

# THYROID TODAY

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## THYROID CANCER: AN OVERVIEW

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Thyroid carcinoma encompasses a group of widely differing diseases ranging from slow-growing, well-differentiated neoplasms that have an excellent prognosis to anaplastic thyroid cancers that have a dismal outcome. This review, however, will be principally concerned with the differentiated forms of thyroid cancer which are clearly the most common of the thyroid cancers and of most immediate concern to the practicing physician.

### Papillary Thyroid Cancer

**Background:** The diagnosis and therapy of well-differentiated forms of thyroid cancer—papillary and follicular thyroid carcinomas—continue to be the subject of lively debate. Because well-differentiated thyroid carcinomas tend to grow slowly, they are often difficult to clinically differentiate from benign thyroid nodules. In addition, the differentiated thyroid carcinomas ordinarily are associated with an excellent prognosis, making assessment of the impact of therapy difficult. However, an understanding of the clinical behavior and prognosis of these tumors can lead to both effective selection of patients for surgery and a reasonable approach to therapy.

\*This discussion will not deal in detail with radiation-associated thyroid cancer since this subject was thoroughly reviewed in *Thyroid Today*, Vol. 1, No. 2, September 1977 by Dr. Leslie J. DeGroot.

Benign thyroid nodules are common, whereas clinically apparent thyroid cancer is relatively rare. The annual incidence of thyroid cancer in a 1969-1971 USPHS survey was only 37 new cases per million population. However, this is an increase over the incidence reported in the past, presumably as a result of the appearance of thyroid cancers induced by head and neck radiation given to children and infants several decades ago.\* In contrast, benign thyroid nodules are common. Vander and his associates<sup>1</sup> examined 5,127 persons aged 30 to 59 years living in Framingham, Massachusetts in 1948 and found that 218 had nontoxic thyroid nodules, which represents a prevalence of 4.2%—6.4% in women and 1.5% in men. Moreover, after following the progress of these people for 15 years, *none* showed evidence of thyroid malignancy and new thyroid nodules were detected at an annual rate of about one per thousand persons, with nodules developing in women at about twice the frequency as in men.

In sharp contrast, when the thyroid is carefully studied at necropsy, as many as 5.7% of the persons dying with no known thyroid disease have occult thyroid cancer.<sup>2</sup> It is apparent, therefore, that well-differentiated thyroid cancer is at times benign in behavior thereby requiring little or no therapy. Difficulty arises, however, when this concept is applied to all patients with well-differentiated forms of thyroid cancer. Certainly these tumors can result in death,

albeit infrequently, which in some instances occurs with striking swiftness.

Even though most thyroid nodules are benign, at surgery about 10% to 20% are generally reported to be malignant, indicating that an effective selective process is operative. In addition, if one carefully defines certain patient and tumor characteristics influencing prognosis, it is possible to avoid unnecessarily extensive treatment on the one hand and clearly inadequate therapy on the other.

**Pathology:** Certain aspects of the pathology of papillary thyroid carcinoma have a direct bearing on prognosis and should influence the choice of therapy. No single pathologic classification of primary malignant neoplasms of the thyroid is universally accepted by clinicians and pathologists. One of the major differences is in the classification of papillary thyroid cancer which is usually formed by a mixture of papillary and follicular elements but occasionally is purely papillary in structure. In the pathologic classification used by Woolner and his associates,<sup>3</sup> no distinction is made between mixed papillary-follicular tumors and those predominantly or purely papillary in architecture. Although some have suggested that mixed tumors are more invasive and recur with greater frequency than pure papillary carcinoma, several large studies<sup>3,4</sup> indicate that these details of histologic structure have no bearing on prognosis or survival with this tumor.

