Conferences and Reviews

Predictors of Thyroid Tumor Aggressiveness

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Thyroid cancers are classified as papillary, follicular (including Hürthle cell), medullary, and anaplastic. Papillary cancers account for about 82% of all thyroid cancers, follicular about 8%, medullary about 6%, Hürthle cell 3%, and anaplastic 1%. The prognosis of patients with papillary thyroid cancer is usually favorable, whereas most patients with anaplastic cancer die within 6 months. The behavior of papillary thyroid cancer can be predicted by patient age, sex, tumor size, local invasion, angioinvasion, lymph node metastases, distant metastases, as well as tumor differentiation and ability to take up radioactive iodine. Thus, older male patients with larger or invasive tumors, with angioinvasion, lymph node or distant metastases, and with tumors that do not take up radioactive iodine or cannot be completely surgically resected have a worse prognosis. Anaploid tumors, tumors with a low adenylate cyclase response to thyroid-stimulating hormone tumors, tumors that are *ras*- and *gsp*-positive, and tumors that are p21-positive and p53-positive also appear to behave in a more aggressive manner. In contrast, lymphocytic thyroiditis associated with papillary thyroid cancer predicts fewer recurrences and an improved survival.

The treatment of patients with papillary thyroid cancer is controversial primarily because most patients do well with relatively minimal therapy, and there are no prospective studies concerning the merits of various treatments. Much of the controversy relates to the safety of thyroidectomy versus other procedures and, to a lesser extent, when to do a central or modified radical neck dissection. The rate of recurrence is lower, and the death rate may also be lower when patients are treated initially by total thyroidectomy. The rationale for total thyroidectomy is that it enables one to use radioactive iodine to detect and treat local and distant metastases, and it makes serum thyroglobulin determination more sensitive for detecting persistent disease. Total thyroidectomy should be associated with a permanent complication rate of less than 2%. Thyroid-stimulating hormone suppression therapy is recommended by most experts for patients with differentiated thyroid cancer and supported by most clinical and laboratory studies. Central and lateral node selection is recommended for patients with palpable lymphadenopathy.

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Thyroid cancer is a fascinating tumor because of its variable and generally favorable course. Many more people have thyroid cancer than are aware of it, and most of them die with their tumor rather than of their tumor. For example, as many as 13% of persons in the United States have thyroid cancer at postmortem examination, and yet clinical thyroid cancer develops in only about 40 per million persons, and only about 6 per million (15%) die of it.[1(p123)] Thyroid cancer is, however, the most lethal endocrine neoplasm, excluding that of the ovary, and accounts for about 1% of all cancer deaths.[2]

The optimal treatment of patients with thyroid cancer is a topic of considerable controversy, and no prospective randomized trials comparing the various means of surgical with other treatments have been done. Most studies document that more extensive initial treatment reduces the recurrence and death rates from thyroid cancer, but more extensive treatment is also generally associated with more complications.[2-6]* Obviously, if the behavior of a particular tumor can be predicted, the use of various treatments such as total thyroidectomy, radioactive iodine ablation, thyroid-stimulating hormone (TSH) suppressive therapy, and external radiation treatment can be selective.

Thyroid cancers are classified as papillary, follicular, medullary, and undifferentiated or anaplastic. Mixed papillary-follicular cancers and follicular variants of

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ABBREVIATIONS USED IN TEXT

AGES = age, grade, extent, and size
AMES = age, metastasis, extent, and size
EGF = epidermal growth factor
EORTC = European Organization for Research and Treatment of Cancer
TSH = thyroid-stimulating hormone

papillary cancers are classified as papillary thyroid cancer because they behave in a similar manner. Hürthle cell cancers are of follicular cell origin and are usually included with follicular cell cancers—"Hürthle cell variant of a follicular cancer."[7] Hürthle cell cancers differ from follicular thyroid cancer because Hürthle cell cancers are often multifocal in the thyroid, are usually associated with regional lymph node metastases, and in general, do not take up radioactive iodine. Follicular thyroid cancers, in contrast, are usually solitary, involve only the regional nodes in 10% of patients, and take up radioactive iodine in about two thirds of patients.[8,9]

