Changing Concepts in the Pathogenesis and Management of Thyroid Carcinoma

Robert F. Gagel, MD
Helmuth Goepfert, MD
David L. Callender, MD

Introduction

Thyroid cancer is a relatively uncommon neoplasm, accounting for about 1.5 percent of all cancers in the United States. This year about 15,600 new cases will be diagnosed in the United States.\(^1\) Death related to thyroid cancer is also uncommon, with no more than about 1,200 deaths annually in the United States.\(^1\) The relative infrequency of death from this disease has led to a viewpoint that thyroid carcinoma is an innocuous tumor. However, this is an incorrect assessment. It is not always possible to determine which patients will develop aggressive and/or recurrent disease,\(^2\) and aggressive thyroid cancer is difficult to manage and associated with a high level of morbidity and mortality.

In the past five years, significant advances have been made in understanding the causes of thyroid carcinoma and improving methods for diagnosis and management. In this context, it is instructive to review the experience at a large referral center for thyroid carcinoma with the goal of understanding how technologic advances during the past decade have altered the concepts of cause and management of the several forms of thyroid carcinoma.\(^3-11\) This review will focus on several aspects of thyroid carcinoma, including classification and diagnosis, recent insights into the molecular pathophysiology of tumors derived from follicular and parafollicular epithelium, and a review of the experience with thyroid carcinoma at the University of Texas M. D. Anderson Cancer Center (UT-MDACC).

Classification, Staging, and Prognosis

Primary carcinomas of the thyroid gland are usually classified as differentiated thyroid cancer (papillary and follicular carcinomas),\(^12\) medullary thyroid carcinomas, and undifferentiated or anaplastic carcinomas. Other less frequent classifications include Hürthle cell carcinomas, squamous cell carcinomas, lymphomas and other hematopoietic lesions, and a variety of unusual carcinomas and soft tissue sarcomas (Table 1).

Papillary thyroid carcinoma, the most common histologic type of thyroid cancer, accounts for about 60 percent of
all thyroid cancers. More than 30 percent of patients with papillary thyroid carcinoma present with metastasis to regional lymph nodes, and about 10 percent of patients develop hematogenous metastasis.

Follicular carcinoma accounts for about 20 percent of all thyroid cancers, although lower frequencies have been reported recently. Hematogenous metastasis is more common for follicular carcinoma than for papillary carcinoma, and the prognosis is somewhat less favorable. Hurthle cell carcinoma, a malignancy derived from the follicular cell, has a prognosis similar to that of follicular carcinoma.

The treatment of patients with differentiated thyroid carcinoma should be based on each patient’s prognostic factors. Several classification and staging schemes have been introduced to facilitate identification of important prognostic variables that can guide the clinician. Some of the more widely used staging systems are summarized below.

AMES
The simplest classification divides patients into low-risk and high-risk groups. The low-risk group includes patients without metastasis if they are male and younger than 41 years or female and younger than 51 years. Patients older than this without metastasis are considered low-risk if they are without extrathyroidal papillary carcinoma, major tumor capsular invasion by follicular carcinoma, or a primary tumor larger than 5 cm in diameter. Patients who do not meet the criteria for low-risk disease are placed in the high-risk group.

Of 310 patients with differentiated thyroid carcinoma seen at the Lahey Clinic during a 20-year period, 89 percent were assigned to the low-risk and 11 percent to the high-risk group. Only 1.8 percent of patients in the low-risk group died during follow-up, while 46 percent of the high-risk patients died. The frequencies of recurrence were five percent for low-risk patients and 55 percent for high-risk patients. When the AMES classification system was applied to patients at UT-MDACC and the University of Chicago, 75 percent and 70 percent, respectively, were classified as low-risk. The 40-year survival probability for low-risk patients was about 95 percent compared with about 45 percent for high-risk patients.

TNM
The International Union Against Cancer and the American Joint Committee on Cancer have adopted a tumor-node-metastasis (TNM) classification system. Age at diagnosis is also an important factor in this schema. Applied to the University of Chicago cohort, this system separates patients into four groups, each having a survival probability that differs significantly from the others. Eighty-two percent of patients were stage I with a 20-year survival of nearly 100 percent. On the other end of the spectrum, five percent of patients were stage IV with a five-year survival of only 25 percent. Similar findings were reported when 1,500 patients with papillary thyroid carcinoma were analyzed.

AGES/MACIS
The first version of the Mayo Clinic staging system for thyroid cancer incorporated a formula based on Age at diagnosis, histologic tumor Grade, Extent of disease...
at presentation, and tumor Size to calculate a prognostic score.\textsuperscript{23} The most significant prognostic variables, in descending order of importance, were distant metastasis, age at diagnosis, tumor size, extrathyroidal extension, and tumor grade. Patients in group I, who accounted for 85 percent of the total cohort, had a 20-year, disease-specific mortality of only one percent. The corresponding mortality was 20 percent for group II, 67 percent for group III, and 87 percent for group IV.\textsuperscript{22,23}

Application of this system to other patient populations was difficult because of the infrequent use of tumor grading as done at the Mayo Clinic. Therefore, a second system was developed based on Metastasis, Age at diagnosis, Completeness of surgical resection, extrathyroidal Invasion, and Size.\textsuperscript{24} The MACIS score is calculated as $3.1 \times \textit{age} \times \left(\frac{\text{tumor size (in centimeters)}}{100}\right) + 1 \times \text{incompletely resected} + 1 \times \text{extrathyroidal extension} + 3 \times \text{distant metastasis}$. Twenty-year mortality from thyroid cancer for group I (score less than 6) is one percent, 11 percent for

| Thyroid carcinoma derived from the follicular cell |
|-----------------------------------------------|
| Papillary thyroid carcinoma                     |
| Mixed papillary-follicular thyroid carcinoma    |
| Follicular thyroid carcinoma                    |
| Hürthle cell carcinoma                         |
| Anaplastic thyroid carcinoma                   |

| Thyroid carcinoma derived from the parafollicular or C cell |
|------------------------------------------------------------|
| Sporadic medullary thyroid carcinoma                      |
| Hereditary medullary thyroid carcinoma                    |
| \begin{itemize} \item Multiple endocrine neoplasia type 2A (MEN 2A) \item Medullary thyroid carcinoma \item Pheochromocytoma \item Parathyroid neoplasia \item Multiple endocrine neoplasia type 2B (MEN 2B) \item Medullary thyroid carcinoma \item Pheochromocytoma \item Marfanoid features \item Mucosal neuromas \item Familial medullary thyroid carcinoma \item Medullary thyroid carcinoma \end{itemize} |
group II (score 6 to 6.99), 44 percent for group III (score 7 to 7.99), and 76 percent for group IV (score 8 or more).

**UNIVERSITY OF CHICAGO**

Another staging scheme for papillary thyroid carcinoma is the Clinical Class system proposed by DeGroot et al. Disease limited to the thyroid gland is assigned to class I, nodal disease to class II, extrathyroidal extension to class III, and distant metastasis to class IV. For 269 patients, disease-specific mortality was markedly increased in the two highest classes, but mortality for patients with class I and II disease was low, and the two groups did not differ.

**OHIO STATE UNIVERSITY/UNITED STATES AIR FORCE**

In the most recent update of Mazzaferri and Jhiang’s series, 1,355 patients were analyzed retrospectively. Patients with stage 1 disease had tumors smaller than 1.5 cm; those with stage 2 disease had tumors 1.5 to 4.4 cm or cervical metastasis or more than three intrathyroidal foci; patients with stage 3 disease had tumors at least 4.5 cm in size or local tumor invasion; and patients with stage 4 disease had distant metastasis. Both 30-year recurrence and cancer mortality rates increased with higher stage. Variables present at diagnosis that predicted cancer-specific mortality for patients with stages 1 to 3 disease included increasing age, primary therapy delayed by at least 12 months, local tumor invasion, lymph node metastasis, tumor size, and male gender.