The primary tumors vary substantially in size and, although usually solid, may be cystic and hemorrhagic. Papillary thyroid cancer is usually unencapsulated and tends to infiltrate surrounding tissue. Multiple intraglandular foci are common which partially may be due to its locally infiltrative characteristics. Generally, about a third to a half of the patients with papillary thyroid cancer, including many with small primary tumors, have obvious cervical lymph node metastases at initial surgery.<sup>4</sup> Cervical lymph node metastases develop in a higher proportion of children, up to 75%.<sup>5</sup> With careful study, even larger numbers of intraglandular foci and cervical lymph node metastases are found.<sup>4</sup> A few patients, ranging from 5% to 10%, have large primary tumors that extend through the thyroid capsule and invade contiguous neck structures. Most of the primary tumors, however, do not violate the thyroid capsule even when extensive cervical lymph node metastases have occurred. Thus, local parenchymal invasion and lymph node metastases are cardinal features of this tumor. In contrast, vascular invasion is rare and distant metastases (usually to lung, but also to bone, brain, and other tissues) occur in only about 5% to 10% of adults and 15% to 20% of children with this neoplasm.<sup>3-5</sup>

Certain of these characteristics have a direct bearing on prognosis. Woolner and his associates<sup>3</sup> clearly demonstrated that the size of the primary lesions but *not* the presence of cervical lymph node metastases substantially influenced prognosis. These investigators found that patients with occult papillary thyroid cancer (defined as a primary tumor 15 mm or less in diameter, with or without metastases) had no demonstrable mortality.<sup>3</sup> We found only two cases briefly mentioned in the literature in which cancer

deaths apparently occurred in persons with occult primary tumors.<sup>4</sup> In contrast, larger tumors, particularly those invading the thyroid capsule, are much more likely to cause death.<sup>3</sup> Nonetheless, the overall net mortality rate from this cancer is extremely low, perhaps in the range of 10% to 20% over several decades.<sup>3,4</sup> Even with distant metastases, survival for years is not uncommon; and children and young adults may survive for decades with pulmonary metastases.<sup>3-5</sup> When death does occur from this neoplasm, in about half the patients it does so as a direct result of local tumor invasion.<sup>4</sup> In a small but important number of persons the tumor becomes anaplastic. Thus, before one begins considering therapy and the impact of intervention, these pertinent features of the pathology must be considered.

**Clinical Aspects:** The most common of the primary thyroid malignancies, papillary thyroid cancer, accounts for between half to two thirds of all thyroid carcinomas in adults<sup>4</sup> and about 70% of those in children.<sup>5</sup> It ordinarily has a peak incidence in the third and fourth decades and occurs two to three times more frequently in females than males. In children, however, this ratio is almost equal.<sup>5</sup>

An asymptomatic neck mass is the presenting feature in more than three fourths of these patients.<sup>4</sup> Although the thyroid usually has an isolated nodule, occasionally it is diffusely enlarged or is multinodular. Cervical lymph nodes are palpable on initial examination in about a third of the patients.<sup>4</sup> Less often, there is evidence of local tumor invasion resulting in clinical signs such as vocal cord paralysis, pain, and dysphagia. In the patient with a thyroid nodule, the importance of a past history of head and neck irradiation cannot be overemphasized. Eliciting a past history of x-ray treatments for an enlarged thymus, tonsils, acne, and a variety of other benign conditions is in most instances a clear indication for surgery. A careful approach to the evaluation of previously irradiated patients was given by Dr. DeGroot in *Thyroid Today* (Vol. 1, No. 2).

Certain laboratory tests are of value in the evaluation of the patient with a thyroid nodule. Papillary thyroid cancer tends to be solid by thyroid echography.<sup>6</sup> However, it may sometimes be a mixed solid-cystic lesion which, on aspiration, may disclose bloody fluid. By <sup>123</sup>I or <sup>99m</sup>Tc scanning, thyroid cancers tend to be hypofunctional or non-functional. However, in the opinion of some,<sup>4,7</sup> unless the thyroid nodule is hyperfunctional by scan, clinical criteria other than scan contribute most to the decision of whether to excise a nodule. Thyroid hormone suppression (150-200 µg L-thyroxine daily in an adult), used to differentiate benign and malignant nodules, is based on the assumption that cancers continue to grow with such therapy. Although usually true, there are important documented exceptions to this generality.<sup>4</sup> Accordingly, thyroid hormone suppression of thyroid nodules can only be done safely in conjunction with long-term follow-up. Recently there has been renewed interest in needle biopsy of thyroid nodules, particularly by using a fine-gauge needle with which material for cytologic examination can be obtained.<sup>8</sup> This appears to be a safe, highly useful adjunctive test that is particularly suitable for the diagnosis of papillary thyroid cancer, providing a

well-trained cytologist is available to interpret the specimen. Fine-needle aspiration biopsy is particularly important in the patient with a thyroid nodule found to be cystic by echography or in the patient (usually a postmenopausal woman with an asymptomatic nodule) assigned to long-term thyroid hormone suppression.