Papillary thyroid cancers account for about 82% of all cases of thyroid cancer in iodine-sufficient areas. Follicular cancers account for about 8%, medullary thyroid cancers 6%, Hürthle cell cancers 3%, and anaplastic thyroid cancer 1%. Other rare tumors of the thyroid include lymphomas (usually B-cell type), squamous cell carcinomas, angiosarcomas, teratomas, liposarcomas, and leiomyosarcomas. Tumors may also metastasize to the thyroid gland, the most common being hypernephroma, breast cancer, lung cancer, and malignant melanoma. Fortunately, about 98% of thyroid cancers are differentiated tumors, and therefore, most patients have a good-to-excellent prognosis. Unfortunately, few patients with anaplastic, squamous cell, and angiosarcoma survive more than six months despite the use of surgical treatment, radiation therapy, or chemotherapy. Therefore, histologic examination is important in predicting the prognosis.[10,11] Patients with poorly differentiated cancers also have more aggressive tumors and a poorer prognosis than do patients with well-differentiated thyroid tumor.[12] Histologic grading using Broders' classification was a cause-specific important prognostic factor by both univariate and multivariate analyses.[13-15] A group of recognized pathologists from World Health Organization collaborating centers in 1988 concluded, however, that "[T]he value of histological grading of papillary carcinoma remains to be substantiated."[16] Despite this statement, histologic differentiation was reported to be an independently important factor concerning thyroid cancer-related deaths.[17,18] I certainly concur with this opinion.

Staging

Numerous classifications have been used to determine prognostic factors, including the following:

- The European Organization for Research and Treatment of Cancer (EORTC) prognostic index based on multivariate analysis and using a Weibull survival model[19];
- The AGES [age, grade, extent, and size] classification using the Cox model[20];
- The AMES [age, metastasis, extent, and size] classification[21]; and
- The International Union Against Cancer or TNM [tumor, node, metastasis] classification (Figure 1).[14]

DeGroot and co-workers have described a simple classification: class 1, intrathyroidal disease; class 2,

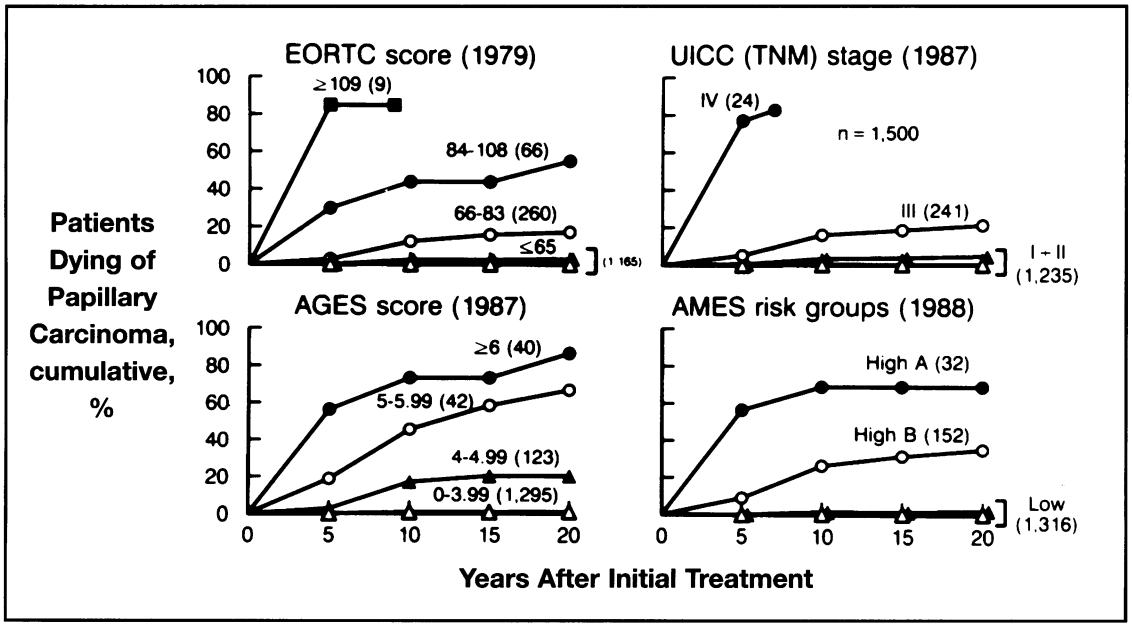

Figure 1.—Various staging indices are shown for patients with papillary thyroid cancer (from Hay,[13] with permission). AGES = age, grade, extent, and size; AMES = age, metastases, extent, and size; EORTC = European Organization for Research and Treatment of Cancer; TNM = tumor, node, metastasis; UICC = International Union Against Cancer.