Any one multivariate prognostic scoring system may not be applicable to another patient population. Nonetheless, it is possible to draw general conclusions from the multiple staging systems that exist. Younger age at diagnosis, smaller size of primary tumor, absence of extrathyroidal extension, complete gross resection at the time of initial surgery, and lack of nodal or distant metastasis are factors common to most prognostic systems that portend low risk for tumor recurrence or disease-specific mortality. It is important to recognize that younger patients do occasionally have poor outcomes, and the generally good prognosis associated with this age factor must not be overly emphasized in patient management. The presence of extrathyroidal extension, distant metastasis, a more aggressive histologic subtype (e.g., the tall-cell variant of papillary thyroid carcinoma or oxyphilic follicular carcinoma), or surgically unresectable disease indicates a need for more aggressive therapy.

**Factors That Increase the Risk of Thyroid Carcinoma**

**PAPILLARY OR FOLLICULAR THYROID CARCINOMA**

The major risk factor predisposing to papillary or follicular thyroid carcinoma is exposure to radiation. Many studies have documented the increased risk of thyroid carcinoma in individuals exposed to low-level radiation. The increase in the diagnosis of thyroid cancer between the 1930s and the 1970s is at least in part attributable to the widespread use of irradiation for treatment of a variety of head and neck disorders in the first half of this century.

More recently the importance of radiation as a risk factor for thyroid carcinoma has been underscored by the startling increase in the diagnosis of pediatric thyroid carcinoma among children exposed to ionizing radiation following the Chernobyl nuclear disaster in the Ukraine in 1986. More than 100 cases of pediatric thyroid carcinoma were observed in the Gomel region of Belorussia between 1989 and the present in an area where no more than one to two pediatric thyroid carcinomas per year had been previously identified. These tumors
were associated with local lymph node metastasis in about 75 percent of children and were poorly differentiated in more than 50 percent. There has been one death attributable to thyroid carcinoma in this group of children. What has been surprising about this experience is the rapidity of development of thyroid carcinoma in these children. One possible explanation is that the true radiation exposure in these children has been underestimated, a point for which there is some supportive evidence.

Other factors that have been implicated in papillary or follicular thyroid carcinoma but are incompletely understood include the role of iodine deficiency and autoimmune thyroid disease. There is increasing evidence that genetic factors may play a role in a small percentage of papillary and follicular thyroid carcinomas. The well-known associations of Gardner’s syndrome (familial colonic polyposis) and Cowden disease (familial goiter and skin hamartomas) with differentiated thyroid carcinoma provide well-defined examples. Papillary thyroid carcinoma may also occur with increased frequency in certain families with breast, ovarian, renal, or central nervous system malignancies, suggesting that insight into the causative genes for these disorders may lead to the identification of genes causative for papillary or follicular thyroid carcinoma.

MEDULLARY THYROID CARCINOMA

About 25 to 35 percent of all medullary thyroid carcinomas are identified as a component of one of the variants of multiple endocrine neoplasia type 2 (MEN 2). These clinical syndromes include multiple endocrine neoplasia type 2A (MEN 2A) (medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism), multiple endocrine neoplasia type 2B (MEN 2B) (medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, and marfanoid-like features), and familial medullary thyroid carcinoma (Table 1).

Medullary thyroid carcinoma is inherited as an autosomal dominant feature of these syndromes, and over 90 percent of individuals who inherit the gene for MEN 2 will develop medullary thyroid carcinoma at some point during life. There is some evidence to suggest a higher than normal incidence of medullary thyroid carcinoma in association with Hashimoto’s thyroiditis, although the mechanism of transformation is not understood.

Molecular Events Involved in the Pathogenesis of Thyroid Carcinoma

Rapid progress in the identification of cancer-causing genes over the past five years has led to a preliminary outline of molecular events likely to be important in the genesis of benign or malignant transformation of the follicular or parafollicular cells of the thyroid gland. Analogous to other neoplasms, the genes involved in the causation of thyroid carcinoma form a subset of important cell growth and differentiation regulatory factors that can arbitrarily be separated into membrane and nuclear factors (Table 2). The discussion below will focus primarily on the role of the RET proto-oncogene in the genesis of thyroid carcinoma because molecular analysis of this gene in medullary thyroid carcinoma has important clinical implications. A detailed discussion of the causative genes involved in differentiated or medullary thyroid carcinoma is provided by several recent reviews.

THE RET PROTO-ONCOGENE

Perhaps the most notable example of the involvement of membrane-related signal transduction pathways in thyroid carcinoma is the role of the RET proto-oncogene in the genesis of malignant transformation both in follicular cells (papillary thyroid...
carcinoma) and parafollicular or C cells (medullary thyroid carcinoma). Two different mutational mechanisms have been implicated in the genesis of these tumors.

**THE 'PAPILLARY THYROID CARCINOMA ONCOGENE'**

The RET proto-oncogene encodes a tyrosine kinase receptor. This gene is not normally expressed in the thyroid follicular cell. As a result of one of several gross rearrangements, the tyrosine kinase portion of the RET proto-oncogene is brought under the control of a promoter for one of three genes expressed constitutively in the thyroid follicular cell (Fig. 1). The resulting chromosome 10 rearrangements have been given the name “papillary thyroid carcinoma oncogene”

---

**Table 2**

Oncogenes Involved in the Pathogenesis of Thyroid Neoplasia

| Oncogene | Mechanism | References |
|----------|-----------|------------|
| **Defects in membrane signal transduction** | | |
| Trk-T1 | Rearrangement | 71, 72, 73 |
| MET | Overexpression | 74 |
| RET | Overexpression in PTC and point mutation in MTC | 57, 75, 76 |
| HRAS, KRAS, and NRAS | Point mutation | 77, 78 |
| GSP | Point mutation | 79, 80, 81 |
| TSH receptor | Point mutation | 82 |
| **Defects in nuclear regulatory factors** | | |
| MYC | Overexpression | 83, 84 |
| FOS | Overexpression | 83 |
| p53 | Point mutation | 85, 86, 87 |

MTC = medullary thyroid carcinoma.
PTC = papillary thyroid carcinoma.

---

Fig. 1. Molecular abnormalities of the RET proto-oncogene in papillary thyroid carcinoma (PTC) or hereditary medullary thyroid carcinoma (MTC). The RET/PTC oncogene is created by one of several chromosome 10 rearrangements that result in promoter sequences—D10S170 (H4), Rlx subunit of protein kinase A, or ele1—driving the expression of the tyrosine kinase portion of the RET proto-oncogene. In hereditary MTC, germline mutations of one of five cysteines in exons 10 or 11 (codons 609, 611, 618, 620, 634) have been identified in multiple endocrine neoplasia type 2A (MEN 2A) or familial medullary thyroid carcinoma (FMTC). A single germline mutation of the tyrosine kinase region (exon 16) that converts a methionine to a threonine at codon 918 has been identified in 98 percent of patients with multiple endocrine neoplasia type 2B (MEN 2B). This same mutation occurs as a somatic (tumor only) mutation in about 25 percent of sporadic MTC.
Breakpoint in intron 11 occurs at a point which separates extracellular and transmembrane portions from the intracellular tyrosine kinase.
(RET/PTC1, 2, and 3). In each of these rearrangements, the normal regulatory sequences for RET and the sequences encoding the extracellular domains are lost (Fig. 1). This results in expression of the tyrosine kinase at a high level in the affected thyroid follicular cell.

**RET Proto-Oncogene Point Mutations in Hereditary Medullary Thyroid Carcinoma**

The RET proto-oncogene is normally expressed in the thyroid parafollicular cell. Studies performed during the past three years have demonstrated germline point mutations of this gene in more than 95 percent of individuals with hereditary medullary thyroid carcinoma. These point mutations affect one of five cysteines (codons 609, 611, 618, 620, or 634) located in a cysteine-rich region of the RET tyrosine kinase receptor and activate it, thereby causing transformation (Fig. 1). Although not yet proven, it is thought that mutation of one of these five cysteines causes activation of the tyrosine kinase receptor, thereby initiating the transformation event. Mutation of codon 634 is the most commonly observed mutation and is found in about 80 percent of all patients with hereditary medullary thyroid carcinoma.

More recently families with familial medullary thyroid carcinoma have been found with codon 768 and 804 point mutations. A germline point mutation in the tyrosine kinase portion of the RET receptor (codon 918) has been identified in 95 percent of individuals with MEN 2B (Fig. 1). The codon 918 mutation has been identified as a somatic (tumor only) mutation in about 25 to 30 percent of individuals with sporadic medullary thyroid carcinoma.