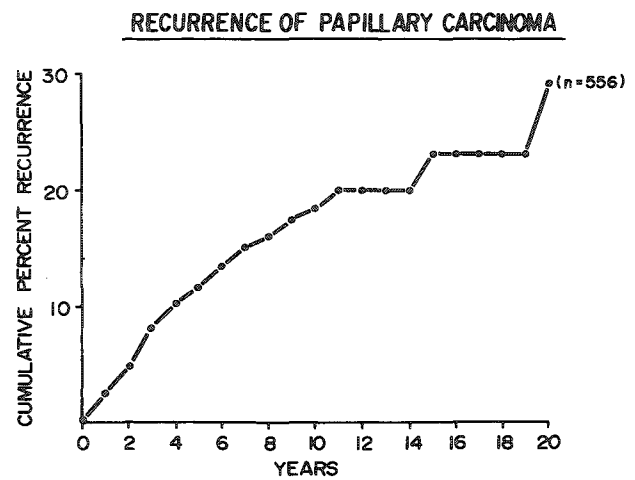
**Therapy:** Although over the past several decades a trend has evolved toward a generally more conservative surgical approach to papillary thyroid carcinoma, there is no uniform opinion regarding the management of this neoplasm. Debate continues to center around the extent of surgery that is required, the indications for radioactive iodine, and the efficacy of thyroid hormone in controlling tumor growth. There are several reasons for divergent opinions. Aside from the fact that this is an uncommon cancer with a characteristically long course, other factors such as the size of the primary lesion, extent of local invasion, and age of the patient clearly interact to influence survival, making the impact of therapy difficult to assess.

Mortality is traditionally considered the end point of therapy for papillary thyroid cancer. In contrast, local recurrences are often regarded as inconsequential, principally because they are usually easily excised or treated with  $^{131}\text{I}$ . However, recurrences of papillary thyroid cancer, which occur with surprisingly high frequency (Fig. 1), may be the first signal to a fatal outcome. Continuing observation of 576 patients with papillary thyroid carcinoma originally reported in 1977<sup>4</sup> in whom follow-up is available in about 90% and averages slightly more than ten years, discloses that 84 have now experienced recurrence of their disease. Perhaps of more importance, of the six patients who died as a direct result of papillary thyroid carcinoma, five considered to have been cured of their disease after initial therapy experienced a recurrence of cancer from which they subsequently died. Deaths occurred as a result of both local tumor recurrences and distant metastases. However, of the several patients with distant metastases at the time of initial presentation who were vigorously treated with surgery,  $^{131}\text{I}$ , and thyroid hormone, all but one remain alive. Tumor characteristics known to influence survival<sup>3</sup> can also be shown to affect the rate of recurrence. Larger, locally invasive tumors are associated with the highest recurrence rates (Fig. 2). Accordingly, in our opinion, efficacy of therapy can be evaluated in an accurate and meaningful manner by using recurrence of tumor as one of the end points.

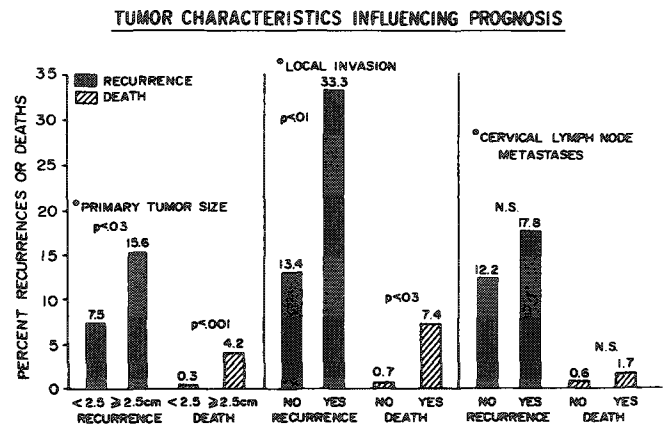
Mortality from papillary thyroid cancer is greatest in persons aged 40 years or older.<sup>3,4</sup> However, recurrence, in our experience, is more frequent in the young. In those younger than 30 years, we found the rate of recurrence to be twice that observed in persons 30 years and older.<sup>4</sup>

