer and Endemic Goiter*. Huefner M, Reimers C, eds. Thieme, Verlag, Stuttgart; 1987;104–11.
33. McDougall IR. *Maternal-fetal Thyroid Hormone Metabolism and Hyperthyroidism Endocrine Disorders in Pregnancy*. Brody SA, Ueland K, eds. Appleton 1987;151–64.
34. Kriss JP, McDougall IR, Donaldson SS, Kraemer HC. Non-thyroidal complications of Graves' disease perspective on pathogenesis and treatment. *Thyroid Autoimmunity*. Pinchera A, Ingbar SH, McKenzie JM, Fenzi GF, eds. New York: Plenum 1987;293–7.
35. Bayer MF, Kriss JP, McDougall IR, Clinical experience with a sensitive immunoradiometric assay for serum thyrotropin: diagnostic and therapeutic implications for hyperthyroid and thyroid cancer patients II. In: *Proceedings of 9th International Thyroid Congress*. Meideiros-Neto GA, Goitah E, eds. New York: Plenum; 1986.
36. Kriss JP, McDougall IR, Donaldson SS. Graves' ophthalmopathy. In: *Current Therapy in Endocrinology 1983–1984*. Krieger DT, Bardin CW, eds. Philadelphia: Mosby; 1984;104–9.
37. Pont A, Spratt DI, Miller MD, McDougall IR, Bayer MF, McLaughlin W. Thyroid function in patients with acute psychiatric illness: the value of free T4 radioimmunoassay. In: *Free hormones in blood, proceeding of the advanced course on free hormone assays and neuropeptides*. Albertini A, Ekins RP, eds. Elsevier; 1982;285–94.
38. Bayer MF, McDougall IR. The value of free thyroxine in hospitalized patients using a two-step antibody coated tube, radioimmunossary. In: *Free Hormones in Blood, Proceedings of the Advanced Course on Free Hormone Assays and Neuropeptides*. Albertini A, Ekins RP, eds. Elsevier; 1982;178–84.
39. McDougall IR, Bayer MF. Limitation of free thyroxine measurements. In: *Free Hormones in Blood, Proceedings of the Advanced Course on Free Hormone Assays and Neuropeptides*. Albertini A, Ekins RP, eds. Elsevier; 1982; 171–8.
40. McDougall IR, Bayer MF, Nierenberg D, Lewis SJ. Disparate effects of heparin on free thyroxine measured by two different radioimmunoassays. *Third World Congress of Nuclear Medicine and Biology*. Raynaud C, ed. Pergamon; 1982;3379–82.
41. McDougall IR. Effect on heparin on free T4 test results. *Perspectives Thyroid*. 1982;5.
42. Kriss JP, McDougall IR, Donaldson SS. Graves' ophthalmopathy: an hypothesis of its pathogenesis and results of treatment by supervoltage orbital radiotherapy. *Thyroid Univ Case Rep*. 1981 Nov;3:3.
43. McDougall IR. Treatment of hyper and hypothyroidism. *J Clin Pharmacol*. 1981;21:365–84.
44. McDougall IR. To the Editor. Radiation-related thyroid dysfunction: implications for the treatment of Hodgkin's disease. *Annals Intern Med*. 1980;92:572.
45. Fries JF, Ehrlich GE, eds. Thyroid cancer. In: *Prognosis*. Charles Press; 1980;140–3.
46. McDougall IR. The thyroid. *International Encyclopedia Pharmacology and Therapeutics*. Oxford: Pergamon; 1978;309–26.
47. McDougall IR, Kriss JP. Management of the eye manifestations of thyroid disease.
48. McDougall IR. Which treatment for hyperthyroidism? Invited commentary. *World J Surg*. 1978;2:185–287.
49. McDougall IR. Treatment with radiopharmaceutical drugs. *Ration Drug Ther*. 1978;12:1–7.
50. McDougall IR, Kriss JP. Management of the eye manifestations of thyroid disease. *Pharmacol Ther (Part C)*. 1977;2:95–111.
51. McDougall IR. Hypothyroidism after 125I therapy. *Annals Intern Med*. 1976;86:823–4.
52. McDougall IR, Kriss JP. Which radioisotope for diagnosis of thyroid disorders? *Clin Nucl Med*. 1976;1: 217–18.
53. Hay I, McDougall IR. Thyrotoxic periodic paralysis in Great Britain. *BMJ*. 1975;4:761.
54. McDougall IR, Kriss JP. New thoughts about the cause and treatment of the severe ocular manifestations of Graves' disease. *Scott Med J*. 1974;19:165–69.
55. McDougall IR. Thyroid cancer after iodine-131 therapy. *JAMA*. 1974;227:438.
56. McDougall IR, Kriss JP. Treatment of endocrine exophthalmos. *BMJ*. 1973;2:711.
57. Greig WR, McDougall IR, Gray HR, The diagnosis of thyrotoxicosis. *Postgrad Med J*. 1973;49:469–76.
58. McDougall IR, Greig WR, Gillespie FC. Correspondence. Persistence of 125I in thyroid. *N Engl J Med*. 1972; 286:161.