These discoveries have already had a great impact on the management of MEN 2. It is now possible to determine whether an individual in a family with a known MEN 2A or MEN 2B mutation is a gene carrier by straightforward DNA analysis. This makes it possible to exclude family members who are not gene carriers from further screening studies.

There are several lines of reasoning that have led workers in this field to suggest that total thyroidectomy should be performed around the age of six years in children who are MEN 2A gene carriers and shortly after birth in children with the MEN 2B mutation. The most compelling argument for thyroidectomy is the finding that the lifetime penetrance for medullary thyroid carcinoma in MEN 2A and MEN 2B are 90 percent and nearly 100 percent, respectively. A second reason for early thyroidectomy is that metastasis has been observed as early as age six years in MEN 2A and at birth in MEN 2B. Finally, experience from several groups, including our own, suggests that the risk of thyroidectomy in children aged six years differs little from that in adults.

It is important to point out that the use of genetic information to manage hereditary medullary thyroid carcinoma is less than three years old, leaving open the possibility that management approaches may change as workers in the field gain greater experience. The approaches outlined above are a logical extension of early screening by pentagastatin testing used during the last 20 years to identify and treat gene carriers at the earliest possible time point. A more comprehensive discussion of the issues is available.

**Other Molecular Abnormalities Involved in Papillary, Follicular, and Anaplastic Thyroid Carcinoma**

A number of other molecular abnormalities have been identified in differentiated and anaplastic thyroid carcinoma. None of these has assumed relevance for clinical management of thyroid carcinoma, but they are of likely importance in...
the pathogenesis of this neoplasm. Table 2 provides a list of these oncogenes and detailed references for the interested reader.71-87

Diagnosis of Thyroid Carcinoma

The identification of a thyroid nodule or mass is the most common presentation for differentiated thyroid carcinoma. Clinical features that raise the level of suspicion for thyroid carcinoma include new-onset hoarseness and vocal cord paralysis, hemoptysis, and extensive lymph node enlargement.

Examination of the neck is usually remarkable for a palpable nodule that is often clinically indistinguishable from a mass associated with a benign condition. Not infrequently in adults and especially in children, the initial manifestation of thyroid carcinoma may be a palpable lymph node in the neck. Palpable metastatic adenopathy is most often found along the middle and lower portions of the jugular vein (Fig. 2, regions II, III, and IV).11,88 Nodal disease is also commonly located lateral to the sternocleidomastoid muscle in the lower portion of the posterior triangle overlying the scalene muscles (Fig. 2, regions IV and V).

Physical examination of a patient with a thyroid nodule should not be confined to the thyroid gland and the neck but should include the larynx, tongue, and cervical spine. Fiberoptic or indirect laryngoscopy should be performed to document vocal cord movement and to examine for the presence of ectopic thyroid tissue in the base of the tongue. Physical findings that might point toward a particular type of thyroid carcinoma include the presence of hypertension (medullary thyroid carcinoma), mucosal neuromas and marfanoid features (med-
illary thyroid carcinoma), and colonic polyposis (papillary thyroid carcinoma). Laboratory findings that point toward a particular diagnosis of thyroid carcinoma include hypercalcemia, hypercalciuria, and increased catecholamine production (medullary thyroid carcinoma).

A variety of diagnostic tests have been employed in an attempt to separate benign from malignant thyroid nodules, including radionuclide scanning, ultrasound, and fine-needle aspiration. Improvements in cytologic analysis over the past decade have made fine-needle aspiration the single most important procedure for assessment of a thyroid nodule.89-93

In a patient with a single thyroid nodule, the initial evaluation consists of thyroid function studies, including an ultrasensitive thyroid-stimulating hormone (TSH) measurement, thyroid antibodies, a serum calcium measurement, and a fine-needle aspiration of the palpable nodule. Ultrasound examination is performed when there is the clinical suspicion of multiple thyroid nodules, when the thyroid is difficult to evaluate by palpation, or to establish a baseline for following the size of the nodule.

A recent report suggests the usefulness of serum calcitonin measurements in the evaluation of thyroid nodules,94 although it seems clear that fine-needle aspiration is a more direct and cost-efficient method for diagnosis of medullary thyroid carcinoma. Thyroid scans, a mainstay of thyroid evaluation in the past, are now used infrequently to evaluate the thyroid gland because of their relative lack of discrimination between benign and malignant disease and the improved sensitivity of TSH assays, making it possible to detect an autonomously functioning thyroid nodule (hot nodule) or early hyperthyroidism by suppression of the serum TSH concentration. A thyroid scan is performed to identify a “hot” nodule in individuals with a suppressed serum TSH concentration.

The results of fine-needle aspiration provide the major determinant in the decision to proceed with surgery. Patients with a fine-needle aspirate indicative of malignancy are treated surgically. Individuals with a finding of a benign colloid nodule or thyroiditis are observed with or without thyroid hormone suppression. Further growth of the nodule while on thyroid hormone suppression is an indication for surgical removal. Surgical removal is also indicated when the fine-needle aspirate shows findings of a follicular neoplasm, because it is not possible to differentiate between benign and malignant follicular neoplasms with certainty without histologic examination of the entire nodule. The management of lymphoma or anaplastic thyroid carcinoma diagnosed by fine-needle aspiration is individualized and will not be discussed in this review.

It is important to emphasize that fine-needle aspiration is only a tool to be used by the clinician in the decision-making process. A decision to proceed with surgical exploration is made in up to five percent of cases where a benign fine-needle aspiration is obtained. Factors that may prompt a decision for surgical removal in the face of a benign-appearing fine-needle aspirate include the presence of a large goiter causing obstructive symptoms, the repetitive finding of a blood-filled cyst, a history of irradiation, or a family history of papillary thyroid carcinoma. In an occasional patient, anxiety regarding the possibility of thyroid carcinoma, uncalmed by a benign fine-needle aspiration result, may be an indication for surgical removal. Despite these occasional exceptions, there is clear evidence that the percentage of patients with thyroid nodules who receive surgical treatment has reduced over the past decade at our institution and others, resulting in a higher percentage of thyroid carcinoma diagnoses in the surgical procedures performed (Table 3).
We limit the use of computerized tomography (CT) or magnetic resonance imaging (MRI) to large or recurrent carcinomas suspected of invading surrounding soft tissue. These imaging techniques are essential for planning an operation in a patient with extrathyroidal extension of tumor and for determining the extent of lymph node metastasis. Neither CT nor MRI offers significant improvement of resolution over ultrasound examination, but both provide superior anatomic localization.95,96

Ultrasound examination of the thyroid and neck is an important technique for evaluation and long-term management of thyroid nodules. It is important, however, to understand the strengths and limitations of the technique to benefit most fully from its use. The technique provides the most sensitive method for characterization of thyroid nodules and lymph nodes.97,98 It is possible to determine the size, consistency (calcification or cyst), and number of thyroid nodules with certainty. In cases where a nodule or lymph node is difficult to palpate or there are multiple nodules, ultrasound-guided biopsy provides the greatest certainty for correct sampling of the nodule. The primary limitation of the technique is the necessity for a skilled operator, an individual often removed from the primary site where the patient is seen. Another limitation of ultrasound is its failure to provide anatomic guidance to the surgeon unless the surgeon participates in the imaging process.

Identification of a thyroid nodule discovered incidentally during ultrasound, CT, or MRI examination for another medical problem has occurred with increasing frequency over the past several years. In the milieu of a cancer center, these nodules most commonly are identified in a patient with an established primary malignancy of another organ previously treated with chemotherapy or

---

Table 3
Specific Indications for Surgical Intervention for Thyroid Abnormalities

- The finding or suspicion of thyroid carcinoma in a fine-needle aspirate of a thyroid nodule, especially if there is a history of prior irradiation.
- The finding of a thyroid nodule in a patient younger than 20 years or a solid thyroid nodule with atypical fine-needle aspiration features in a patient older than 60 years.
- A thyroid mass with any physical findings suggestive of malignant disease (hard fixed tumor, vocal cord paralysis, regional tissue invasion).
- Proof of metastasis to cervical lymph nodes (by fine-needle aspiration).
- Metastasis of thyroid carcinoma to a distant site.
- A hyperfunctioning thyroid nodule in a young patient.
- Unrelieved fear of thyroid carcinoma in a patient with a thyroid nodule in spite of the finding of a benign-appearing fine-needle aspirate.
radiation therapy. In addition to thyroid carcinoma, consideration must be given to the possibility of metastasis to the thyroid gland. In our institution a decision is made to proceed with fine-needle aspiration in most nodules greater than one cm in diameter.

