THYROID CANCER

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This is to acknowledge that Dr. Kovacs has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Kovacs will not be discussing off-label uses in his presentation.

INTRODUCTION

On February 12, 1972 a 52 year-old man was being taken to surgery in a hospital in New York. In the previous month he had been examined by his doctor and told that he was in perfect health--except for a thyroid tumor. The patient described himself as capable of only two emotions--anxiety and hilarity. So it was no surprise to him that, as he was being wheeled into surgery on the gurney, he waved his arms and sang at the top of his voice. When he encountered his surgeon inside the operating suite he reached up, grabbed him, and intoned:

> "Doctor, Doctor, with green coat,
> Doctor, Doctor, cut my throat.
> And when you've cut it, doctor, then,
> Won't you sew it up again?"

The patient was the popular science and science fiction writer Isaac Asimov. He underwent thyroid lobectomy and was treated with thyroid hormone until his death in 1992 from causes unrelated to thyroid cancer. It is not documented in his autobiographical material whether Asimov actually had thyroid cancer, but his story could be fairly typical for either a benign hyperplastic nodule or a thyroid cancer. Most people have the abnormality discovered when they are asymptomatic, and many times the diagnosis of thyroid cancer does not alter life expectancy. Since the time of Asimov's diagnosis a number of diagnostic and therapeutic advances have changed the way we find and treat thyroid nodules and thyroid cancers. Nevertheless, considerable challenge persists in dealing with thyroid neoplasia, and, sadly, some forms of the disease remain totally beyond the reach of any useful therapy.

Thyroid nodules are an extremely common finding but thyroid cancer is an uncommon disease. Thyroid cancers are generally diagnosed after the discovery of a thyroid nodule by either physical examination or by an imaging procedure. Such thyroid nodules are common, regardless of the method of ascertainment. In the Framingham cohort 6.4% of women and 1.5% of men were found to have palpable thyroid nodules (1). These data have been replicated in other surveys and it is generally agreed that about 5% of the adults in the United States have thyroid nodules detectable on

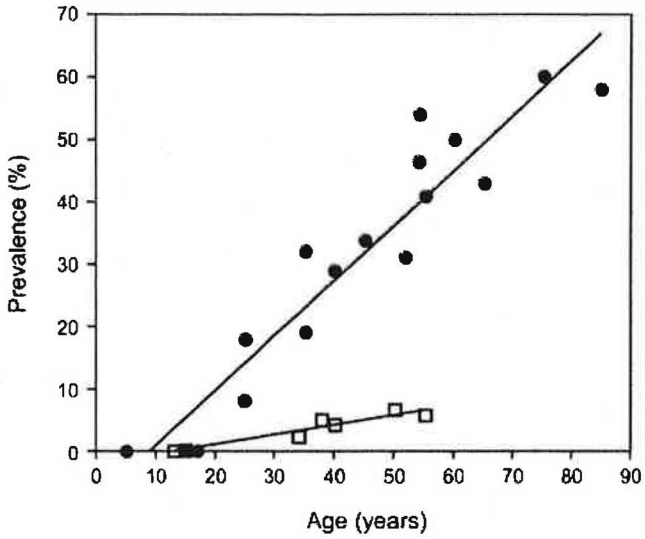


Figure 1 *Prevalence of palpable thyroid nodules detected at autopsy or by ultrasonography (closed circles) or by palpation (open squares). Mazzaferri et al N Engl J Med 328:553 (1993)*

physical exam (2, 3) Thyroid nodules are much more common than estimated from such observations--in autopsy series over 50% of persons with clinically normal thyroids can be found to have nodules (4). The advent of high resolution neck ultrasonography reveals a prevalence of thyroid nodules comparable to that observed in autopsy series--neck ultrasound done for other reasons has revealed thyroid nodules in nearly ½ of patients (Figure 1) (3, 5). Endocrinologists now see increasing numbers of referrals for nodules incidentally discovered during imaging procedures of neck or chest performed for other reasons.

Most thyroid nodules are not thyroid cancer--about 95% of such nodules are benign lesions, including hyperplastic nodules, adenomas, and cysts. Current data from the United States National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program estimates that about 327,000 Americans have thyroid cancer--about 0.1% of the population. This number contrasts with the estimate of nearly 14,800,000 nodular thyroids in the current U.S. population. Thyroid cancer incidence rates are estimated by the American Cancer Society at 25, 690 new cases this year (19, 490 women and 6,500 men).

The annual incidence rate has been increasing for several decades. The reason for such increase is not known, but a likely partial explanation is ascertainment--average tumor size at diagnosis seems to be decreasing--probably because more nodules are being detected by imaging procedures (2). Supporting this are the data from SEER that show falling mortality rates (at least for women) in the face of the rising incidence (Figure 2).