Chapter 2

Thyroid Anatomy and Physiology

This chapter on thyroid anatomy and physiology is included because knowledge and understanding of the information helps with the clinical evaluation and management of the patient. It also aids in the interpretation of laboratory results, cytopathology and histopathology, the principles of surgery, and the pathophysiological changes from excess and insufficient thyroid hormones. Most readers have received basic education on the anatomy and physiology of the thyroid. The gross anatomy has not changed with time, but there are considerable advances in knowledge of molecular events. For some, including patients, there is no such grounding. The goal is to make the information clinically relevant. The chapter is not encyclopedic and references have been selected to provide reviews that include extensive bibliographies.

The thyroid is an endocrine gland that produces and secretes the thyroid hormones thyroxine and triiodothyronine. Thyroid hormones control the development of the embryo and the metabolism at all times of life. Prolonged deprivation of thyroid hormone results in slowing of the function of all systems and with time the patient becomes comatose (myxedema coma) and eventually dies. Excess thyroid hormone results in an increase in function of all systems, and this can also cause the life-threatening syndrome of thyroid crisis, which has a significant mortality.

Thyroid Anatomy: Gross Anatomy

The thyroid is a bilobed gland. The left and right lobes lie on each side of the trachea. The isthmus that joins the lobes is usually anterior to the second to fourth tracheal cartilages. The lobes extend superiorly and inferiorly from the isthmus and the shape is similar to a butterfly as shown in Figure 2.1A,B,C and Figure 2.2 in which the structures are labeled. The inferior margins of the lateral lobes in a normal gland are at the level of the sixth tracheal ring. In regions where there is adequate intake of iodine the thyroid weighs between 10 g and 20 g. Because human soft tissues are predominantly water, the gland has a volume of 10 ml to 20 ml. It is the largest endocrine gland. In an adult the dimensions of each lobe are approximately in length 5 cm, breadth 2 cm to 2.5 cm, and depth 1 cm to 1.5 cm. There is a fibrous capsule that sends septae into the gland dividing it into lobules. Branches of the arteries and veins run through the capsule with the connective tissue. The pretracheal fascia covers the gland and anterior to that are three pairs of infrahyoid strap muscles, the sternohyoids, sternothyroids and omohyoids. In front of the strap muscles the sternocleidomastoids muscles run at an angle from the mastoid superiorly and laterally to the manubrium and clavicle inferiorly and medially.

When palpating the thyroid, it is necessary to pull the sternocleidomastoid gently laterally in order to be able to feel the body and edges of the gland. There are different approaches to examination of the gland by palpation. Some prefer to sit in front of the seated patient and use the thumbs to identify anatomic landmarks, the edge of the gland, and any nodule or nodules. All authorities agree that looking at the gland with the patient seated can provide information about the size and shape of the gland, the presence of nodules and scars, and significantly enlarged lymph nodes. After inspection, most authorities, including myself, prefer to stand behind the patient and use the first and second fingers of both hands to palpate. I place my thumbs on the patient's spine at about the level of the thyroid and then position my first and second fingers gently on the trachea. The fingers are gently moved up and down to identify the isthmus, which is not covered by strap muscles. When that is felt, the examining fingers move to one lobe using the isthmus as a focal point to identify the medial border of the lobe, and the sternocleidomastoid is gently maneuvered to the side to allow the body of the lobe and its lateral margins to be felt. Then the opposite lobe is examined. When a nodule is palpated: Its size,