The collective cost of the procedures described can be substantial. Sound management calls for deletion of procedures of marginal value in the evaluation of a thyroid nodule.

The Decision for Surgical Treatment

Despite the certainty that fine-needle aspiration brings to decision analysis, clinical judgment remains an important factor in the selection of patients for surgery. The presence of localized pain, especially bloody fluid, or a dominant nodule in a patient with lymphocytic or Hashimoto’s thyroiditis or Grave’s disease. Specific indications for thyroid surgery are outlined in Table 3.

A total or near-total thyroidectomy should be performed for most patients with papillary, follicular, or medullary thyroid carcinoma.

A prior history of radiation exposure, age less than 20 years, or more than 60 years, or growth of a thyroid nodule on suppressive therapy with thyroid hormone increase the likelihood of finding cancer in a thyroid nodule. The incidence of thyroid carcinoma in children or adolescents with a solitary nodule is as high as 40 percent, and there is some evidence to suggest that earlier intervention may improve prognosis. Other factors that should concern the clinician include the reaccumulation of fluid in a thyroid cyst, dysphagia, or hoarseness suggests the possibility of malignancy. Rapid enlargement of a thyroid mass, particularly when associated with dyspnea, is indicative of a more aggressive local tumor growth and should prompt consideration for surgical resection.

The Extent of Thyroidectomy

A total or near-total thyroidectomy should be performed for most patients with papillary, follicular, or medullary thyroid carcinoma. A total thyroidectomy is defined as the removal of both lobes and isthmus with preservation of parathyroid glands and superior and recurrent laryngeal nerves. Exceptions to
this recommendation include the finding of occult carcinoma or a papillary thyroid carcinoma less than 1.5 cm. We do not routinely perform a total thyroidectomy for multicentric carcinoma found on permanent sections after lobectomy for a less than 1.5 cm tumor.

Discussions regarding the necessity for total thyroidectomy are always controversial. In low-risk patients, a thyroid lobectomy may suffice for treating small (less than 1.5 cm and noninvasive) thyroid carcinomas. A recent study confirmed the safety of such an approach. We treat patients with a papillary or follicular thyroid carcinoma by total thyroidectomy when there is a history of previous radiation, gross disease in both lobes, or the presence of metastasis in regional lymph nodes or distant tissues. Our rationale for these recommendations is based on the prevention of local recurrence and the facilitation of postoperative treatment and long-term surveillance.105

Perhaps the most compelling argument for total thyroidectomy in papillary thyroid carcinoma is that central neck recurrence is less common after total thyroidectomy.16

Reasons for recurrence after lesser surgical procedures could include the presence of microscopic foci in the remaining thyroid lobe (found in 80 percent of thyroid glands in a whole organ section study performed at UT-MDACC over 30 years ago), which leads to recurrent cancer in the remaining lobe in 4.7 to 24 percent of cases. Although there is debate about the impact of recurrence on survival, 40 to 50 percent of patients who die of thyroid carcinoma do so because of recurrent disease in the central compartment of the neck, and a high percentage of patients with recurrence in the thyroid bed (as high as 50 percent) will die of their carcinoma. Finally, radioactive iodine therapy for treatment of thyroid carcinoma is more effective in the absence of thyroid tissue, and complete removal of thyroid tissue makes it possible to use plasma thyroglobulin levels to screen for recurrent carcinoma during the follow-up period.

The rationale for total thyroidectomy for medullary thyroid carcinoma is based on several important facts. First, in a patient who presents with apparent sporadic medullary thyroid carcinoma, there is about a 10 to 15 percent chance it is hereditary and, therefore, bilateral and multicentric. Second, intrathyroidal metastasis is not uncommon in sporadic medullary thyroid carcinoma. In the patient treated by lobectomy with elevated postoperative calcitonin values, there is always the question of whether disease exists in the contralateral lobe (indicating either hereditary disease or intrathyroidal metastasis) or in extrathyroidal sites such as lymph nodes. These issues are more readily addressed if total thyroidectomy is performed at the time of primary surgery.

An infrequent but recurring dilemma following thyroid lobectomy for an apparent benign nodule is the identification of papillary thyroid carcinoma in the nodule on the final histologic sections. Lobectomy is considered adequate treatment in this clinical situation if the papillary thyroid carcinoma is less than 1.5 cm in diameter with no evidence of multcentricity or metastasis. Our practice is to complete the thyroidectomy in all other patients.

GOALS OF SURGICAL INTERVENTION

The primary surgical approach should focus on the thyroid lobe containing the suspicious nodule(s). During a meticulous dissection of the affected side, the recurrent laryngeal nerve is identified and protected, followed by resection of the isthmus and ipsilateral lobe. Parathyroid tissue is identified and preserved except in instances where there is extensive invasion by cancer or extensive metastasis in the paratracheal area. In patients with a nodule greater than 1.5 cm show-
ing papillary thyroid carcinoma or evi-
dence of local metastasis, a total thy-
roidectomy is completed by resection of
the opposite lobe with particular care to
identify and preserve parathyroid tissue
and vasculature.

We routinely examine the posterior
surface of the thyroid gland for parathy-
roid tissue by loupe magnification and
send a piece of any tissue identified for
frozen-section examination. Tissue
proven to be parathyroid gland is minced
and implanted in a small pocket created
in the sternocleidomastoid muscle.

We also advocate a compartmental
lymph node dissection (interjugulo-par-
atracheal nodal dissection). Performance
of this procedure during the primary sur-
gical procedure makes it less likely to be
required on a subsequent reexploration if
there is a recurrence (Fig. 3).

It is important to preserve all
parathyroid tissue, and if during the dis-
section the vascular supply of the
parathyroid gland becomes compromised
or is removed with the specimen, we rec-
ommend identification of it through
frozen-section examination of a portion
of it and reimplantation of the gland into
muscle tissue, either at the surgical site or
in the forearm.109

Judgment is required when balanc-
ing the necessity for a complete thyroid
cancer removal and lymph node dissec-
tion against the possibility of permanent
hypoparathyroidism caused by such a re-
moval. The recurrent laryngeal nerves
should be preserved whenever possible,
and the superior laryngeal nerves, which
usually run parallel to the superior vascu-
lar pedicle of the gland, should be identi-
ified and preserved as well.

Local invasion of tissues surround-
ing the thyroid gland is rare, but when
present it is a significant cause of morbidi-
ty and mortality. It is important to define
the extent of extrathyroidal extension of
thyroid carcinoma and determine whether
surgical removal is feasible. During pri-
mary surgery, it is important to determine
whether it is necessary to resect laryngeal
nerves, tracheal rings, or portions of the
larynx.110-116 In most cases resection of
these structures is indicated if there is in-
volvement by thyroid carcinoma, and
these indications are discussed in detail
with the patient prior to surgery.117 Al-
though radioactive iodine and external-
beam radiation are excellent adjuvant
forms of therapy, permitting narrower
margins than are commonly employed in
squamous carcinoma, the optimal goal of
surgery is to completely remove all iden-
tifiable carcinoma.

**NECK DISSECTION**

A decision to proceed with neck dissec-
tion should be based on the type of thy-
roid carcinoma and evidence of tumor ex-
tension to local lymph nodes.11,17,96 There
are several general observations that
make decision making easier. Palpable
papillary or medullary thyroid carcinoma
metastasizes to regional lymph nodes fre-
quently, while follicular thyroid carcino-
ma does so rarely. Careful preoperative
assessment of lymph nodes by ultrasound
and fine-needle biopsy or intraoperative

![Fig. 3. Diagram illustrating the lymph node
groups at highest risk for regional metastasis
from differentiated thyroid carcinoma. (Reproduced with permission from Cancer
of the Head and Neck, W.B. Saunders
Company.)](image-url)
inspection and biopsy is important to determine the necessity for dissection. Elective dissection of lymph node tissue for papillary thyroid carcinoma in the absence of demonstrable metastasis is of dubious value, whereas dissection is of value for cases in which metastasis is identified. In most cases it will be necessary to examine and biopsy central or other compartment lymph nodes to make a determination regarding the presence of metastasis (Fig. 3).