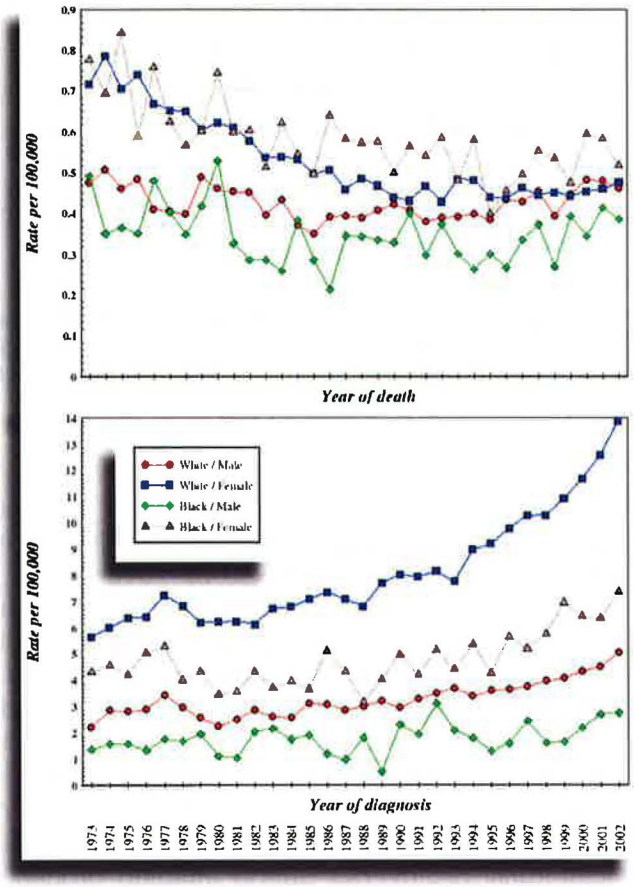


Figure 2. *Rates of thyroid cancer diagnosis per 100,000 population (bottom panel) and rates of death due to thyroid cancer per 100,000 population for the years 1973 to 2002. Data from NCI SEER database.*

FINDING THYROID CANCER

The tools for the diagnosis of thyroid cancer are the physical examination, thyroid imaging (by ultrasound) and fine needle aspiration (FNA) biopsy for cytologic examination. The challenge is to find the uncommon malignancies in the vast sea of benign thyroid abnormalities that are present in the general population. While some features of the patient's history (explosive growth of a thyroid lesion, hoarseness) and physical examination (rock-hard nodules, associated adenopathy with fixation to underlying tissues) may suggest malignancy, there has been no reliable noninvasive way to distinguish a benign thyroid nodule from a carcinoma (2). With the growing numbers of patients referred with nonpalpable thyroid nodules detected incidentally by various imaging modalities a renewed effort has been undertaken to identify imaging characteristics that might serve to identify low risk nodules that might simply be observed (3, 5, 6). Previous criteria were based on size alone--nodules greater than 10 mm or greater than 15 mm were recommended by various experts for FNA sampling the rest were to be followed. It is estimated that about one-third of non-palpable nodules would meet the 10 mm criterion--necessitating thyroid FNA in 11-12% of the population of the United States (if the entire population were screened with thyroid ultrasound) (3). New criteria based on the imaging characteristics of thyroid nodules provide guidance on how to avoid unnecessary procedures by subjecting only higher-risk non-palpable nodules to FNA (6). Such characteristics include blurred margins of the nodule, intranodular microcalcification, and intranodular vascularization evidenced on color flow Doppler examination.

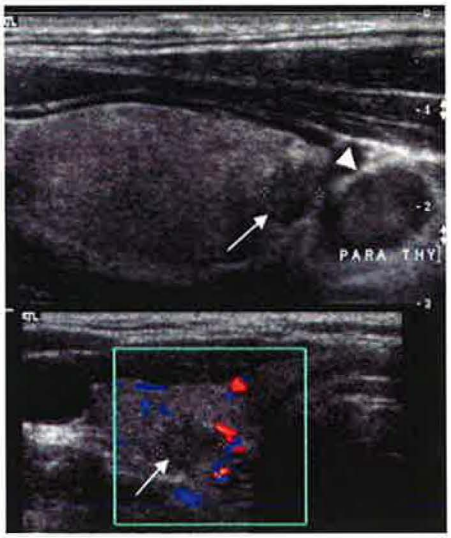


Figure 3 *Incidentally discovered 6 mm papillary thyroid cancer found on US performed for parathyroid adenoma. Top panel; sagittal view w nodule (thin arrow). Bottom panel: color flow Doppler shows increased vascularity in nodule (from ref 6)*

	Solitary nodule	Hypoechoic nodule	Nodule > 10 mm	Blurred margins	Intranodular vascularization	Microcalcifications
			Individual features			
No.	195	237	271	80	94	27
Sensibility	58.0%	87.1%	61.3%	77.5%	74.2%	29.0%
Specificity	52.3%	43.4%	32.0%	85.0%	80.8%	95.0%
Predictive value for malignancy	10.0%	11.4%	7.0%	30.0%	24.0%	33.0%
			In conjunction with hypoechoic appearance			
No.	119		136	68	73	22
Sensibility	45.1%		54.8%	74.2%	61.0%	26.0%
Specificity	71.7%		68.0%	87.8%	85.5%	96.3%
Predictive value for malignancy	11.7%		12.5%	39.0%	26.0%	36.0%