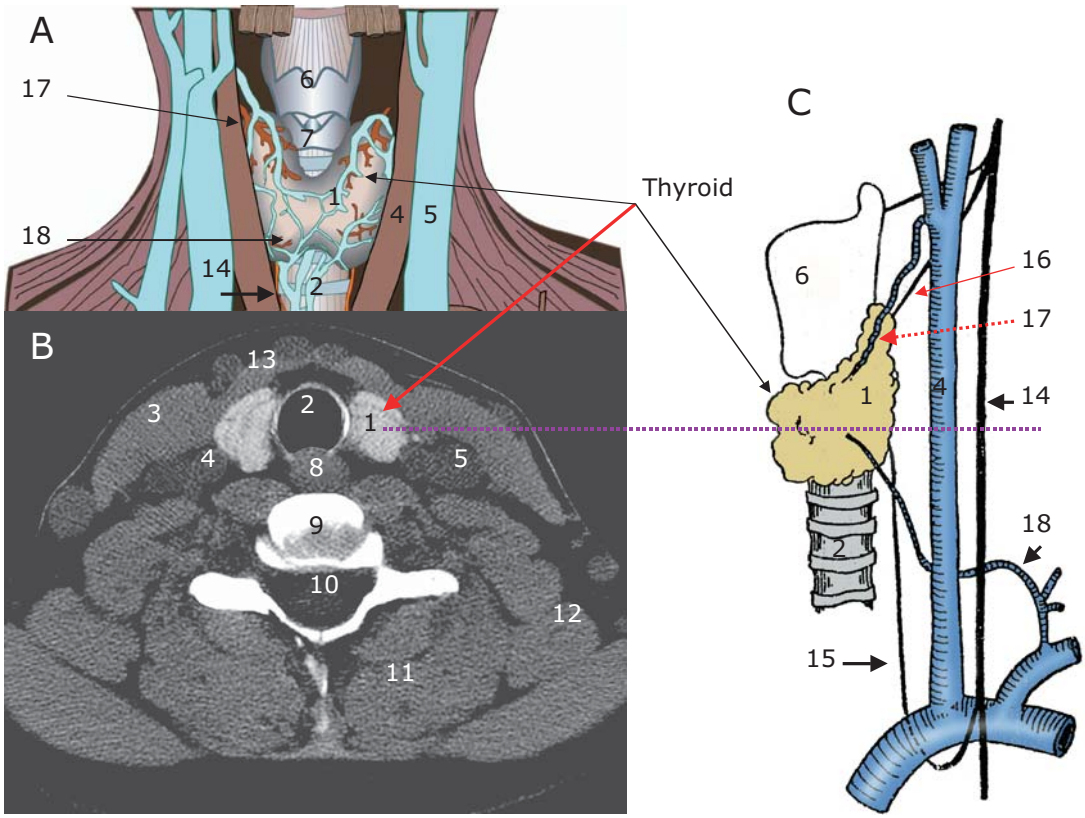

Figure 2.1. (A, B, C) Coronal, transaxial and sagittal images at the level of the thyroid. A and C are diagrams, and B is a computed tomogram. The anatomy is coded numerically. (1) is the thyroid gland, (2) the trachea, (3) the sternocleidomastoid muscles, (4) the common carotid artery, (5) the internal jugular vein, (6) the thyroid cartilage, (7) the hyoid cartilage, (8) the esophagus, (9) the body of a cervical vertebra, (10) the spinal canal and cord, (11) the erector spinae muscle, (12) the levator scapulae muscle, (13) the sternohyoid, sternothyroid muscles, (14) the vagus nerve, (15) the recurrent laryngeal nerve, (16) the external laryngeal nerve, (17) the superior thyroidal artery, and (18) the inferior thyroidal artery. In C the close proximity of the external laryngeal nerve and the superior thyroidal artery should be noted. Also of note is the close proximity of the recurrent laryngeal nerve to the inferior aspect of the thyroid.