There are several lymph node groups that form the most likely route of lymphatic spread and should be considered for inclusion in a neck dissection. The so-called central or interjugular tracheal compartment forms the primary route for lymph node metastasis because of its proximity to the thyroid gland and pathway of lymph drainage. A second frequent route of lymphatic spread involves the nodes along the jugular vein from the subdigastic area to the root of the neck (levels II through IV, Fig. 2). A third common route of lymphatic spread is along the pathway of the inferior thyroid artery behind the common carotid artery and to the lower portion of the posterior triangle of the neck (level V, Fig. 2). A dissection strategy is planned to include these areas. This type of dissection differs from the classic radical neck dissection in that it does not include removal of internal jugular veins, sternocleidomastoid muscle, or the spinal accessory nerve. There is no evidence that a radical dissection improves outcome in most patients with thyroid cancer, although in a rare patient with direct extension of tumor into one of these structures, removal may be indicated. Dissection of the level I or submandibular triangle nodes is seldom necessary.

It is also prudent to perform a central compartment lymph node dissection in patients with palpable medullary thyroid carcinoma because of the high probability of regional lymph node metastasis. This is true for both hereditary and sporadic medullary thyroid carcinoma. Medullary thyroid carcinoma differs from most other head and neck tumors because the measurement of serum calcitonin provides a sensitive and relatively specific tumor marker.

A major question confronting the surgeon at the time of primary exploration is whether a more extensive lymph node dissection for medullary thyroid carcinoma will alter the clinical course of the disease. Experience in several centers over the past decade indicates that 15 to 20 percent of patients with limited nodal metastasis can be cured by extensive lymph node dissection, suggesting that consideration should be given to performing this procedure at the time of primary surgery. If extensive lymph node removal is considered, it is important to exclude the presence of distant metastasis prior to surgery by performance of CT, MRI, or octreotide scans of the neck, chest, and abdomen because extensive lymph node dissection is generally not indicated in patients with distant metastasis except for local control of disease.

Total thyroidectomy and lymph node dissection are generally well tolerated and may require a hospitalization of less than 24 hours for thyroidectomy and two to three days when combined with neck dissection. It is important to monitor the serum calcium concentration in the postoperative period and provide calcium and/or vitamin D supplementation if hypocalcemia develops. In an attempt to shorten the length of hospitalization, we begin calcium carbonate (1 to 2 g three times a day) and oral 1,25 dihydroxy vitamin D$_3$ supplementation (0.5 μg orally three times a day) if the calcium remains below 7.5 mg more than 24 hours after the conclusion of the operation. If the serum calcium returns to normal in the first 48 to 72 hours postoperatively, this supplementation is discontinued. Thyroid hormone supplementation is generally deferred until a final decision has been made regarding adjunctive radioactive iodine therapy.
Fig. 4. Impact of radioactive iodine (RAI) on recurrence and survival rates in papillary thyroid carcinoma. These results were updated and replotted from data presented in Samaan et al.\textsuperscript{21}
Postoperative Management of Thyroid Carcinoma

RADIOACTIVE IODINE THERAPY

Experience over the past 40 years with radioactive iodine (RAI) therapy in many centers has demonstrated a significant effect on survival and recurrence rates in papillary and follicular thyroid carcinoma, although there is some controversy.22,122-124 The UT-MDACC recognized the potential value of RAI treatment and has used this therapeutic modality in more than 50 percent of patients treated for thyroid cancer over the past 35 to 40 years,3,21 although patients with thyroid carcinoma limited to the thyroid gland have been less likely to receive RAI.

The practice at the UT-MDACC for patients who have received a total thyroidectomy and have a tumor size greater than 2.0 cm has been to ablate residual thyroid tissue with 100 mCi RAI and to treat residual tumor with a dose of 150 mCi. Total-body radioactive iodine scans are repeated at six-month intervals until there is no uptake or the patient has received a total dose approximating 500 mCi RAI.

Figure 4 shows the effect of radioactive iodine therapy on both survival and recurrence in three groups of patients: those with disease limited to the thyroid gland, patients with metastasis to lymph

---

Table 4
Schedule for Long-Term Management of Papillary Thyroid Carcinoma

| Initial treatment |
|-------------------|
| Surgical management and treatment with radioactive iodine one or more times (see text) |

| Long-term |
|-----------|
| Years 1-3 | Clinical examination, serum thyroxine, T₃ resin, thyroid-stimulating hormone, and thyroglobulin every six months. Baseline and yearly neck ultrasound and chest x-ray |
| Years 4-10 | Clinical examination, serum thyroxine, T₃ resin, thyroid-stimulating hormone, thyroglobulin, and chest x-ray annually. Neck ultrasound examination every two years |
| Years 11-20 | Clinical examination, serum thyroxine, T₃ resin, thyroid-stimulating hormone, and thyroglobulin annually. Chest x-ray and neck ultrasound examination every three years |
| Years 21-40 | Clinical examination, serum thyroxine, T₃ resin, thyroid-stimulating hormone, thyroglobulin annually. Chest x-ray and neck ultrasound examination every three to five years |
nodes, and patients with extension to soft
tissue of the neck. Although these sur-
vival curves are not adjusted for particu-
lar risk factors, in each of the groups ra-
dioactive iodine therapy had an effect on
the rate of recurrence and survival. It is
only in those patients with extension to
soft tissue of the neck that the impact of
radioactive iodine does not reach statisti-
cal significance.21 Although these data are
retrospective and the populations includ-
ed are heterogeneous, the results support
a role for RAI in the postoperative man-
agement of papillary and follicular thy-
roid carcinoma and mirror results from
other centers.

We routinely withhold thyroid hor-
monal therapy for a four- to six-week peri-
od following total thyroidectomy in pa-
tients who have tumors greater than 1.5
to 2.0 cm and perform a total body scan
following administration of 5 mCi of sodi-
um iodide I 131. Patients with positive
scans are generally treated with 100 mCi
of radioactive iodine or 150 mCi if there is
obvious uptake in lymph nodes or an ex-
trathyroidal area of metastasis. The pa-
tient is rescanned in six to eight months
and retreated with 100 to 150 mCi if there
is residual (defined as greater than two
percent of administered dose) or newly
developed uptake. This process may be
repeated several times, although a total
dose of greater than 500 to 600 mCi is
rarely given. Most commonly one or two
treatments with radioactive iodine will
eliminate any residual uptake. The recent
positive experience with recombinant
TSH to stimulate radioactive iodine up-
take in patients with thyroid cancer sug-
gests that cessation of thyroid hormone
may be unnecessary in the future.125,126

LONG-TERM FOLLOW-UP

Papillary thyroid carcinoma is a rare
cause of death, in part because of the
generally benign course of the disease
and in part because of the success of
treatment of recurrence.26 Detection and
treatment of such recurrences play an
important role in the prevention of mor-
bidity and mortality from papillary thy-
roid carcinoma.

General experience, including our
own, suggests that no single diagnostic
tool will detect all recurrences.97,125 We
apply a series of overlapping strategies
that include clinical examination, serum
thyroglobulin measurements, ultrasound
examination, and chest roentgenography
on a periodic basis to detect recurrence of
tumor. Ultrasound use has led to periodic
identification of recurrent disease in pa-
tients with no evidence of RAI uptake
and normal thyroglobulin levels. The fre-
cency of follow-up examinations is
greatest during the first three to four
years following surgery, the time period
during which a recurrence is most likely
to occur, and less in subsequent years and
decades (Table 4). The appearance of tu-
mor recurrence in an occasional patient
decades after the initial treatment sug-
gests that surveillance should not be dis-
continued but performed less frequently
when a decade or more has passed with
no evidence of relapse.

We do not routinely perform total-
body radioactive iodine scans for follow-
up once the patient has a negative scan.
Our experience indicates that most recur-
rent tumors following radioactive iodine
therapy do not concentrate iodine, mak-
ing regular RAI scanning of dubious val-
ue. When this observation is combined
with the debilitating symptoms of hy-
pothyroidism caused by discontinuance
of thyroid hormone, enthusiasm for rou-
tine follow-up scans falls further. We do
perform RAI scanning in patients with a
rising thyroglobulin or other evidence of
recurrent thyroid carcinoma because of
the small possibility that radioactive io-
dine uptake may provide an additional
therapeutic modality.