Table 1. *Sensitivity, specificity, and predictive values of ultrasound and color flow Doppler characteristics of non palpable thyroid nodules in the study of Papini et al (J Clin Endocrinol Metab 87: 1941 (2002)*

A reasonable recommendation would be to perform fine needle aspiration biopsy of palpable thyroid nodules as well as incidentally discovered nodules greater than 15 mm or between 8-15 mm size but with ultrasound features (irregular margins, microcalcifications, or vascularity) suggestive of higher risk. FNA under ultrasound guidance is becoming the standard and is certainly required for non-palpable nodules or complex nodules with both cystic and solid components. Obviously, the procedure should only be performed if the results will lead to an altered plan of care--i.e., thyroidectomy in the case of an unequivocal diagnosis of carcinoma and excisional biopsy (at least a thyroid lobectomy) in the case of an equivocal result.

Benign Nodules (95%)	Carcinomas (5%)
Hyperplastic nodules (85%)	Papillary (81%)
Adenomas (15%)	Follicular and Hurthle-cell (14%)
Cysts (<1%)	Medullary (3%)
	Anaplastic (2%)

Table 2. *Common varieties of thyroid nodules. Adapted from Utiger, NEJM 352: 2376-2378 (2005)*

What results might one expect to obtain from thyroid FNA? Unselected for ultrasonographic characteristics, the vast majority (over 90%) of thyroid nodules will show benign cytology (Table 2). The characteristic finding is a "macrofollicular" pattern with sheets of benign appearing follicular cells and abundant colloid characteristic of a hyperplastic nodule (Figure 4--top panels). Thyroid carcinomas arise both from thyroid follicular epithelium and from the parafollicular "C" cells that produce calcitonin. Papillary and follicular cancer as well as anaplastic thyroid cancer arise from the follicular cells, whereas medullary carcinoma of the thyroid is a C cell neoplasm. The most frequent finding of malignancy is that of the histologic subtype of papillary carcinoma of the thyroid. The cytologic findings are characteristic--with nuclear grooving and atypia, inclusions, and, occasionally, psammoma bodies. The cytologic finding of "microfollicular" aggregates of cells, with sparse colloid is impossible to differentiate between benign and malignant lesions--that differentiation can only be made by histologic examination of the tissue--to assess whether the follicular lesion shows characteristic invasion into the thyroid capsule or into blood vessels.

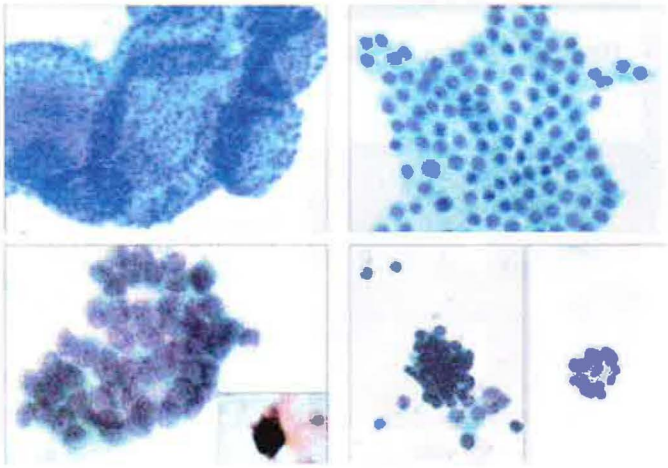


Figure 4. *Thyroid FNA cytology specimens. Sample from benign nodule (upper panels, right and left) shows "macrofollicular" sheets of typical follicular cells (abundant colloid was also present on the slide). Papillary carcinoma (lower left) cells show nuclear grooving, "powdery chromatin", and inclusion bodies. The inset shows a psammoma body. The "microfollicular" pattern with scant colloid (lower right panel) is a follicular neoplasm for which excisional biopsy is needed for histologic evaluation--with attention to capsular breach and vascular invasion. Figure from Mitchell, Sem US CT MRI 26:37-46 2005*

The molecular genetics of cancer arising from the thyroid follicular epithelium

Attempts to understand the genetic alterations present in cancers arising from the thyroid epithelium could be of considerable importance in establishing diagnoses and assigning prognosis to individual tumors. In papillary thyroid cancer attention has focused on two genetic alterations--in the RET and BRAF protooncogenes. The RET alterations are chromosomal rearrangements which fuse the RET tyrosine kinase domain to 5' sequences of unrelated genes, creating "RET/PTC" rearrangements of several types (7). While such rearrangments are commonly found in sporadic and radiation-induced childhood papillary thyroid cancers, they are present in only about 30% of adult sporadic papillary thyroid cancer (8, 9). More common in adult papillary thyroid cancer is a stereotypic somatic mutation in a gene called BRAF (9, 10). This serine/threonine kinase is a component of the raf/MEK/ERK pathway--a MAP kinase signaling cascade (Figure 5) (11). The T to A transversion at nucleotide 1796 results in a V599E substitution that creates a constitutively active Raf kinase. This somatic mutation has been observed in as many as 70% of adult sporadic papillary thyroid cancers in some series (10, 12)