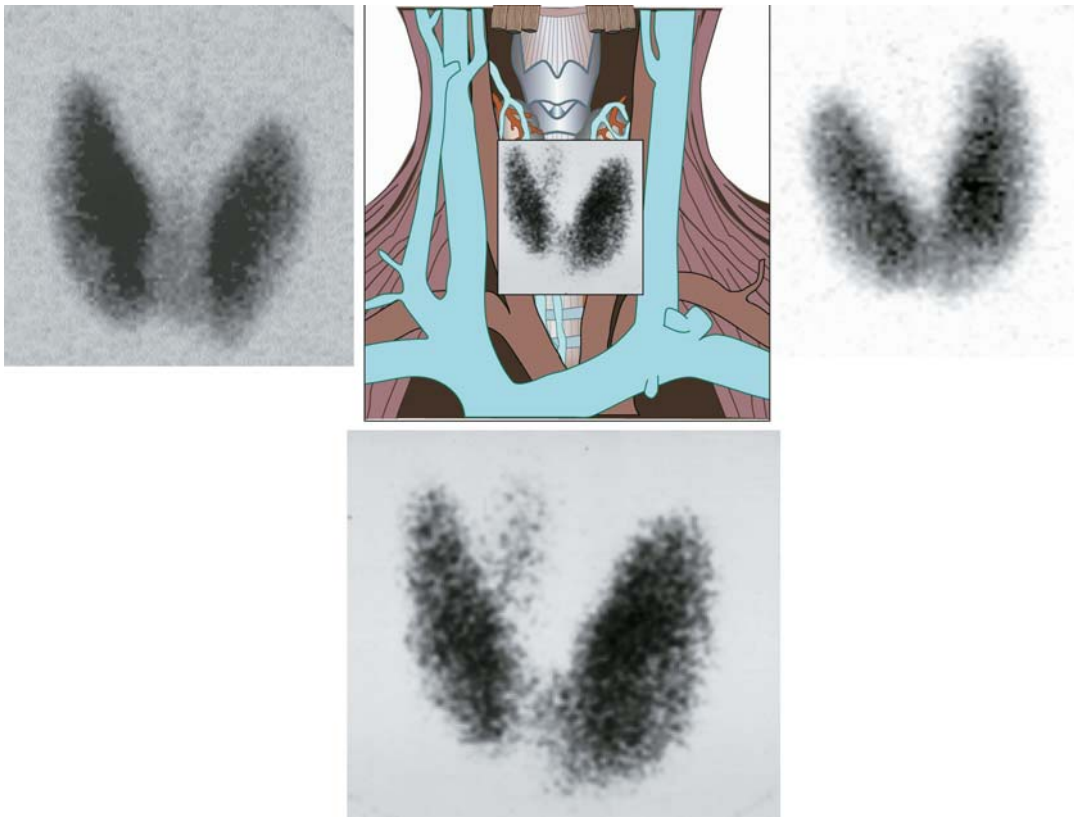

Figure 2.2. Figure shows the lobes and isthmus in three normal thyroid glands demonstrating variations in shape and the anatomic position in a coronal diagram of the neck.

consistency, movement, or fixation is documented. The thyroid moves when the patient swallows, so the examination is aided by having a glass of water available.

Then the cervical lymph nodes on each side should be examined. Although spread of cancer to the posterior cervical nodes is not common, they should be examined as part of a routine. Auscultation over an enlarged gland can identify the bruit usually associated with Graves' hyperthyroidism. A bruit over a large nodule, especially when it is pulsatile, should be a sign not to proceed to a biopsy without an ultrasound to identify the arterial flow.

In countries where the intake of dietary iodine is low, the thyroid tends to be larger. An enlarged thyroid is called a goiter. The term endemic goiter is used when 10% or more of the population have an enlarged thyroid. As the thyroid enlarges, it becomes visible and easier to feel on clinical examination. In addition when the gland enlarges, there is a tendency for nodules to form. In regions of iodine deficiency the thyroid gland in older people is almost always enlarged and nodular. This is called a multinodular goiter. In older patients as the thyroid enlarges, there is also a tendency for the inferior margin of the gland to move downwards until it enters the thoracic inlet. This movement is partly dictated by the pretracheal fascia that is denser anteriorly and superiorly, so an enlarging gland is guided inferiorly and posteriorly. Once the inferior border of the thyroid has entered the thoracic cavity the reduced pressure in the thorax caused by breathing, along with gravity, can cause the inferior migration to continue into the mediastinum. This results in a sub- or retro-sternal goiter.