TABLE 1.—*Prognostic Index System for Papillary Carcinoma**

Factor	MACIS Score
Age, years	
<39	3.1
≥40	0.08 × age
Diameter of primary	0.3 × cm
Incomplete resection	1
Extrathyroidal invasion	1
Distant metastases	3

MACIS = metastases, age, completion of resection, invasion, and size

*From Hay et al,[22] with permission.
†The MACIS scoring system is from the Mayo Clinic. Low risk ≤ 6, highest risk > 8.

regional lymph node metastasis; class 3, local invasion; and class 4, distant metastasis.[6] A newer classification has also been described by Hay and associates, with emphasis not only on age, size, and metastases, but also on the completeness of resection (Table 1).22 All of these classifications are helpful in predicting low and high risk. Unfortunately, some patients in the low-risk group still die of thyroid cancer, so better prognostic predictors are obviously necessary.

Virtually all studies document that young patients with thyroid cancer, such as men younger than 40 and women younger than 50, do better than older patients.[14] Patients with small tumors (<2 cm) do better than those with moderate-sized tumors (2 to 4 cm), and these patients do better than those with larger tumors (≥4 cm). Patients with locally invasive tumors and those with metastatic disease have a worse prognosis.14,21 Patients with tumors that cannot be resected have a poorer prognosis.[22] It should be noted, however, that the trachea can be resected with the preservation of a normal voice and that the esophageal wall can be resected with excellent results (Figure 2).

The site and number of metastases are also important. About 15% of children and 10% of adults will have pulmonary micrometastases at the time of the initial treatment.[23,24] Patients with pulmonary micrometastases have a considerably better survival rate than those with macrometastases, and these patients in turn have a better prognosis than those with skeletal metastases.[25]

We might question whether the AGES or other classifications are preoperative or postoperative classifications. Obviously, the age of a patient and the approximate size of the tumor can be determined preoperatively, and cytologic examination, as obtained by percutaneous aspiration biopsy, can usually determine the histologic type. Other proven risk factors such as invasion and distant metastases can often be determined only at or after surgical treatment. Other minor or major risk factors such as the presence of multifocal tumor,[26] lymph node involvement,[27,28] or focal areas of poorly or undifferentiated tumor are also best determined after examination of the entire specimen. Other predictors of aggressiveness include sex (women do somewhat better than men)[13,29,30]; ploidy (patients with aneuploid papillary, Hürthle cell, and medullary thyroid tumors do worse than those with diploid thyroid cancers)[31–34]; radioactive iodine uptake (patients whose tumors fail to take up radioactive iodine have a worse prognosis)[35,36]; adenylate cyclase response to TSH therapy (patients whose tumors have a low response do worse)[37]; epidermal growth factor (EGF) receptors (patients with higher EGF binding appear to do worse)[38]; oncogenes (patients with several oncogenes such as *ras* and *gsp* appear to do worse)[39]; and tumor suppressor genes (patients with p53, in general, appear to do worse).[40–42]

Tumor cell nuclear DNA content has been documented to be one of the best prognostic indicators of malignant potential,[13] and Bäckdahl and associates have said that the nuclear DNA content has a "predictive power significantly greater than that of all other prognostic factors combined."[31(p977)] Subsequent investigations have shown that the DNA ploidy pattern as determined by flow cytometry is an important and independent prognostic variable.[13,34] As shown in Figure 3, patients with an aneuploid DNA pattern have a worse prognosis than those with a tetraploid or diploid pattern. The DNA ploidy is a better prognostic factor for some tumors such

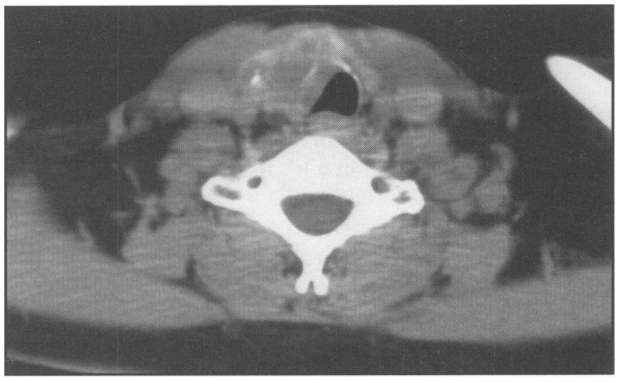

Figure 2.—A magnetic resonance imaging scan shows papillary thyroid cancer invading through tracheal wall.