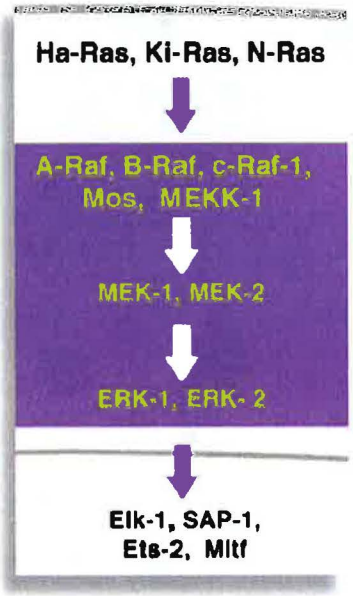


Figure 5. *The Raf/MEK/ERK signaling pathway. A kinase cascade transmitting signals from cell membrane to nucleus. Activating mutations in BRAF are common in adult PTC*

RET/PTC rearrangements and BRAF mutations do not appear together in the same tumor and neither type of genetic alteration is observed in other forms of differentiated thyroid cancer (i.e., follicular thyroid cancer).

While understanding the molecular events underlying the development of papillary thyroid cancer is of importance, such a genetic marker of the malignant phenotype would be of much more immediate value in the diagnosis of follicular thyroid cancer. Since the malignant forms of these thyroid neoplasms are indistinguishable from benign nodules on FNA sampling, surgical removal of the involved lobe of the thyroid is required for histologic diagnosis. A reasonable estimate is that 20% of all FNAs fall into this category, and that 10-20% of those cases are actually found to be a malignancy on final histologic examination (13, 14). None of a number of proposed candidate markers, including galectin, PAX8/PPARγ fusion gene, thyroid peroxidase, telomerase reverse transcriptase, p53, and HBME-1 has proven to be suitable for making the distinction between follicular adenoma and follicular cancer (14).Recent studies have used

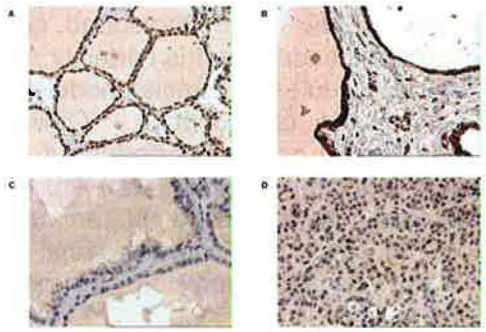


Figure 6. *Immunohistochemical confirmation of underexpression of cyclin D2 in follicular thyroid cancer. Top panels: normal nuclear staining with anti-CCND2 in follicular adenomas. Bottom panels: absence or diminution of staining in follicular cancers (supplementary data from Weber et al)*

serial analysis of gene expression (SAGE) and microarray analysis of RNA from benign follicular adenomas and follicular thyroid cancers to attempt to identify genes differentially expressed in these entities, and to define minimal gene sets for analysis (13, 14) that would serve to distinguish benign lesions from follicular thyroid cancer. One report identified a set of four genes (DDIT, ARG2, ITM1, C1orf24) that could serve to distinguish benign from malignant follicular tumors (14). The second report identified a set of three genes (cyclin D2, protein convertase 2, and prostate differentiation factor) that they found to differentiate between follicular adenomas and follicular cancers (Figure 6). While these diagnostic tools look promising, they remain to be confirmed.