Surgery is clearly the preferred initial treatment. Opinions differ, however, regarding the extent of surgery that is appropriate. In our study group, the recurrences after subtotal thyroidectomy were almost twice as frequent as after total thyroidectomy (Fig. 3). Also, a greater proportion of deaths from cancer occurred after subtotal thyroidectomy. In contrast, the extent of lymph node surgery had no significant influence on recurrence and survival. It is clear, how-

ever, that permanent hypoparathyroidism or recurrent laryngeal nerve damage occurs with greater frequency in those persons treated with total thyroidectomy. However, modification of the procedure to a near-total thyroidectomy consisting of total lobectomy on the side of the cancer and partial lobectomy leaving the posterior capsule intact on the contralateral side substantially reduces complications to an acceptable level. Of equal importance, such surgery should be done by a surgeon thoroughly trained in and fully experienced with thyroid cancer surgery.



**Figure 1**  
Cumulative recurrence rate in patients with papillary thyroid carcinoma (from Mazzaferri et al<sup>4</sup> with permission).



**Figure 2**  
Tumor characteristics influencing prognosis in patients with papillary thyroid carcinoma in 576 patients seen for follow-up for slightly more than ten years.

Indications for the use of therapeutic  $^{131}\text{I}$  are not uniform. In our study, when  $^{131}\text{I}$  at an average dose of 140 mCi and thyroid hormone were given postoperatively, recurrences were significantly fewer than when thyroid hormone alone, external irradiation, or no adjunctive therapy was used (Fig. 4). It is clear, however, that not every patient with papillary thyroid carcinoma should be treated with  $^{131}\text{I}$ . For instance, the patient with a *single* microscopic or small, clinically nonpalpable papillary thyroid carcinoma has such an excellent prognosis that, except for the patient

with cervical lymph node metastases, total thyroidectomy and  $^{131}\text{I}$  hardly seem warranted. On the other end of the spectrum is the patient with a large, locally invasive primary tumor who clearly should be treated with near-total thyroidectomy and ablative doses of  $^{131}\text{I}$ . Radical neck dissection does not seem warranted in most instances. We prefer to simply excise obviously involved nodes and to use therapeutic  $^{131}\text{I}$  to ablate any remaining tumor. However, between these extremes lies the majority of patients with papillary thyroid carcinoma in whom the lesion is clinically apparent, with or without cervical node metastases, but in whom thyroid capsule invasion is not present. It is in this group that the greatest judgment regarding therapy must be exercised. We found that when  $^{131}\text{I}$  was given to ablate the thyroid remnant after surgery and the patient was placed on a regimen of thyroid hormone, the recurrence rate was 2.7%.<sup>4</sup> Using a multivariable analysis, we found the age of the patient, size of the primary lesion, extent of local invasion, extent of thyroidectomy, and use of  $^{131}\text{I}$  and thyroid hormone all influence recurrence rates with this disease. We observed about a 1% yearly recurrence rate in patients with occult ( $\leq 15\text{mm}$ ) papillary carcinoma which we presume indicates that some lesions were multicentric or had neck metastases that were initially not apparent and, in retrospect, should have been more vigorously treated.

McCowen and his associates,<sup>9</sup> using bilateral subtotal thyroidectomy and low doses of  $^{131}\text{I}$  (less than 30 mCi), reported results comparable to those observed in their patients initially treated with higher doses (80 to 100 mCi) of  $^{131}\text{I}$ . In another prospective, long-term study, no deaths resulting from thyroid cancer were observed when total ablation was achieved and maintained.<sup>10</sup> It would appear, therefore, that for those patients at greatest risk of recurrent disease, total thyroid ablation is effective in reducing mortality.

Concern continues to center around the potentially serious adverse effects of therapeutic doses of  $^{131}\text{I}$ . Evaluation of this concern begins with an assessment of the efficacy of  $^{131}\text{I}$  therapy. Beierwaltes<sup>11</sup> recently reviewed the treatment of thyroid carcinoma with  $^{131}\text{I}$  and again emphasized the efficacy of such therapy on metastatic disease, particularly pulmonary metastases. His patients treated with  $^{131}\text{I}$  until the lung metastases disappeared had a fourfold lower death rate than those not treated until the lung metastases disappeared. With vigorous  $^{131}\text{I}$  therapy, Beierwaltes<sup>11</sup> reported that in 36 patients with lung metastases survival was 92% at five years and 87% at ten years. However, patients with bone metastases had a 44% survival at ten years. Reviewing the possible adverse effects of large doses of  $^{131}\text{I}$ , Beierwaltes makes several important points. Using his method of  $^{131}\text{I}$  therapy, which essentially permits long intervals between treatment doses, he has observed only one case of leukemia out of 400 treated with  $^{131}\text{I}$ . Pochin,<sup>12</sup> however, observed a 2% incidence of leukemia in his patients treated with  $^{131}\text{I}$  on a somewhat more frequent schedule of  $^{131}\text{I}$  administration. Another concern in the past has been the appearance of pulmonary fibrosis in patients with lung metastases treated with  $^{131}\text{I}$ . However, with currently