Long-term follow-up for medullary
thyroid carcinoma is dependent on the
extent of disease at the time of primary
surgery. In those patients with intrathy-
roidal disease and no detectable calcitonin after a provocative pentagastrin injection, a periodic pentagastrin test measurement and clinical examination may suffice. In patients with local lymph node metastasis at the time of primary thyroidectomy and elevated calcitonin values postoperatively, we perform periodic ultrasound examinations to identify local recurrence.

Another important component of long-term management of medullary thyroid carcinoma is to identify individuals with hereditary medullary thyroid carcinoma. Preliminary analyses suggest that five to six percent of patients previously considered to have sporadic medullary thyroid cancer have RET proto-oncogene molecular abnormalities indicative of hereditary medullary thyroid carcinoma (R.F. Gagel, unpublished observations). Molecular analysis of the RET proto-oncogene, a commercially available test performed on a single blood sample from the affected patient, makes it possible to exclude hereditary medullary thyroid carcinoma with 99 percent certainty.64,66 It seems likely that this analysis will become a routine part of the evaluation of a patient with apparent sporadic medullary thyroid carcinoma. In individuals with a RET proto-oncogene mutation, the analysis should be expanded to determine whether the gene has been transmitted within the family. It is particularly important to study children and young adults because thyroidectomy in gene carriers at this age is most likely to result in cure.

**MANAGEMENT OF RECURRENT THYROID CARCINOMA**

The most common site of recurrence for papillary thyroid carcinoma is in lymph nodes of the neck. Recurrence is most commonly detected by clinical or ultrasound examination. The primary therapy is surgical removal of the affected node with consideration of a more extensive lymph node dissection on the side of recurrence if not previously performed. Four to six weeks following surgical removal of the recurrence and cessation of thyroid hormone therapy, a total-body radioactive iodine scan is performed to determine whether additional radioactive iodine therapy might be beneficial.

Management of recurrent disease in which there is invasion of soft tissue, larynx, trachea, esophagus, or other structures in the neck or upper mediastinum must be individualized. A wide variety of techniques have been developed to remove and reconstruct or replace parts of the trachea, larynx, or esophagus and are routinely employed at our institution.110-116 A discussion of the indication and use of these techniques is beyond the scope of this review. In patients with extension of tumor into neck structures, external-beam radiation is considered in addition to radioactive iodine therapy.21,127

Chemotherapy is considered in patients with a large papillary thyroid carcinoma following primary thyroidectomy, aggressive tumor that cannot be removed by surgical excision, or metastatic tumor that is disseminated and does not take up radioactive iodine.5,128

**Summary**

A wealth of knowledge regarding the molecular causation of thyroid carcinoma has been accumulated over the past five years. This information has already had a significant impact on the management of some forms of thyroid carcinoma. The challenge during the next 10 years will be to incorporate newly acquired information into diagnostic and therapeutic approaches to thyroid carcinoma and to coordinate use of this information with time-tested approaches to further decrease morbidity and mortality from thyroid carcinoma.
References

1. Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics, 1996. CA Cancer J Clin 1996;46:5-27.

2. Beenenk S, Guillamondegu O, Shallenberger R, et al: Diagnostic factors in patients dying of well-differentiated thyroid cancer. Arch Otolaryngol Head Neck Surg 1989;115:326-330.

3. Frankenthaler RA, Sellin RV, Cangir A, Goepfert H: Lymph node metastasis from papillary-follicular thyroid carcinoma in young patients. Am J Surg 1990;160:341-343.

4. Samaan NA, Maheshwari YK, Nader S, et al: Impact of therapy for differentiated carcinoma of the thyroid: An analysis of 706 cases. J Clin Endocrinol Metab 1983;56:131-138.

5. Maheshwari YK, Hill CS, Haynie TP III, et al: 13I therapy in differentiated thyroid carcinoma: M. D. Anderson Hospital experience. Cancer 1981;47:664-671.

6. Venkatesh YS, Ordonez NG, Schultz PN, et al: Anaplastic carcinoma of the thyroid: A clinicopathologic study of 121 cases. Cancer 1990;66:321-330.

7. Goepfert H, Dichtel WJ, Samaan NA: Thyroid cancer in children and teenagers. Arch Otolaryngol 1984;110:72-75.

8. Vassilopoulou-Sellin R, Klein MJ, Smith TH, et al: Pulmonary metastases in children and young adults with differentiated thyroid carcinoma. Cancer 1993;71:1348-1352.

9. Samaan NA, Schultz PN, Haynie TP, Ordonez NG: Pulmonary metastasis of differentiated thyroid carcinoma: Treatment results in 101 patients. J Clin Endocrinol Metab 1985;60:376-380.

10. Samaan NA, Schultz PN, Ordonez NG, et al: A comparison of thyroid carcinoma in those who have and have not had head and neck irradiation in childhood. J Clin Endocrinol Metab 1987;64:219-223.

11. Frankenthaler R, Goepfert H, Smith RJH: Papillary and follicular carcinoma of the thyroid in children and adolescents, in Falk SA (ed): Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy. New York, Raven Press Ltd, 1990, pp 553-561.

12. LiVolsi VA: Surgical Pathology of the Thyroid. Philadelphia, WB Saunders Co, 1990.

13. LiVolsi VA, Asa SL: The demise of follicular carcinoma of the thyroid. Thyroid 1994;4:233-236.

14. Tennvall J, Birkklund A, Moller T, et al: Is the EORTC prognostic index of thyroid cancer valid in differentiated thyroid carcinoma? Retrospective multivariate analysis of differentiated thyroid carcinoma with long follow-up. Cancer 1986;57:1405-1414.

15. Cady B, Rossi R: An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988;104:947-953.

16. Tollefson HR, Shah JP, Huvos AG: Papillary carcinoma of the thyroid: Recurrence in the thyroid gland after initial surgical treatment. Am J Surg 1972;124:468-472.

17. Simpson WJ, McKinney SE, Carruthers JS, et al: Papillary and follicular thyroid cancer: Prognostic factors in 1,578 patients. Am J Med 1987;83:479-488.

18. Sloan LW: Of origin, characteristics, and behavior of thyroid cancer. J Clin Endocrinol Metab 1954;14:1309-1335.

19. DeGroot L, Kaplan EL, Straus FH: Does the method of management of papillary thyroid carcinoma make a difference in outcome? World J Surg 1994;18:123-130.

20. Rosen IB, Luk S, Katz I: Hurthle cell tumor behavior: Dilemma and resolution. Surgery 1985;98:777-783.

21. Samaan NA, Schultz PN, Hickey RC, et al: The results of various modalities of treatment of well differentiated thyroid carcinomas: A retrospective review of 1599 patients. J Clin Endocrinol Metab 1992;75:714-720.

22. Hay ID: Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19:545-576.

23. Hay ID, Grant CS, Taylor WF, McConahey WM: Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: A retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102:1088.

24. Hay ID, Bergrstrahl EJ, Goellner JR, et al: Predicting outcome in papillary thyroid carcinoma: Development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050.

25. DeGroot LJ, Kaplan EL, McCormick M, et al: Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;75:414-424.

26. Mazzaferrri EL, Jhiang SM: Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-428.

27. Hannequin P, Liehn JC, Delisle MJ: Multifactorial analysis of survival in thyroid cancer: Pitfalls of applying the results of published studies to another population. Cancer 1986;58:1749-1755.

28. Modan B: Cancer and leukemia risks after low level radiation—controversy, facts and future. Med Oncol Tumor Pharmacother 1987;4:151-161.

29. Reizenstein P: Carcinogenicity of radiation and prevention of possible tumors. Med Oncol Tumor Pharmacother 1987;4:151-161.

30. Wright PA, Williams ED, Lemoine NR, Wynford-Thomas D: Radiation-associated and prediction of oncogenic risk of the irradiation of the thyroid gland in humans. Vestn Akad Med Nauk SSSR 1991;1991:32-36.