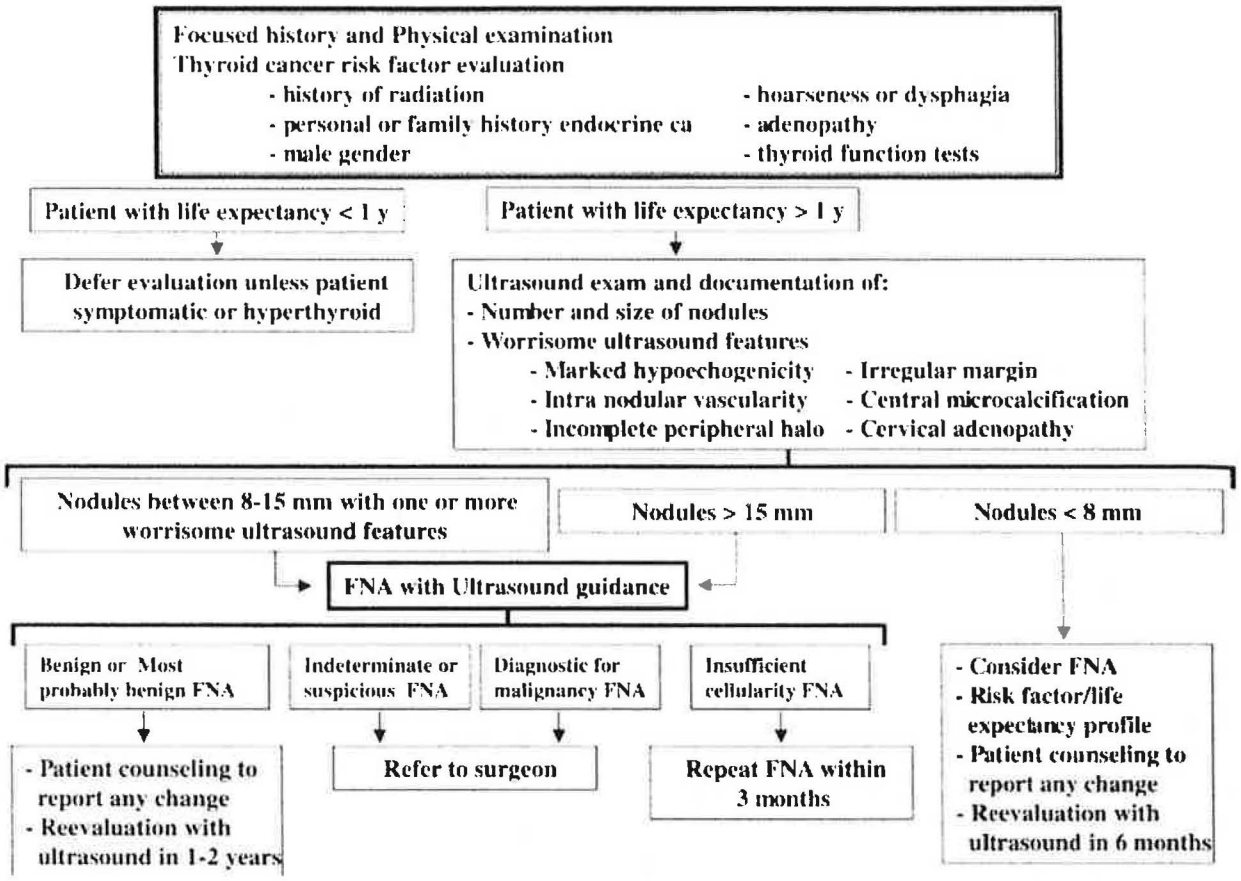


Figure 7. *One proposed algorithm for the management of thyroid nodules detected incidentally during radiologic imaging (from Mitchell and Parangi Sem US CT and MRI 26:37 (2005).*

Fine needle aspiration sampling with cytologic examination remains the essential diagnostic step in the evaluation of palpable thyroid nodules. For incidentally discovered nodules current practice generally follows algorithms similar to that shown in Figure 7. Such algorithms recommend US-guided FNA sampling for nodules of a size that might usually be palpable (1.5 cm) and for small nodules with worrisome imaging characteristics; nodules lacking such findings are followed by repeat ultrasound exam.

TREATING THYROID CANCER

There have been no prospective randomized clinical trials of the treatment of the treatment of differentiated thyroid cancer (papillary and follicular thyroid cancer), which comprises 90% of thyroid cancers and accounts for 70% of thyroid cancer deaths. Ten year survival rates are estimated at over 90% for papillary thyroid cancer and around 85% for follicular thyroid cancer (15). Deaths from thyroid cancer are most frequently caused by respiratory insufficiency--either from pulmonary metastatic disease or from airway compromise. Recurrences are most frequent in the first decade after initial therapy. Mazzaferri and colleagues have observed 40-year recurrence rates of 35%. The highest rates of recurrence are observed in people diagnosed at a young age, but the highest death rates are in those diagnosed at ages greater than 50 years.

Accumulated data on the risk of recurrence are generally used to classify patients as "low risk" or "high risk"--the variables of interest are shown in Table 3. Low risk groups are women, young adults (ages 15-45) and persons with small tumors and no extrathyroidal disease. Such risk stratification data, while useful for epidemiologic studies and for decisions on follow-up, include information that is only available after surgery--so that decisions about initial surgical therapy need to be made on the basis of less complete information (15).

Factors predictive of high risk	Factors predictive of moderate-to-low risk
Patient variables	
Age <15 yr or >45 yr	Age 15–45 yr
Male sex	Female sex
Family history of thyroid cancer	No family history of thyroid cancer
Tumor variables	
Tumor >4 cm in diameter	Tumor <4 cm in diameter
Bilateral disease	Unilateral disease
Extrathyroidal extension	No extrathyroidal extension
Vascular Invasion (both papillary and follicular thyroid cancer)	Absence of vascular invasion
Cervical, or mediastinal lymph node metastases	No lymph node metastases
Certain tumor subtypes: Hürthle cell, tall cell, columnar cell, diffuse sclerosis, insular variants	Encapsulated papillary thyroid carcinoma, papillary microcarcinoma, cystic papillary thyroid carcinoma
Marked nuclear atypia, tumor necrosis, and vascular invasion (*i.e.* histologic grade)	Absence of nuclear atypia, tumor necrosis, and vascular invasion
Tumors or metastases that concentrate radioiodine poorly or not at all	Tumors or metastases that concentrate radioiodine well
Distant metastases	No distant metastases