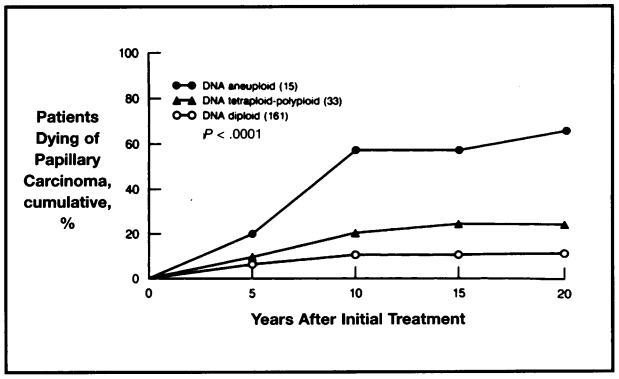

Figure 3.—The DNA ploidy pattern, prognosis, and cumulative mortality from papillary thyroid carcinoma are shown in 209 patients. Nuclear suspensions were obtained from paraffin-embedded archival tumor specimens (from Hay,[13] with permission). The numbers in parentheses indicate the number of patients.

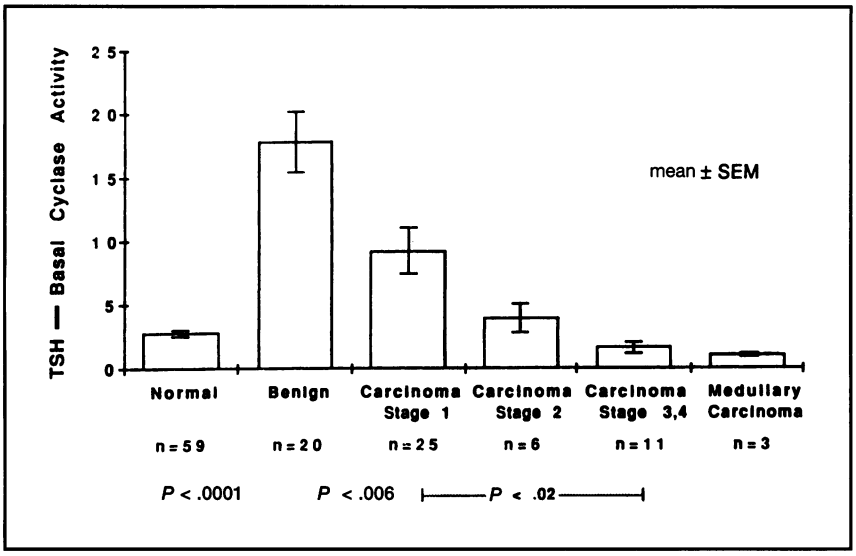

Figure 4.—The adenylate cyclase response to thyroid-stimulating hormone (TSH) therapy by tumor class is shown (from Siperstein et al,[37] with permission). SEM = standard error of the mean.

as papillary and Hürthle cell cancers than it is for others such as follicular cancer.[13,34,43] Ploidy is not useful for determining whether a particular thyroid tumor is benign or malignant.

About two thirds of all papillary and follicular thyroid cancers take up radioactive iodine, whereas few Hürthle cell, medullary, or anaplastic thyroid cancers take up radioactive iodine.[7,25] It is not surprising that patients whose thyroid cancers take up radioactive iodine have a better prognosis because such tumors are usually better differentiated and can sometimes be ablated with radioactive iodine.[3,35,36]