31. Zvonova IA, Likhtarev IA, Filiushkin IV, et al: Assessment of oncogenic risk of the irradiation of the thyroid gland in humans. Vestn Akad Med Nauk SSSR 1991;1991:32-36.
33. Brennan M: USSR: Medical effects of Chernobyl disaster. Lancet 1990;335:1086. News
34. Baverstock K, Egloff B, Pinchera A, et al: Thyroid cancer after Chernobyl. Nature 1992;359:21-22. Letter.
35. Malone J, Unger J, Delange F, et al: Thyroid consequences of Chernobyl accident in the countries of the European Community. J Endocrinol Invest 1991;14:701-717.
36. Furmanchuk AW, Averkin JI, Egloff B, et al: Pathomorphological findings in thyroid cancers of children from the Republic of Belarus: A study of 86 cases occurring between 1986 (‘post-Chernobyl’) and 1991. Histopathology 1992;21:401-408.
37. Furmanchuk AW, Roussak N, Ruchti C: Occult thyroid carcinomas in the region of Minsk, Belarus: An autopsy study of 215 patients. Histopathology 1993:23:319-325.
38. Romanenko AE, Likhtarov IA, Shandala NK, et al: Health-related evaluation of thyroid irradiation doses in inhabitants of the Ukrainian S.S.R. after the Chernobyl AES accident. Vestn Akad Med Nauk SSSR 1991;8:44-47.
39. Franceschi S, Talamini R, Fassina A, Bidoli E: Diet and epithelial cancer of the thyroid gland. Tumori 1990;76:331-338.
40. Gaitan E, Nelson NC, Poole GV: Endemic goiter and endemic thyroid disorders. World J Surg 1991;15:205-215.
41. Mizukami Y, Michigishi T, Nonomura A, et al: Carcinoma of the thyroid at a young age: A review of 23 patients. Histopathology 1992;20:63-66.
42. Ott RA, Calandra DB, McCall A, et al: The incidence of thyroid carcinoma in patients with Hashimoto’s thyroiditis and solitary cold nodules. Surgery 1985;98:1202-1206.
43. Plail RO, Bussey HJ, Glazer F, Thomson JP: Adenomatous polyposis: An association with carcinoma of the thyroid. Br J Surg 1987;74:377-380.
44. Camiel MR, Mule JE, Alexander LL, Beninghoff DL: Association of thyroid carcinoma with Gardner’s syndrome in siblings. N Engl J Med 1991;324:1050-1058.
45. Mogil RL, Sugarawa M, Gordon HE, et al: Cowden’s disease: Familial goiter and skin hamartomas: A report of three cases. West J Med 1983;139:324-328.
46. McTiernan A, Weiss NS, Daling JR: Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. Cancer Res 1987;47:292-295.
47. Lote K, Andersen K, Nordal E, Brennhovd IO: Familial occurrence of papillary thyroid carcinoma. Cancer 1980;46:1291-1297.
48. Stoff SS, Van Dyke DL, Bach JV, et al: Familial papillary carcinoma of the thyroid. Am J Med Genet 1986;278:1055-1058.
49. Steiner AL, Goodman AD, Powers SR: Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing’s disease: Multiple endocrine neoplasia, type 2. Medicine 1968;47:371-409.
50. Sipple JH: Multiple endocrine neoplasia type 2 syndromes: Historical perspectives. Henry Ford Hosp Med J 1984:32:219-221.
51. Carney JA, Sizemore GW, Hayles AB: Multiple endocrine neoplasia, type 2b. Pathobiol Annu 1978;8:105-153.
52. Farrond JR, Leight GS, Dilley WG, et al: Familial medullary thyroid carcinoma without associated endocrinopathies: A distinct clinical entity. Br J Surg 1986;73:278-281.
53. Weiss LM, Weinberg DS: Medullary carcinoma arising in a thyroid with Hashimoto’s disease. Am J Clin Pathol 1983;80:534-538.
54. Biddinger PW, Brennan MF, Rosen PP: Symptomatic C-cell hyperplasia associated with chronic lymphocytic thyroiditis. Am J Surg Pathol 1991;15:590-604.
55. Farid NR, Shi Y, Zou M: Molecular basis of thyroid cancer. Endocr Rev 1994:15:202-232.
56. Wynford-Thomas D: Molecular basis of epithelial tumorigenesis: The thyroid model. Crit Rev Oncog 1993;4:1-23.
57. Cote GJ, Wohlk N, Evans D, et al: RET proto-oncogene mutations in multiple endocrine neoplasia type 2 and medullary thyroid carcinoma. Baillieres Clin Endocrinol Metab 1995;9:609-630.
58. Ishizaka Y, Ushijima T, Sugimura T, Nagao M: cDNA cloning and characterization of RET activated in a human papillary thyroid carcinoma cell line. Biochem Biophys Res Commun 1990;168:402-408.
59. Pierotti MA, Santoro M, Jenkins RB, et al: Characterization of an inversion on the long arm of chromosome 10 juxtaposing D10S170 and RET and creating the oncogenic sequence RET/PTC. Proc Natl Acad Sci U S A 1992;89:1616-1620.
60. Grieco M, Santoro M, Berlingieri MT, et al: PTC is a novel rearranged form of the RET proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. Cell 1990:60: 557-563.
61. Bongarzone I, Butti MG, Coronelli S, et al: Frequent activation of ret protooncogene by fusion with a new activating gene in papillary thyroid carcinomas. Cancer Res 1993;53:7787-7795.
62. Donis-Keller H, Dou S, Chi D, et al: Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993;2:851-856.
63. Mulligan LM, Kwok JB, Healey CS, et al: Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363:458-460.
64. Baglin RF, Cote GJ, Martinis Bugalho MJ, et al: Clinical use of molecular information in the management of multiple endocrine neoplasia type 2A. J Intern Med 1995;238:333-341.
65. Mulligan LM, Eng C, Healey CS, et al: Specific mutations in the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet 1994;6:70-74.
66. Baglin RF, Cote GC: Decision making in multiple endocrine neoplasia type 2, in Mazzaferr E (ed): Advances in Endocrinology and Metabolism, Volume 5. St. Louis, Mo, Mosby, 1994, pp 1-23.
67. Eng C, Smith DP, Mulligan LM, et al: A novel point mutation in the tyrosine kinase domain of the RET proto-oncogene in sporadic medullary thyroid carcinoma and in a family with FMTC. Oncogene 1995;10:509-513.
68. Hofstra RM, Landsvater RM, Ceccherini I, et al: A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 1994; 367:375-376.
69. Khorana S, Gagel RF, Cote CJ: Direct sequencing of PCR products in agarose gel slices. Nucleic Acids Res 1994;22:3425-3426.
70. Wells SA Jr, Chi DD, Toshima K, et al: Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. Ann Surg 1994;220:237-250.
71. Santoro M, Carlomagno F, Hay ID, et al: Overexpression of the c-MET/HGF receptor gene in human thyroid papillary carcinoma. Oncogene 1994;9:1457-1462.
72. Collier F, Martin-Zanca D, Ernst M, Barbacid M: Mechanism of activation of the human TRK oncogene. Mol Cell Biol 1989;9:15-23.
73. Greco A, Pierotti MA, Bongarzone I, et al: TRK-T1 is a novel oncogene formed by the fusion of TPR and TRK genes in human papillary thyroid carcinomas. Oncogene 1992;7:237-242.
74. Di Renzo MF, Olivero M, Ferro S, et al: Overexpression of the c-MET/HGF receptor gene in human thyroid carcinomas. Oncogene 1992;7:2549-2553.
75. Santoro M, Carломagno F, Hay ID, et al: RET oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype. J Clin Invest 1992;89:1517-1522.
76. Jhiang SM, Caruso DR, Gilmore E, et al: Detection of the PTC/ret/TPC oncogene in human thyroid carcinomas. Oncogene 1992;7:1331-1337.
77. Karga H, Lee JK, Vickery AL Jr, et al: Ras oncogene mutations in benign and malignant thyroid neoplasms. J Clin Endocrinol Metab 1991;73: 885-886.
78. Wright PA, Lemoine NR, Mayall ES, et al: Papillary and follicular thyroid carcinomas show a different pattern of ras oncogene mutation. Br J Cancer 1989;60:576-577.
79. Goretzki PE, Lyons J, Stacy-Plivp S, et al: Mutational activation of RAS and GSP oncogenes in differentiated thyroid cancer and their biological implications. World J Surg 1992;16:576-582.
80. O’Sullivan C, Barton CM, Staddon SL, et al: Activating point mutations of the gsp oncogene in human thyroid adenomas. Mol Carcinog 1991;4: 345-349.