Table 3. *Risk stratification of variables influencing cancer recurrence and cancer death in individuals with differentiated thyroid cancer. Table from Mazzaferri and Kloos J Clin Endocrinol Metab 86:1447 (2001)*

Initial Surgery

The vast majority of surgery for differentiated thyroid cancer in the United States and Europe is done as a "near total" thyroidectomy. As will be discussed below, this is generally considered an essential step to allow careful follow-up monitoring. Some experts have argued that, for low risk tumors (1-4 cm diameter with no metastases) thyroid lobectomy is sufficient. Other data indicate higher recurrence rates in the remaining lobe and higher rates of subsequent pulmonary metastases in individuals treated with thyroid lobectomy (15-17). Whether the more extensive surgery influences overall survival for people with low risk lesions is not proven, but disease-free survival is extended and with 14% rate of local recurrence and 19% rate of nodal metastases over 20 years for individuals undergoing lobectomy compared to 2% and 6% rates for those who underwent near total thyroidectomy (18). Guidelines from the National Comprehensive Cancer Network (http://www.nccn.org) recommend total thyroidectomy and central compartment lymph node dissection or lateral modified radical neck dissection for high risk thyroid cancer.

What should be done for persons who have undergone thyroid lobectomy but are judged to have potential for tumor recurrence? Our practice and the recommendation of the NCCN panel is that the remaining lobe should be resected--a "completion thyroidectomy." A remaining thyroid lobe with predominantly normal tissue is extremely difficult to ablate with radioiodine and the presence of this functioning thyroid tissue limits the capability to continue surveillance for tumor recurrence.

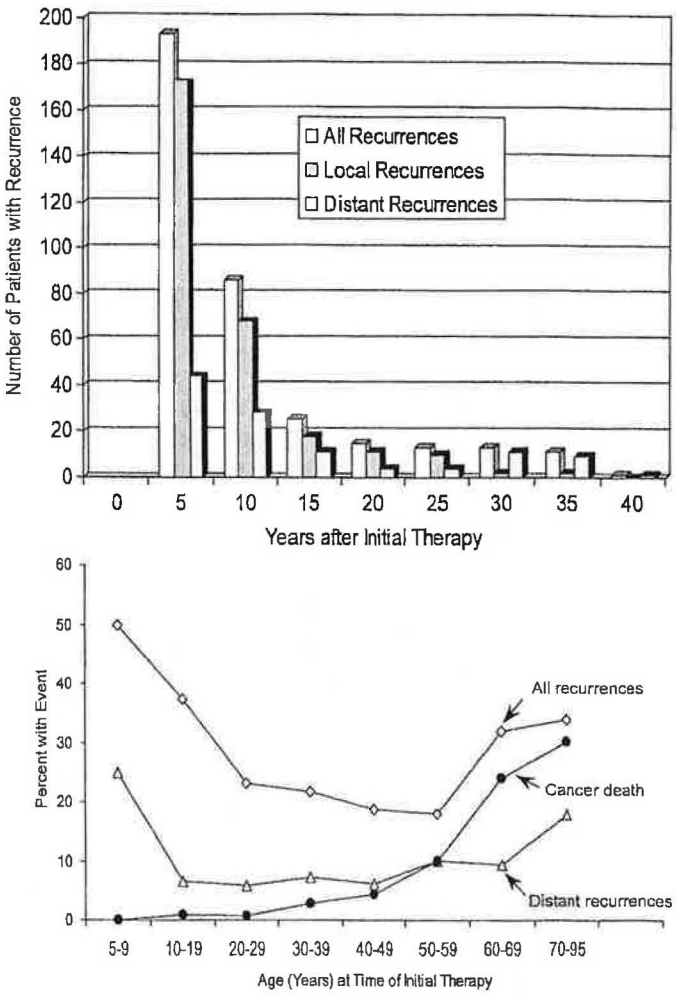
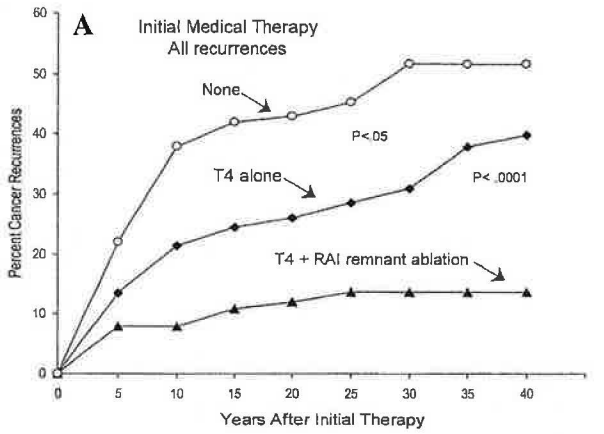