It has been documented that patients with tumors that are more extensive or disseminated have a lower adenylate cyclase response to TSH therapy (Figure 4).[37] Patients with tumors localized in the thyroid gland or nodal metastases had a ninefold to seventeenfold increase in adenylate cyclase activity, whereas those with more extensive tumors had only a twofold to threefold increase. Some of the decreased adenylate cyclase response in the more extensive or disseminated tumors was due to an increased basal adenylate cyclase activity, suggesting that such tumors are constitutively activated. In another study, two of three patients with constitutively activated adenylate cyclase and follicular thyroid carcinomas and one of three patients with a constitutively activated papillary thyroid cancer had a *gsp* (stimulating G protein) oncogene.[44] These oncogenes were initially identified in a "hot" thyroid nodule and subsequently in 5 of 13 (38%) autonomous nodules.[45,46] In another investigation, patients with both *ras* and *gsp* oncogenes appeared to have more aggressive tumors (Table 2).[39] Elsewhere it was found that *ras* mutations are present in about 40% of follicular thyroid cancers.[47] In addition, the overall prevalence of *ras* mutations was the same in 68 spontaneous and 12 radiation-associated thyroid tumors, although thyroid carcinomas in the radiated group had significantly more K-*ras* mutations (60% to 67%) ($P < .005$).[48] A history of irradiation increases the frequency of multifocal thyroid tumors, but probably does not influence tumor aggressiveness.[49] It has been documented that the *ras* oncogene product, p21, is only weakly expressed in normal thyroid tissue, but it is more strongly expressed in thyroid neoplasms.[50] In another study, p21 staining was positive in 35 of 51 (65%) thyroid neoplasms, and a significantly positive correlation was found between outcome and p21 tumor staining.[51] Overall, in patients with papillary and follicular thyroid cancers, 83% of those who died had thyroid cancers that stained positively, whereas staining was positive in 52% of the survivors ($P < .02$).

An oncogene (*ptc*) has been identified in papillary thyroid cancers.[52] This oncogene is a variant of the ret proto-oncogene. Subsequently the *ptc* oncogene was found on chromosome 10q11-12 in the same region as that for multiple endocrine neoplasm type 2A.[53] The *ptc* oncogene has tyrosine kinase activity. This signal transduction pathway has been reported to be involved in the

TABLE 2.—*Oncogene gsp and ras Mutations in Differentiated Thyroid Cancer**

Tumor Stage	Patients, No.	Patients Positive, No. (%) ras	gsp	ras and/or gsp
Unilocal intrathyroidal, T1-2, N0-1, M0	10	1	5	5 (50)
Multifocal and lymph node metastases, T3-4, N2-3, M0	13	3	7	8 (62)
Distant metastases, TX, NX, M1	9	5	6	8 (89)

*From Goretzki et al.[39]

TABLE 3.—*Effects of Prophylactic Neck Dissection on Recurrence and Survival**

Elective Neck Dissection	Patients No.	Later Active Disease, No. (%)	Dead of Disease, No. (%)
Yes	76	3 (4)	2 (3)
No	88	18 (20)	5 (6)
Total	164	21 (13)	7 (4)

*From Hunter et al.[39]

pathogenesis of papillary thyroid cancer.[53]

The p53 gene acts as a tumor suppressor gene or as a dominant transforming oncogene. Although only 1 of 130 thyroid tumors was initially found to have a p53 mutation,[54] mutations were recently identified in 6 of 7 undifferentiated thyroid carcinomas[40] and in thyroid cancer cell lines.[41] Subsequent studies using single-strand conformation polymorphism analysis of complementary DNA fragments amplified by reverse transcriptase polymerase chain reaction documented the presence of mutations in exons 5, 6, 7, and 8 of the p53 gene in 12 of 49 thyroid carcinomas, but in 0 of 8 benign thyroid tumors.[42] The presence of p53 mutations was not associated with tumor stage or histologic type. We have also recently identified p53 mutations in three of the four thyroid cancer cell lines that we have established in our laboratory. The documentation of various combinations of oncogenes and tumor suppressor genes will probably prove to be useful for predicting tumor behavior.

There has been confusion concerning whether the presence of metastatic thyroid cancer in cervical lymph nodes is a prognostic factor. Numerous studies have documented that about 80% of patients with papillary thyroid cancer have at least micrometastases in cervical lymph nodes.[27,55,56] Palpable lymph nodes, however, are found in about 15% of adults and in about 50% to 80% of children.[23]