### INFLUENCE OF SURGERY

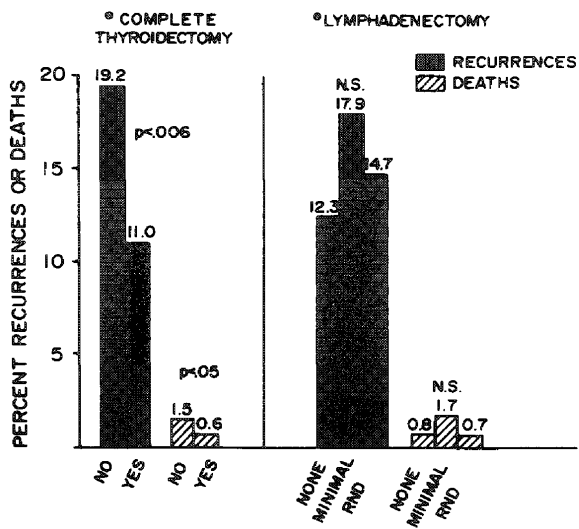


Figure 3 The influence of surgery on papillary thyroid carcinoma in 576 patients.

### CUMULATIVE RECURRENCE AFTER DIFFERENT TYPES OF ADJUNCTIVE MEDICAL THERAPY

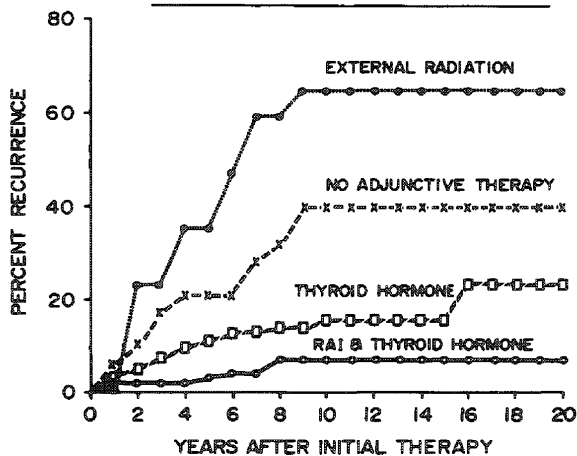


Figure 4 Cumulative recurrence rates of papillary thyroid carcinoma in 576 patients.

recommended dosage schedules, pulmonary fibrosis and leukemia are not major problems.<sup>11</sup> Another concern has been <sup>131</sup>I-induced genetic damage leading to birth defects. Beierwaltes' group published information on 33 children treated for thyroid cancer with <sup>131</sup>I in whom, with long-term follow-up, there has been no decrease in fertility and no increased incidence of congenital birth defects.<sup>13</sup> Transformation of well-differentiated to anaplastic carcinoma has been suggested as a possible adverse effect of <sup>131</sup>I. In a review of the literature, we found no evidence to clearly document such an effect.<sup>4</sup>

In summary, papillary thyroid carcinoma usually has a good prognosis. Certain tumor characteristics, the age of the patient, and the type of therapy all interact to influence the outcome of this disease. Consideration of these factors and the adverse effects of therapy permit one to make certain reasonable judgments regarding treatment. An initial, very conservative approach would therefore indicate that the thyroid should be ablated with surgery and <sup>131</sup>I (assuming that the tumor concentrates <sup>131</sup>I adequately) followed by thyroid hormone suppression in those patients with primary lesions that are: (1) multiple, (2) locally invasive, (3) larger than 2.5 cm, or (4) metastatic. In others, one can modify this therapy but must bear in mind that the treatment may be less than optimal. From a practical standpoint, considering the large number of tumors that are multicentric or locally metastatic, it would seem that the majority of patients with clinically palpable cancers are best treated with therapy that totally ablates the thyroid. Whether treatment should be modified in patients with radiation-induced thyroid cancer is presently uncertain.