Embryology

Embryologically, the thyroid forms from an invagination in the floor of the pharynx between the first and second pharyngeal pouches. That region ends up as a spot at the back of the tongue (1). At day 24 in utero the tissues migrate inferiorly to their final position in the neck, which is reached by about the eighth week in utero. Texts refer to the forming tissue as an anlage, which the dictionary defines as "the basis for later development". The thyroid is dragged by the forming heart. Three thyroid transcription factors, TTF-1, TTF-2, and PAX-8, are essential for normal development and migration of the thyroid (2). Mice that are homozygotes for a defect in the TTF-1 gene have no thyroid tissue and have severe defects of the hypothalamus, forebrain, and lungs. Similarly mice with homozygous defects in the Pax-8 gene have no thyroid (follicular) cells. In a proportion of TTF-2 knockout mice the thyroid is an ectopic position. This suggests that TTF-2 is required for migration of the forming thyroid. These three factors are also involved in the production of functional proteins by follicular cells that are essential for the formation of thyroid hormones. These include the sodium iodide symporter (NIS), thyroid peroxidase (TPO), and thyroglobulin (Tg), which are discussed individually below. The midline thyroid fuses with tissues derived from the fourth and fifth branchial clefts, which combine to form the lateral lobes. These bring neuroendocrine cells from the ultimobranchial body that forms parafollicular cells (also called C cells). C cells produce and secrete calcitonin.

Three functional stages in the development of the thyroid have been described, called precolloid, colloid, and follicular. These occur at 7 weeks to 12 weeks, 13 weeks to 14 weeks, and after 14 weeks. (3) Their appearances can be mirrored by adult pathologies that are labeled as embryonal and fetal lobulation. The thyroid can produce hormones by week 12 and some state as early as day 74.

The embryological origin of the thyroid can be seen as the foramen cecum, which is in the midline of the tongue, approximately at the junction of the anterior 2/3 and the posterior 1/3. The migratory route from the foramen cecum to the cervical position is called the thyroglossal tract. In early embryological formation this is a tube, the thyroglossal duct, but during embryologic development it usually becomes fibrotic, and after birth it is even difficult to identify at operation. Rarely the gland fails to migrate from its original site of development, resulting in a lingual thyroid, as shown in Figure 2.3. The condition presents with a mass at the base of the tongue that can cause dysphagia, dysphonia, and dyspnea (4, 5). In general a maldescended thyroid does not produce physiological quantities of thyroid hormones, and the patient is hypothyroid and has an elevated thyroid stimulating hormone (TSH). One of the reasons is because the lateral lobes have not fused with the median thyroid; therefore, the volume of cells is insufficient for adequate production of thyroid hormones. In most patients with an ectopic thyroid that is the only functioning tissue, but there are exceptions, including one report where the lingual thyroid was recognized 20 years after the patient had undergone thyroidectomy for a multinodular goiter (6). The high TSH perpetuates the growth of ectopic dysfunctional thyroids. The treatment of an uncomplicated lingual thyroid is administration of thyroid hormone for life to suppress TSH. Very occasionally the mass needs to be ablated with ^{131}I (7). Because the patients are hypothyroid it does not make sense to autotransplant the tissue since thyroid hormone will be necessary for life in any case (8). Very rarely thyroid cancer arises from follicular cells in a lingual thyroid, and its management is discussed in Chapter 6 (9, 10). The main clinical issues are to recognize that a mass in the midline at the back of the tongue can be the thyroid, and if there are any suspicious symp-

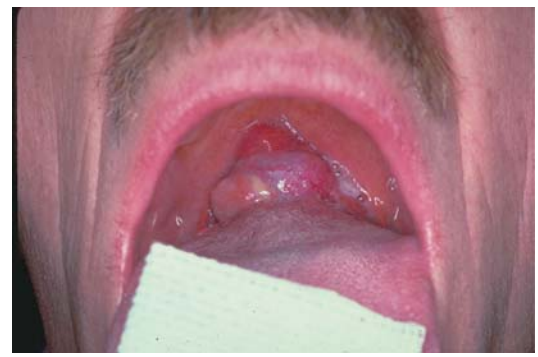

Figure 2.3. Figure shows a lingual thyroid in a middle-aged man.