81. Suarez HG, du Villard JA, Caillou B, et al: GSP mutations in human thyroid tumours. Oncogene 1991;6:677-679.
82. Parma J, Duprez L, Van Sande J, et al: Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature 1993; 365:649-651.
83. del Senno L, Gambari R, degli Uberti E, et al: C-myc oncogene alterations in human thyroid carcinomas. Cancer Detect Prev 1987;10:159-166.
84. Terrier P, Sieng ZZ, Schlumberger M, et al: Structure and expression of c-myc and c-fos proto-oncogenes in thyroid carcinomas. Br J Cancer 1988; 57:43-47.
85. Chang F, Suryanen S, Kurvinen K, Suryanen K: The p53 tumor suppressor gene as a common cellular target in human carcinogenesis. Am J Pathol 1993;88:174-186.
86. Fagin JA, Matsuo K, Karmakar A, et al: High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. J Clin Invest 1993;91:179-184.
87. Ito T, Seyama T, Mizuno T, et al: Unique association of p53 mutations with undifferentiated but not with differentiated carcinomas of the thyroid gland. Cancer Res 1992;52:1369-1371.
88. Cucchiarelli C, Pacini F, Lippi F, et al: Thyroid cancer in children and adolescents. Surgery 1988;104:1143-1148.
89. Grant CS, Hay ID, Gough IR, et al: Long-term follow-up of patients with benign thyroid fine-needle aspiration cytologic diagnoses. Surgery 1989; 106:980-986.
90. Hamburger JJ: Consistency of sequential needle biopsy findings for thyroid nodules. Management implications. Arch Intern Med 1987;147:97-99.
91. Hamburger JJ, Husain M: Semiquantitative criteria for fine-needle biopsy diagnosis: Reduced false-negative diagnoses. Diagn Cytopathol 1988; 4:14-17.
92. Piromalli D, Martelli G, Del Prato I, et al: The role of fine needle aspiration in the diagnosis of thyroid nodules: Analysis of 795 consecutive cases. J Surg Oncol 1992;50:247-250.
93. Walchsh PG, Hazani E, Strawbridge HT, et al: Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. Ann Intern Med 1977; 87:270-274.
94. Pacini F, Fontanelli M, Fugazzola L, et al: Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab 1994;78:826-829.
95. Leeper RD: Thyroid cancer. Med Clin North Am 1985;69:1079-1096.
96. Strong EW: Evaluation and surgical treatment of papillary and follicular carcinoma, in Falk SA (ed): Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy. New York, Raven Press, Ltd., 1990, pp 485-499.
97. Ross DS: Long-term management of differentiated thyroid cancer. Endocrinology Clinics of North America 1990;19:719-739.
98. Jongenelen JF, van der Hulst J, Edmonds CJ, et al: Comparison of fine needle aspiration cytology, radiostereotopic and ultrasound scanning in the management of thyroid nodules. Postgrad Med J 1990;66:914-917.
99. Bretzel RG, Schatz H: Prognostic factors in thyroid cancer. Zentralbl Chir 1985;110:1304-1314.
100. Rosen IB, Provias JP, Wallfish PG: Pathologic nature of cystic thyroid nodules selected for surgery by needle aspiration biopsy. Surgery 1986;100:606-613.
101. Ravinsky E, Safneck JR: Differentiation of Hashimoto's thyroiditis from thyroid neoplasms in fine needle aspirates. Acta Cytol 1988;32:854-861.
102. Nishiyama RH, Ludwig GK, Thompson NK: The prevalence of small papillary thyroid carcinomas in 100 consecutive necropsies in an American population, in DeGroot LJ, Frohman LA, Kaplan EL (ed): Radiation-Associated Thyroid Carcinoma. New York, NY, Grune and Stratton, 1977, p 123.
103. Sampson RJ, Woolner LB, Bahn RG, et al: Occult thyroid carcinoma in Olmsted County, Minnesota: Prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. Cancer 1974;34:2072-2076.
104. Shah JP, Loree TR, Dharker D, et al: Lobectomy versus total thyroidectomy for differentiated carcinoma of the thyroid: A matched-pair analysis. Am J Surg 1993;166:331-335.
105. Clark OH, Levin K, Zeng QH, et al: Thyroid cancer: The case for total thyroidectomy. Eur J Cancer 1988;24:305-313.
106. van der Velde CJH, Hamming JF, Goslings BM, et al: Report of the consensus development conference on the management of differentiated thyroid cancer in the Netherlands. Eur J Cancer 1988;24:87-94.
107. Donovan DT, Gagel RF: Medullary thyroid carcinoma and the multiple endocrine neoplasia syndromes, in Falk SA (ed): Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy. New York, NY, Raven Press, Ltd, 1990, pp 501-525.
108. Grauer A, Raue F, Gagel RF: Changing concepts in the management of hereditary and sporadic medullary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19:613-635.
109. Wells SA Jr, Gunnels JC, Shelburne JD, et al: Transplantation of the parathyroid glands in man: Clinical indications and results. Surgery 1975;78:34-44.
110. Drale H, Scheumann GF, Meyer HJ, et al: Cervical interventions on the airway and esophagus in infiltrating thyroid cancer. Chirurgie 1992;63:282-290.
111. Ishihara T, Kobayashi K, Kikuchi K, et al: Surgical treatment of advanced thyroid carcinoma invading the trachea. J Thorac Cardiovasc Surg 1991;102:717-720.
112. Yoshimura Y, Nakajima T: Tracheoplasty with palatal mucoperiosteal graft. Plast Reconstr Surg 1990;86:558-562.
113. McCaffrey TV, Lipton RJ: Thyroid carcinoma invading the upper aerodigestive system. Laryngoscope 1990;100:824-830.
114. Friedman M: Surgical management of thyroid carcinoma with laryngotracheal invasion. Otolaryngol Clin North Am 1990;23:495-507.
115. Nomori H, Kobayashi K, Ishihara T, et al: Thyroid carcinoma infiltrating the trachea: Clinical, histologic, and morphometric analyses. J Surg Oncol 1990;44:78-83.
116. Segal K, Abraham A, Levy R, Schindel J: Carcinomas of the thyroid gland invading larynx and trachea. Clin Otolaryngol 1984;9:21-25.
117. Breaux EP, Guillamondegui OM: Treatment of locally invasive carcinoma of the thyroid: How radical? Am J Surg 1980;140:514-517.
118. Robbins KT: Pocket guide to neck dissection: Classification and TNM staging of head and neck cancer. Alexandria, VA, American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc., 1991.
119. Miller HH, Melvin KE, Gibson JM, Tashjian AH Jr: Surgical approach to early familial medullary carcinoma of the thyroid gland. Am J Surg 1972;123:438-443.
120. Samaan NA, Schultz PN, Hickey RC: Medullary thyroid carcinoma: Prognosis of familial versus nonfamilial disease and the role of radiotherapy. Horm Metab Res Suppl 1989;21:21-25.
121. Tisel LE, Hansson G, Jansson S, Salander H: Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. Surgery 1986;99:60-66.
122. Mazzaferri EL: Papillary thyroid carcinoma: Factors influencing prognosis and current therapy. Semin Oncol 1987;14:315-332.
123. Silver CE, Strong EW, Guillamondegui OM, et al: Papillary thyroid carcinoma. Contemp Surg 1988;32:107.
124. Snyder J, Gorman C, Scanlon P: Thyroid remnant ablation: Questionable pursuit of an ill-defined goal. J Nucl Med 1983;24:659-665.
125. Joshi L, Murata Y, Wondisford FE, et al: Recombinant thyrotropin containing a beta-subunit chimera with the human chorionic gonadotropin-beta carboxy-terminus is biologically active, with a prolonged plasma half-life. Endocrinology 1995;136:3839-3848.
126. Thotakura NR, Desai RK, Bates LG, et al: Biological activity and metabolic clearance of a recombinant human thyrotropin produced in Chinese hamster ovary cells. Endocrinology 1991;128:341-348.
127. Tubiana M, Haddad E, Schlumberger M, et al: External radiotherapy in thyroid cancers. Cancer 1985;55:2062-2071.
128. Gottlieb JA, Hill CSJ: Chemotherapy of thyroid cancer with adriamycin: Experience with 30 patients. N Engl J Med 1974;290:193-197.