### Follicular Thyroid Cancer

This tumor, which accounts for about 15% of all thyroid cancer, is often included in discussion of papillary thyroid carcinoma. This is appropriate in the sense that many of the statements regarding diagnosis and therapy of papillary carcinoma apply to follicular carcinoma. However, there are certain important differences between these tumors which warrant emphasis.

**Pathology:** These tumors tend to be encapsulated and have a marked tendency toward vascular invasion.<sup>3</sup> The most common sites of metastasis are the bones or lungs but, unlike papillary thyroid cancer, this tumor seldom spreads to regional lymph nodes. Histologically, the tumor displays a wide spectrum of architectures ranging from tumors with small, fairly well-differentiated follicles to solid sheets of cells. Woolner and his associates<sup>3</sup> found a wide difference in prognosis depending on whether or not the tumor had capsular and angioinvasion. In a long-term follow-up study<sup>14</sup> from the Mayo Clinic, only 3 of 104 patients with noninvasive follicular thyroid carcinoma died of their tumor. In contrast, the 10- and 20-year survival rates were 34% and 16%, respectively, for 98 patients with histologically more angioinvasive follicular carcinoma.

**Clinical Aspects:** There are only a few important differences between the clinical presentation and diagnosis of follicular and papillary thyroid carcinomas. Like papillary cancer, follicular carcinoma is usually slow growing. How-

ever, unlike papillary thyroid carcinoma, metastatic lymph nodes are almost never palpable in patients with follicular cancer. Also, unlike papillary cancer, bone metastases may occur early and are extremely destructive. They also tend to respond poorly to <sup>131</sup>I therapy. As opposed to papillary thyroid cancer, patients with this disease not infrequently present with an obvious distant metastasis from a thyroid lesion that is small and easily overlooked. On at least four occasions in recent years, we have seen patients with serious metastatic disease (one to brain, another to the spinal cord, and two to bone) in whom the primary lesion was small enough to have been initially overlooked. Another important difference between follicular and papillary thyroid carcinoma is the occurrence of thyrotoxicosis; it can occur in those patients with extensive metastatic follicular carcinoma.<sup>14</sup> Thyrotoxicosis in this setting is easily overlooked and is occasionally due to T<sub>3</sub> alone.

The principles of therapy are the same for follicular thyroid cancer and the disagreements are similar. There is no doubt, however, that surgery is the preferred treatment and that near-total thyroidectomy followed by ablative doses of <sup>131</sup>I and thyroid hormone are indicated for those with tumors demonstrating angioinvasion.<sup>10,11</sup> Unlike papillary thyroid carcinoma, the size of the primary lesion does not seem to influence prognosis. Distant metastases, similar



**Figure 5**

This girl demonstrates the typical facies, "bumpy lips," a neuroma of the left upper eyelid, and a neuroma of the upper lip that are characteristic of the neurofibromatosis phenotype of medullary thyroid cancer. (Reproduced from Khairi et al<sup>16</sup> with permission.)

to papillary carcinoma, can only be treated effectively with <sup>131</sup>I when all normal thyroid tissue has been ablated. Treatment of the generally benign, noninvasive forms of this disease is less certain but clearly leaves room for a less aggressive approach to both surgery and the use of <sup>131</sup>I.

Even with therapy, the angioinvasive forms of this tumor tend to have an outcome that is less satisfactory than with papillary cancer. Although this tumor may avidly concentrate <sup>131</sup>I, osseous lesions tend not to respond well. However, dramatic regression of soft tissue lesions can be seen with <sup>131</sup>I therapy.<sup>11</sup> With the foregoing exceptions and differences in mind, most of the comments regarding the diagnosis and treatment of papillary thyroid cancer are applicable to follicular carcinoma.