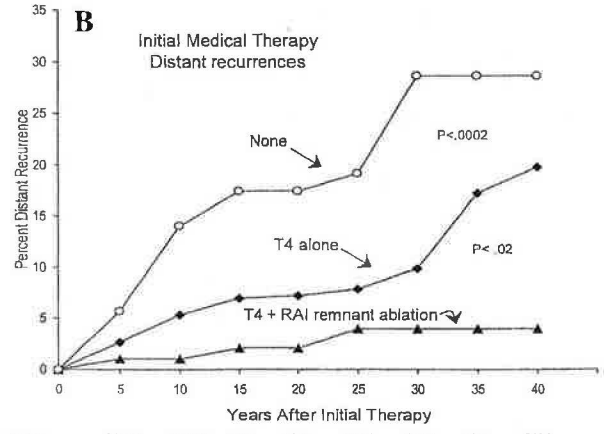
Figure 8. *40 years of follow-up data on a cohort 1528 patients with differentiated thyroid cancer. Median follow up was 16.6 years. From Mazzaferri and Kloos J Clin Endocrinol Metab 86:1447 (2001)*

Thyroid Remnant Ablation

The administration of an ablative dose of radioiodine has been a standard of care for patients with differentiated thyroid cancers who have undergone total thyroidectomy. Even after such surgery, significant amounts of thyroid tissue remain in the thyroid bed. Typical data on the effect of such therapy on rates of tumor recurrence are shown in Figure 9 (15). However, the low mortality rates associated with differentiated thyroid cancer (particularly papillary cancer) have caused some to question the necessity of such treatment in patients thought to be at low risk (19) and a recent meta analysis concluded that radioiodine therapy might be beneficial in reducing recurrences, but that the results were variable among the centers whose data were analyzed (20).



None	34/163	22/112	5/82	1/66	2/54	4/39	0/25	0/13
T4 + RAI	15/230	0/135	3/102	1/84	1/67	0/38	0/26	0/18
T4 alone	101/789	51/603	17/462	7/378	10/326	6/229	10/135	1/51



None	8/163	9/112	3/82	0/66	1/54	4/39	0/25	0/13
T4 alone	19/789	15/603	7/462	0/378	2/326	4/229	8/135	1/51
T4+RAI	2/230	0/135	1/102	0/84	1/67	0/38	0/26	0/11

Figure 9. *Tumor recurrence during prolonged follow-up of patients treated for differentiated thyroid cancer after surgery with thyroxine (T4) alone on with radioiodine ablation followed by T4. Data are from Mazzaferri J Clin Endocrinol Metab 86: 1447 (2001)*

The potential side effects of radioiodine ablation are mainly damage to salivary glands that can result in parotitis or sialadenitis, which can be chronic. The side effects can be minimized by using modest doses of radioiodine (25-50 mCi) which, a recent randomized study confirms, are effective for remnant ablation (21).

Practical considerations of follow up care convince most physicians that radioiodine ablation of the thyroid remnant is advisable. In order to use the most sensitive methods of detection for recurrent disease (TSH stimulate thyroglobulin measurements and whole-body scanning with radioiodine) the thyroid remnant must be ablated. In addition, recent data on the clonal origins of multifocal papillary thyroid cancers (22). Such multifocality is observed in a large proportion of cases of thyroid cancer. Examination of the patterns of X-chromosomal inactivation in multifocal papillary thyroid cancers indicates that these foci arise from independent clonal events--since a single X chromosome was inactivated in each focus of cancer. The data imply that, at least for recognized multifocal disease, residual thyroid tissue is at risk for the development of recurrent disease (22).

Long-term follow-up

Two recent advances have changed important aspects of the long-term management of differentiated thyroid cancer. Standard practice in the not too distant past was to withdraw patients from thyroid hormone therapy and allow endogenous TSH to rise, thus stimulating iodine uptake in thyroid tissue--which could then be imaged using ^{131}I. With prior total thyroidectomy and remnant ablation the uptake of radioiodine in residual, recurrent, or metastatic disease could be detected and decision taken about further therapy. It is now recognized that measurement of serum thyroglobulin (TG), the protein product of the thyroid follicular epithelial cells, can be used as a marker of residual thyroid tissue. In addition, the development of recombinant human TSH (rhTSH) has given clinicians an agent that can be used to stimulate residual thyroid tissue without the necessity of induction of a protracted hypothyroid state.