It was initially suggested that the finding of clinically involved cervical lymph nodes was beneficial in patients with thyroid cancer.[57] This seemed surprising because the presence of nodal metastases is detrimental for all other cancers. Some investigators have reported that the presence of nodal metastases has no detrimental effect on survival.[13,58] Others have found that the presence of involved lymph nodes adversely influences tumor recurrence, especially in patients older than 40, but does not influence survival.[5] Today in the United States, patients with thyroid cancer are generally treated by therapeutic (palpable lymph node metastases present) rather than by elective (no palpable lymph node metastases present) modified neck dissection because in most patients with microscopic nodal metastases, clinically evident nodal metastases do not subsequently develop.[59] Hutter and co-workers, in their classic article concerning elective radical neck dissection for papillary thyroid cancer, concluded that "[W]e find no real evidence to support the philosophy of radical neck dissection for patients with papillary carcinoma of the thyroid who have no clinical evidence of cervical lymph node metastases."[59(p92)] This study is of interest, but on reanalyzing their data the above conclusion is questionable. In their retrospective review of 164 patients, 76 patients had an elective radical neck dissection and 88 patients did not. The mean age of the patients having elective dissection was 47.9 years, whereas the mean age of the patients not having an elective neck dissection was 37.4 years. As shown in Table 3, the recurrence rate was 4% in the 76 patients having prophylactic neck dissection and 20% in the 88 patients who did not. The death rate was 3% in patients having prophylactic neck dissections and 6% in those who did not. These findings are of even more interest because only 38 of the 76 patients (50%) having elective node dissection were found to have thyroid cancer in their cervical nodes. We also do not know how these patients were selected for prophylactic neck dissection, but we might guess that more patients at higher risk would have been treated prophylactically. Also of interest, as seen in Table 3, none of the patients who had a neck dissection had recurrence in their cervical nodes, although recurrent disease developed in the thyroid gland of two patients and in both the thyroid gland and at distant sites in one patient.[59]

These data document that neck dissection is effective in preventing recurrence in patients with occult thyroid cancer in the cervical nodes. It is also of interest, even though the groups are small, that there were fewer recurrences and fewer deaths in the group treated by prophylactic dissection. This is surprising because, as mentioned, the group treated prophylactically was an average of ten years older and would have been expected to have a worse prognosis.

It is certainly understandable why most surgeons at medical centers in Japan continue to do ipsilateral modified radical neck dissection.[59,60] Such treatment decreases the incidence of local recurrence in the cervical nodes, especially when less than total thyroidectomy and no radioactive iodine is used, and this perhaps may improve survival.[60] Perhaps we should examine the nodal status of patients with papillary thyroid cancer with ultrasonography to select those patients with large nodes, as they are more likely to have involved nodes. A modified neck dissection that preserves the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein might be indicated for these patients.

Previous studies documented that when patients were matched by age and sex, those with differentiated thyroid cancer of follicular cell origin who had clinically palpable cervical lymph nodes had a higher recurrence and death rate at all ages of life.[27] The EORTC study also documented that having palpable cervical metastases had an adverse effect on survival, although the presence of palpable cervical nodes is a minor rather than a major risk factor.[19,27] In another study using univariate and multivariate analyses, it was reported that lymph node metastases adversely influence recurrence and sur-

Patients with matted or clinically fixed nodes also appear to have a worse prognosis.[62] These patients should be treated by a modified radical or en bloc neck dissection that preserves the sternocleidomastoid muscle, spinal accessory nerve, and in most cases, the internal jugular vein. We do this dissection using the MacFee lateral extension of the Kocher transverse collar incision.[63] Most patients can be discharged within 48 hours of this procedure without adverse functional or cosmetic sequelae.

In summary, the presence of cervical lymph node metastases in patients with thyroid cancer indicates more extensive disease. These patients have an increased recurrence rate and seem to have a slightly worse prognosis.[19,27] The overall prognosis remains good, however.[4,19,27,28] Therapeutic modified radical neck dissection is generally recommended.

Extent of Therapy

The value of more extensive surgical treatment such as total thyroidectomy and the use of radioactive iodine is also debated for patients with papillary thyroid cancer. Numerous studies have shown that about 80% of patients with papillary thyroid cancer have micrometastases in their cervical lymph nodes at the time of thyroidectomy, and about 10% to 15% have occult pulmonary metastases despite no clinical evidence of tumor.[23,55,56] Despite this observation, clinically recurrent disease develops in the cervical nodes of only about 8% to 20% of patients. Many microscopic tumors must therefore remain occult or are ablated by the administration of radioactive iodine.