### **Anaplastic Thyroid Carcinoma**

About 10% to 15% of thyroid cancers are anaplastic.<sup>14</sup> Clinically, these tumors usually develop in older patients in their sixth or seventh decade. However, this tumor is reported to occur in children and younger adults.<sup>4,5</sup> The ratio of men to women is almost equal. Patients tend to have a rapidly expanding, very symptomatic thyroid mass that causes dysphagia, pain, hemoptysis, and hoarseness. Outcome with this rapidly growing tumor is uniformly fatal.<sup>14</sup>

The most common histologic pattern is extremely anaplastic spindle or giant cells. However, occasionally, small cell carcinoma or clear cell carcinoma resembling hypernephroma can be seen. This tumor must be clearly differentiated from primary lymphoma of the thyroid because the latter is extremely responsive to therapy.

In the study by Woolner and co-workers,<sup>14</sup> all but one of 160 patients with anaplastic thyroid cancer died of the disease. Death usually occurs within six to eight months of diagnosis despite therapy with x-ray or adriamycin. Surgery is usually not possible or is only palliative because of the extensive local invasion characteristic of this tumor.

### **Medullary Thyroid Cancer (MTC)**

This tumor accounts for about 7% of all thyroid cancer. A neoplasm of the thyrocalcitonin-secreting, parafollicular or C cell, this tumor and its metastases contain amyloid, secrete thyrocalcitonin, and can be familial when it is transmitted as an autosomal dominant trait.<sup>15</sup> The familial tumors are associated with bilateral pheochromocytomas and hyperparathyroidism (Sipple's syndrome). Rarely, the tumor occurs in persons with a typical phenotype characterized by mucosal neuromas, a typical facial appearance (Fig. 5), a Marfanoid habitus, medullated corneal nerve fibers, and intestinal ganglioneuromas.<sup>16</sup>

Remarkable advances have occurred in our understanding of this lethal disease. When familial, the tumor usually occurs bilaterally in the thyroid. In this setting, by using plasma thyrocalcitonin as measured by radioimmunoassay as a marker,<sup>17</sup> the disease can be detected in affected members of the kindred long before it is clinically detectable and, in some instances, at a preneoplastic stage when the thyroid simply demonstrates C-cell hyperplasia.<sup>18</sup>

When sporadic, MTC presents as a thyroid nodule.

Diarrhea, which occurs for uncertain reasons, is seen in 30% of those patients with MTC. Thyrocalcitonin testing will disclose abnormally high basal serum concentrations or an abnormal response to calcium or pentagastrin infusion.

The only highly effective means of therapy is surgical excision. When surgery is done before regional lymph node metastases have developed, survival is in the range of 90% at ten years compared with about 40% when cervical lymph nodes have become involved.

**To prescribe any drug mentioned in this article, the reader should consult full prescribing information.**

### **REFERENCES**

1. Vander JB, Gaston EA, Dawber TR: *Ann Intern Med* 69:537, 1968.
2. Sampson RJ, Woolner LB, Bahn RC, Kurland LT: *Cancer* 34:2072, 1974.
3. Woolner LB, Beahrs OH, Black BM, et al: *Am J Surg* 102:354, 1961.
4. Mazzaferri EL, Young RL, Oertel JE, et al: *Medicine* 56:171, 1977.
5. Winship T, Rosvoll RV: *Clin Proc Child Hosp* 26:327, 1970.
6. Blum M: *Am J Med* 59:301, 1975.
7. Nelson RL, Wahner HW, Gorman CA: *Ann Intern Med* 88:41, 1978.
8. Gershengorn MC, McClung MR, Chu EW, et al: *Ann Intern Med* 87:265, 1977.
9. McCowen KD, Adler RA, Ghaed N, et al: *Am J Med* 61:52, 1976.
10. Krishnamurthy GT, Bland WH: *Cancer* 40:195, 1977.
11. Beierwaltes WH: *Semin Nucl Med* 8:79, 1978.
12. Pochin EE: *Semin Nucl Med* 1:503, 1971.
13. Sarkar SD, Beierwaltes WH, Gill SP, et al: *J Nucl Med* 17:460, 1976.
14. Woolner LB: *Semin Nucl Med* 1:481, 1971.
15. Melvin KEW, Tashjian AH Jr, Miller HH: *Recent Prog Horm Res* 28:399, 1972.
16. Khairi MRA, Dexter RN, Burzynski NJ, Johnston CC: *Medicine* 54:89, 1975.
17. Melvin KEW, Miller HH, Tashjian AH Jr: *N Engl J Med* 285:1115, 1971.
18. Wolfe HJ, Melvin KEW, Cervi-Skinner SJ, et al: *N Engl J Med* 289:437, 1973.