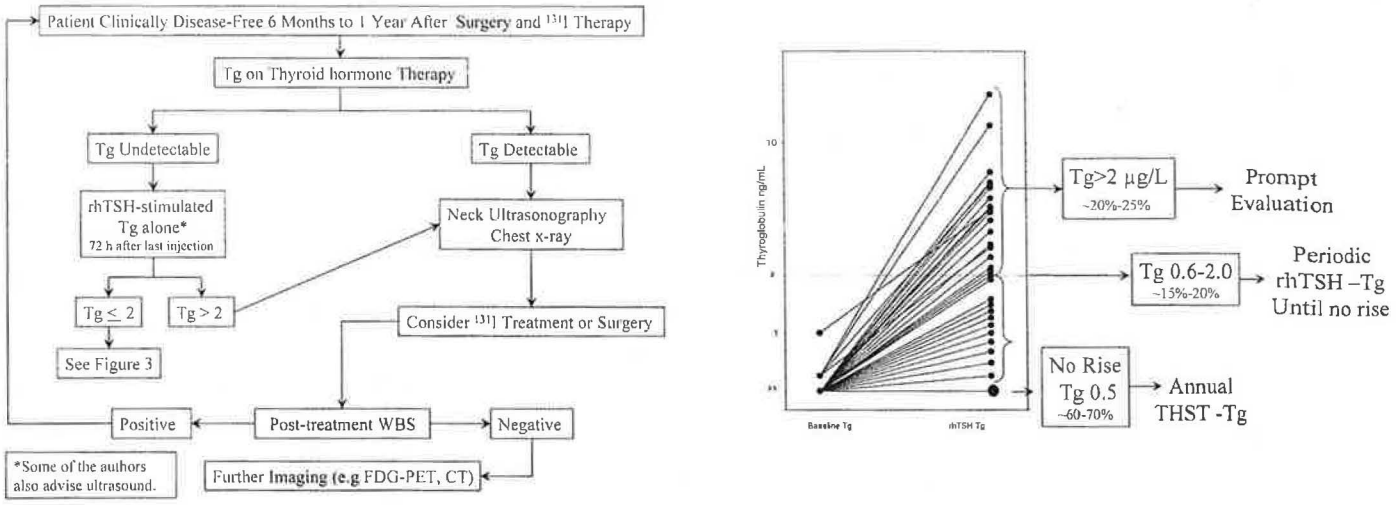


Figure 10. *Follow up care pathway for patients with low-risk differentiated thyroid cancer who have undergone total thyroidectomy, remnant ablation, and have no anti thyroglobulin antibodies in serum. Left panel: overall algorithm. Right panel is "Figure 3"--detail of algorithm for patients with rhTSH-stimulated TG less than or equal to 2 ng/ml. Figures from Mazzaferri and Kloos J Clin Endocrinol Metab 87: 1490 (2002).*

Measurements of serum thyroglobulin have proved in a number of studies to be more sensitive reflections of residual thyroid tissue or residual/recurrent thyroid cancer than diagnostic scans (4-5 mCi ^{131}I) after thyroxine withdrawal (23-26). When thyroglobulin levels are clearly elevated (greater than 2 ng/ml) in a patient on thyroid hormone suppression who has undergone total thyroidectomy and remnant ablation, there is no need for diagnostic scanning with ^{131}I (27). Instead, thyroid hormone withdrawal, and treatment dose (100 mCi) of radioiodine with post-treatment scan (4-7 days later) would be more rational. In addition, diagnostic scanning also is unnecessary in low-risk patients with thyroglobulin levels below the detectability limit of the assay. In these individuals rhTSH-stimulated thyroglobulin levels can be flowed to detect recurrence without diagnostic scanning (23-25). The recombinant TSH is administered as two 0.9 mg doses IM on successive days. Serum thyroglobulin is measured 72 hours after the last dose. If diagnostic scanning is to be performed, it is done 24 hours after the second dose fo rhTSH. An example of an algorithm for the use of rhTSH and thyroglobulin measurements in patients with low risk for recurrence of their thyroid cancer is shown in Figure 10 (28). Note that some authorities recommend the use of high-resolution ultrasound exams of the neck in conjunction with the rhTSH-stimulated thyroglobulin levels (29). The advantages of using thyroglobulin levels are lost in individuals with anti-thyroglobulin antibodies in serum, since accurate measurements of serum thyroglobulin cannot currently be made in the presence of such antibodies.

Anaplastic Thyroid Cancer

While great advances have been made in our understanding and clinical approach to differentiated thyroid cancers, anaplastic cancer remains a dismal prognosis, with life expectancy averaging about 6 months. Some anaplastic carcinomas bear genetic alterations in BRAF and RET/PTC rearrangements as are observed in papillary and follicular cancer. Despite this apparent common origin in follicular epithelium, these tumors share none of the indolent characteristics of more differentiated thyroid cancers. A good reflection of the state of the art is the sparsely populated algorithm from NCCN for management of anaplastic thyroid cancer (Figure 11).

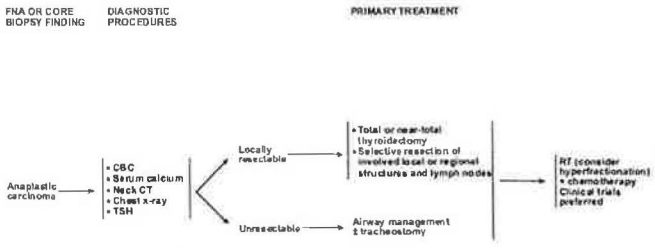


Figure 11. *NCCN algorithm for management of anaplastic thyroid carcinoma. No known therapy alters the course of this neoplasm*

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