



Rony Léonidas. *Sugar Cane Harvesting Scene.* From the collection of Cynthia Gandee and John Schoo.

To treat thyroid malignancies appropriately, clinicians must have methods to accurately assess the behavior and outcomes from treatment of differentiated thyroid carcinoma.

Prognostic Indicators in Differentiated Thyroid Carcinoma

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Background: *Thyroid cancer ranges from well-differentiated lesions with an excellent prognosis to anaplastic carcinoma, which is almost uniformly fatal. Thus, methods to assess the behavior of thyroid malignancies are necessary to arrive at appropriate treatment decisions.*

Methods: *We discuss the factors that affect the prognosis of patients with well-differentiated thyroid malignancies, including papillary, follicular, Hürthle cell, and medullary thyroid carcinomas. We also review the presentation, therapy, and outcome of patients seen at our center over a span of 50 years. These data have identified those prognostic factors that are predictive of survival and recurrence in differentiated thyroid cancer.*

Results: *Several classifications with different variables have been developed to define risk-group categories. Three widely used systems, in addition to the TNM staging system, include AGES, AMES, and MACIS.*

Conclusions: *A better understanding of independently important prognostic variables will result in improved patient care and treatment.*

Introduction

While thyroid nodules are seen commonly in clinical practice, the majority of these lesions are benign. In fact, thyroid cancer is found in less than 5% to 10% of

hypofunctioning thyroid nodules, and only approximately 18,000 new cases of thyroid malignancy were diagnosed during 1999 in the United States. Because of this low incidence, thyroid cancers in the United States account for only 0.17% and 0.26% of cancer deaths in men and women, respectively.¹ Interestingly, the biology of thyroid cancer represents a spectrum of behavior ranging from well-differentiated lesions with an excellent prognosis to anaplastic carcinoma, which is almost uniformly fatal. For this reason, it is important that clinicians have methods at their disposal to assess the behavior of a patient's thyroid malignancy. Without such information, appropriate decisions regarding treatment cannot be made. In this review, we consider the

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factors that are known to affect the prognosis of patients with well-differentiated thyroid malignancies.

Internationally, the most widely accepted system of classifying solid organ malignancies is the postoperative tumor-node-metastasis (pTNM) system, endorsed by both the International Union against Cancer (UICC) and the American Joint Commission on Cancer (AJCC).² Generally, this system stages malignant lesions according to tumor size and invasiveness, nodal spread, and distant metastases. Histology and patient age are also utilized to further classify disease stage in thyroid can-

Table 1. — American Joint Committee on Cancer Staging for Papillary, Follicular, and Medullary Thyroid Carcinoma

| | | |
|---|--|-----------------------------|
| | Papillary or Follicular: | |
| | Age <45 yrs | Age 45 or Older |
| Stage I | Any T, any N, M0 | Any T1, N0, M0 |
| Stage II | Any T, any N, M1 | T2 or 3, N0, M0 |
| Stage III | - | T4, N0, M0 or any T, N1, M0 |
| Stage IV | - | Any T, any N, M1 |
| | Medullary: | |
| Stage I | T1, N0, M0 | |
| Stage II | T2-4, N0, M0 | |
| Stage III | Any T, N1, M0 | |
| Stage IV | Any T, any N, M1 | |
| | Undifferentiated: | |
| Stage IV (all cases) | Any T, any N, any M | |
| Definition of TNM: | | |
| Primary Tumor (T) | T0 = No evidence of primary tumor | |
| | T1 = Tumor 1 cm or less in greatest dimension limited to the thyroid | |
| | T2 = Tumor more than 1 cm but not more than 4 cm in greatest dimension limited to the thyroid | |
| | T3 = Tumor more than 4 cm in greatest dimension limited to the thyroid | |
| | T4 = Tumor of any size extending beyond the thyroid capsule | |
| Regional Lymph Nodes (N) | N0 = No regional lymph node metastasis | |
| | N1 = Regional lymph node metastasis | |
| | N1a = Metastasis in ipsilateral cervical lymph node(s) | |
| | N1b = Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s) | |
| Distant Metastasis (M) | M0 = No distant metastasis | |
| | M1 = Distant metastasis | |
| Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago Ill. The original source for this material is the <i>AJCC Cancer Staging Handbook</i> , 5th ed (1997), published by Lippincott-Raven Publishers, Philadelphia, Pa. | | |

cer.² On the basis of this AJCC staging system, all patients younger than 45 years of age with papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) have stage I disease unless they have distant metastases, in which circumstance the disease is classified stage II. Older patients (45 years of age or older) with node-negative papillary or follicular microcarcinoma (T1 N0 M0) have stage I disease. Intrathyroidal tumors 1.1 cm or larger are stage II, and either nodal involvement or extrathyroid invasion in older patients with PTC or FTC leads to stage III classification. For medullary thyroid carcinoma (MTC), the scheme is similar in that microcarcinoma (tumor 1 cm or smaller) is stage I and node-positive is stage III. There is no age distinction for MTC, however, and local (extrathyroid) invasion is defined as stage II. For both MTC and older patients with PTC or FTC, stage IV denotes the presence of distant metastases (Table 1).