Numerous studies support the use of postoperative radioactive iodine, but no prospective studies have been done. In one study of 576 patients with papillary thyroid cancer, it was found that for lesions greater than 1.5 cm, the recurrence rate was 13.1% when patients were not treated with postoperative radioactive iodine and 6.4% when they received sodium iodide I 131($P < .001$ by Cox regression analysis).[5] In another study, patients with follicular thyroid cancer who were treated with radioactive iodine had a five-year survival rate of 100%, whereas the survival rate was 33.3% in untreated patients.[64] Patients with papillary thyroid cancers larger than 1 cm had fewer recurrences ($P < .01$) and fewer deaths when treated with radioactive iodine ($P < .05$; χ^2 analysis).[6] Fewer patients were reported to have pulmonary metastases develop, and fewer died when they were treated by total thyroidectomy and ^{131}I-sodium iodide therapy.[65] Other investigators noted that two thirds to three fourths of patients whose pulmonary metastases were detected only by radioiodine scanning were likely to be successfully treated, whereas when macrometastases were identified on chest x-ray film or computed tomographic scan, only 4% to 10% of patients could be cured.[35,66] Thus, when macronodular disease was present, the relative risk of death increased sixfold. Further data supporting the prophylactic use of ^{131}I-sodium iodide for patients with differentiated thyroid cancer is provided by Wong and associates.[67] Their use of radioactive iodine reduced the recurrence rate of thyroid cancer by 54%. The change in life expectancy gained by the ablation of thyroid remnants was about equal to that gained by lowering serum cholesterol levels to less than 5.20 mmol per liter (<200 mg per dl) in 35-year-old adults or by coronary artery bypass in patients with two-vessel coronary artery disease.

Despite the fact that the value of treating patients with radioactive iodine has been questioned[68] and that some think that radioactive iodine therapy is only as effective as thyroid hormone suppression therapy,[69] the vast majority of data suggest that prophylactic treatment with radioactive iodine is therapeutically efficacious.[2,4–6,25,35,66]

Radioactive iodine therapy, unfortunately, is less effective when metastatic thyroid cancer is clinically evident.[35,66,70] For example, the use of radioactive iodine was effective for treating patients with nonpalpable cervical lymph node metastases,[5] but it was rarely, if ever, effective in ablating clinically palpable nodes.[71] In contrast, when relatively large doses of ^{131}I-sodium iodide are used, a 74% success rate in treating nodal disease is reported.[72] Maxon says that when the projected radiation dose to the tumor is less than 30 Gy (3,000 rad), he prefers surgical excision, but he does not say how often this occurs.[25] The response of pulmonary micrometastases and macrometastases to ^{131}I-sodium iodide has already been discussed briefly.[35,66,70] In an analysis of the five-year mortality in patients with pulmonary metastases, the mortality was 38% in patients whose metastases concentrated radioactive iodine and 69% in those whose metastases did not ($P < .001$).[36]

Patients with skeletal metastases have an even poorer response to treatment with radioactive iodine, and the presence of bony metastases predicts an ominous prognosis. Unfortunately, about 70% of bony metastases are multiple and 30% solitary, and only about 10% of these usually lytic bone metastases take up radioactive iodine. A similar number of patients respond to treatment after ^{131}I-sodium iodide therapy (about 8%), so that external radiation therapy is often required.[25] The data concerning clinically evident metastatic thyroid cancer suggest that when cervical lymph nodes or pulmonary or skeletal metastases can be completely removed surgically, this should be done. The patient should then receive a large ablative dose of radioactive iodine (about 150 mCi). Serum thyroglobulin levels, especially when patients are hypothyroid in preparation for a radioiodine scan, are useful in determining the presence of persistent disease.

Conclusion

Most patients with differentiated thyroid cancer have an excellent prognosis. Numerous clinical and laboratory techniques are available that help predict whether a particular tumor will behave in an aggressive or benign manner. Until better predictors of tumor behavior are available, such as the presence or absence of certain oncogenes or tumor suppressor genes, I advocate doing total

thyroidectomy with the removal of central neck nodes and a modified radical neck dissection when the lateral neck nodes are clinically involved. I and others recommend that radioactive iodine be used postoperatively for all but low-risk patients and for patients whose tumors take up radioactive iodine.[73] I also recommend treatment with ^{131}I-sodium iodide for patients with elevated thyroglobulin levels whose metastatic thyroid cancers are not evident on routine scanning after total thyroidectomy.[74-77] We will prescribe enough thyroid hormone to suppress TSH production. Such combined therapy seems to result in fewer recurrences and better survival than less aggressive initial therapy.

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