At our institution, a team of clinicians and statisticians have developed a comprehensive, computerized thyroid cancer database that includes the details of presentation, therapy, and outcome of 2,278 patients receiving primary treatment for papillary, follicular, Hürthle cell, and medullary thyroid carcinomas at our center during 1940 through 1990. These patients have now been observed for a period exceeding 36,800 patient-years. Table 2 provides further details of this group of patients with differentiated thyroid cancer (DTC).³ Data derived from outcome analysis in this cohort of patients have permitted the identification of those prognostic factors that are independently predictive of survival and recurrence in DTC.

Risk-Group Classifications

The relative rarity of thyroid cancer has precluded the development of prospective, randomized trials to determine which patient and treatment variables affect both cause-specific mortality and disease-free survival. Accordingly, most information on prognostic indicators has been derived from large retrospective uncontrolled studies.^{4,5} Recently, authors have used data collected by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute between 1973 and 1991 to investigate prognostic factors for each of the major histologic types of thyroid carcinoma in a population-based patient series and to assess the effect of these factors as predictors of survival in 15,698 cases.⁴ For the accession years 1985-1995, the National Cancer Data Base (NCDB) captured information on demographics, patterns of care, stages, treatments, and outcomes for a sample of 53,856 thyroid carcinoma cases (1% of total NCDB cases).⁵ From such studies, numerous patient and

Table 2. — Papillary, Follicular, and Medullary Thyroid Carcinoma at Mayo Clinic, 1940-1990

| Tumor Histology | Number (n=2,278) | Mean Age (yrs) | Surviving (%) | |
|---------------------------|---------------------|----------------|---------------|--------|
| | | | 10 yrs | 20 yrs |
| Papillary | 1,851 (81%) | 44.4 | 95.5 | 94.7 |
| Follicular (nonoxyphilic) | 153 (7%) | 51.0 | 80.5 | 71.1 |
| Follicular (oxyphilic) | 93 (4%) | 58.4 | 84.4 | 78.7 |
| Medullary | 181 (8%) | 41.4 | 82.9 | 79.7 |

tumor factors, including age, gender, tumor size, histologic grade and type, local invasion, multicentricity, and the presence of metastatic disease, have been studied and found to be independent predictors of prognosis. Knowledge of these relevant prognostic factors has led, during the past two decades, to several staging or scoring systems that have been derived from extensive analysis and allow the classification of patients with follicular cell-derived carcinomas into categories at low-, intermediate-, or high-risk of cause-specific mortality. Because most cancer-related deaths are mediated through biologically significant recurrent events at local or distant sites, these schemes also provide data relevant to tumor recurrence rates in patients who have undergone complete resection of their primary tumors.⁶

The variables used in the creation of the original prognostic index system devised by the European Organization for Research on Treatment of Cancer (EORTC)⁷ are contrasted in Table 3 with those used in six other schemes developed in the United States and described during 1987 through 1998.⁷⁻¹⁴ Of note, all of these prognostic schemes include extrathyroid invasion and distant metastatic involvement. Almost all include tumor size, and the majority take histologic type into consideration. A few consider nodal metastatic lesions and patient sex.^{9,10} Some include histologic grade¹¹ and the presence of multiple (more than three) tumors.¹² Only one scheme (MACIS) includes the presence of gross residual disease after primary surgical resection.

The calculations used in the three most widely used systems have been summarized in Table 4. It should be noted that these systems do not include several other variables such as DNA ploidy,^{15,16} adenylate cyclase activity,¹⁷ extent of surgical resection,^{18,19} p53 gene mutations,²⁰ and the presence of epidermal growth factor,²¹ which have also been reported to have prognostic significance in patients with DTC.

Table 3. — Components of Prognostic Schemes Used for Defining Risk-Group Categories in Patients With Follicular Cell-Derived Carcinoma

| Prognostic Variable | EORTC ⁷ (1979) | AGES ¹¹ (1987) | AMES ¹⁴ (1988) | MACIS ¹³ (1993) | OSU ¹² (1994) | MSKCC ⁹ (1995) | NTCTCS ¹⁰ (1998) |
|--|------------------------------|------------------------------|------------------------------|-------------------------------|-----------------------------|------------------------------|--------------------------------|
| Patient factors | | | | | | | |
| Age | X | X | X | X | — | X | X |
| Sex | X | — | X | — | — | — | — |
| Tumor factors | | | | | | | |
| Size | — | X | X | X | X | X | X |
| Multicentricity | — | — | — | — | X | — | X |
| Histologic grade | — | X | — | — | — | X | — |
| Histologic type | X | Y | X | Y | — | X | X |
| Extrathyroidal invasion | X | X | X | X | X | X | X |
| Nodal metastatic lesion | — | — | — | — | X | X | X |
| Distant metastatic lesion | X | X | X | X | X | X | X |
| Operative factors | | | | | | | |
| Incomplete resection | — | — | — | X | — | — | — |
| X = variable used in defining risk group Y = schemes devised only for PTC — = variable not used | | | | | | | |
| EORTC = European Organization for Research on Treatment of Cancer AGES = patient age, histologic grade of the tumor, tumor extent (extrathyroidal invasion or distant metastases), and size of the primary tumor AMES = patient age, presence of distant metastases, extent and size of the primary tumor MACIS = metastasis, patient age, completeness of resection, local invasion, and tumor size OSU = Ohio State University MSKCC = Memorial Sloan-Kettering Cancer Center NTCTCS = National Thyroid Cancer Treatment Cooperative Study | | | | | | | |

Table 4. — Prognostic Scoring Systems for AGES, AMES, and MACIS

| | |
|---------------------|--|
| AGES ¹¹ | <p>Prognostic score = $0.05 \times \text{age}$ (if age ≥ 40)</p> <ul style="list-style-type: none"> + 1 (if grade 2) + 3 (if grade 3 or 4) + 1 (if extrathyroid) + 3 (if distant spread) + $0.2 \times \text{tumor size}$ (cm maximum diameter) <p>Survival by AGES score (20-yr):</p> <ul style="list-style-type: none"> $\leq 3.99 = 99\%$ 4-4.99 = 80% 5-5.99 = 67% $\geq 6 = 13\%$ |
| AMES ¹⁴ | <p>Low risk: Younger patients (men ≤ 40, women ≤ 50) with no metastases</p> <p>Older patients (intrathyroid papillary, minor capsular invasion for follicular lesions)</p> <p>Primary cancers < 5 cm</p> <p>No distant metastases</p> <p>High risk: All patients with distant metastases</p> <p>Extrathyroid papillary, major capsular invasion follicular</p> <p>Primary cancers ≥ 5 cm in older patients (men > 40, women > 50)</p> <p>Survival by AMES risk-groups (20-yr):</p> <ul style="list-style-type: none"> Low risk = 99% High risk = 61% |
| MACIS ¹³ | <p>Score = 3.1 (if age < 40 years) or $0.08 \times \text{age}$ (if age ≥ 40 yrs)</p> <ul style="list-style-type: none"> + $0.3 \times \text{tumor size}$ (cm maximum diameter) + 1 (if incompletely resected) + 1 (if locally invasive) + 3 (if distant spread) <p>Survival by MACIS score (20-yr):</p> <ul style="list-style-type: none"> $< 6 = 99\%$ 6-6.99 = 89% 7-7.99 = 56% $\geq 8 = 24\%$ |

Papillary Thyroid Carcinoma (PTC)

Most PTC patients present with either pTNM stage I (55% to 60%) or stage II (14% to 22%) disease.^{5,22} Patients aged 45 years or older with either nodal metastases or extrathyroid extension (stage III) account for fewer than 20% of cases.²² Only approximately 1% to 3% of older PTC patients present with distant metastases and have stage IV disease. Fig 1 demonstrates cause-specific survival according to pTNM stage in a cohort of 1,851 patients who underwent surgical treatment at our institution during 1940 to 1990.²²

From 859 PTC patients treated at the Mayo Clinic from 1946 through 1970, 16 prognostic variables were identified and studied initially by univariate analysis.

Those found to be statistically significant by univariate analysis were then submitted to multivariate analysis.¹¹ These analyses revealed that only four factors associated with a worse prognosis were independently significant: age of the patient, histologic grade of the tumor, extent of the tumor (extrathyroidal invasion or distant metastases), and size of the primary tumor (AGES). These were combined according to their weighted significance into a prognostic score (Table 4) that would accurately distinguish low-risk from high-risk patients. The high-risk group of PTC patients (AGES score 4+) comprised only 13% of the overall group. Whereas the low-risk patients (score < 4) had a cause-specific mortality rate at 20 years of only 1.1%, the mortality rate for high-risk patients was 39%. The mortality (all causes) for the low-risk group was identical to that predicted by actuarial curves. In PTC, lymph node status has almost never been shown to influence cause-specific mortality. However, nodal metastases found at presentation are predictive of an increased risk of subsequent locoregional disease recurrence.²³

One year after introduction of the AGES score, Cady and Rossi¹⁴ reported an analysis of 821 DTC patients initially treated at the Lahey Clinic between 1941 and 1980. From this analysis they developed the AMES system, which was based on age of the patient, presence of distant metastases, extent of the primary tumor, and the size of the primary cancer (Tables 3-4). Its prognostic value was found to be similar to the AGES system, with low- and high-risk mortality rates at 20 years of 1.2% and 39.5%, respectively. These rates are each nearly identical to the 1.1% and 39% rates predicted by comparable AGES scores. Unfavorable factors were male gender, older age (greater than age 40 for men, greater than age 50 for women), major capsular invasion for follicular lesions, tumors more than 5 cm in size, extrathyroidal extension of tumor, and distant metastases at presentation.

In an attempt to overcome the impediment in the AGES system resulting from the lack of an accepted histologic grading system for PTC, the Mayo Clinic outcome data were reanalyzed, excluding tumor grade. Incorporating 1,779 patients, this analysis found the following to be independently significant parameters: metastasis, age of the patient, completeness of primary tumor resection, presence of extrathyroidal invasion, and tumor size (Tables 3-4).¹³ A total of 84% of the PTC patients had a MACIS score of less than 6 (low-risk) and a 20-year cause-specific mortality of only 1% (Fig 2). The MACIS scheme (using metastasis, patient age, completeness of resection, local invasion, and tumor size) represents a very accurate prognostic scoring system for PTC. Since 1994 MACIS has been used at the Mayo Clinic to delineate likely postoperative outcome and to

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tems, all of which accurately predicted the prognosis of patients with PTC.

A recent paper by Learoyd et al²⁷ analyzed the clinical outcome in patients with PTC on the basis of the presence or absence of ret/PTC oncogene expression. In their series of 50 adult patients with PTC, only 4 had ret/PTC activation. They found no significant difference between the two clinical patient groups (MACIS score <6 vs 6+) with respect to the presence or absence of ret/PTC in the patient's tumor. Previously, it had been suggested that the presence of ret/PTC may be associated with a greater likelihood of metastatic spread and poorer

determine the aggression of postoperative treatment and the intensity of surveillance for tumor recurrence.

In the past decade, DNA ploidy analysis has been highly regarded as a prognostic factor in PTC, and Pasięka²⁴ advised its addition to the AMES risk-group classification. The predictive value of DNA ploidy analysis has been verified by data from both the Mayo Clinic²³ and the Karolinska Institute.¹⁵ Such analysis may not see widespread acceptance in clinical practice, however, because it requires additional time, expense, equipment, and special expertise and, realistically, the results cannot be available at the time of surgical resection. By contrast, the MACIS, AGES, and AMES scores can be determined from data available before and during initial neck exploration. Based on these systems, operative intervention may be tailored to fit the individual patient's disease, and whether postoperative adjunctive therapy is needed can be more rationally discussed.²⁵ Recently, Brierley et al²⁶ evaluated 382 patients with DTC using all of these scoring systems and found no significant difference among AGES, TNM, EORTC, MACIS, and AMES sys-

prognosis.²⁸ In studies from the Chernobyl area, most of the children had lymph node involvement and some required early reoperation for local recurrence, suggesting an aggressive behavior on the part of the tumor. In these cases, the ret/PTC3 isoform was more prevalent than ret/PTC1.²⁹ Cumulative data presently available suggest that ret/PTC cannot be considered as a single entity but rather as variants, eg, ret/PTC1 and ret/PTC3,

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that could have different biological behaviors. If further confirmed, these data suggest that constitutive activation of *ret* in papillary cancers determines a different carcinogenetic pathway according to the different fused gene, with *ret*/*PTC1* possibly having a better prognosis and *ret*/*PTC3* a worse prognosis.³⁰

Our knowledge of the molecular genetics of PTC has grown significantly over the past few years. Flow cytometric data have revealed a correlation between aneuploid DNA patterns and poor outcomes for PTC patients.^{15,16,31} A retrospective review of fine-needle aspirate smears by image cytometry has likewise demonstrated evidence of associations between aneuploid or aggressive DNA patterns and both distant metastases and death from disease.³² Several types of oncogene alterations have been described in papillary carcinomas, including the *ret*/*PTC* rearrangement, tyrosine-receptor kinase rearrangement, and *N-ras* point mutation.³³ Immunohistochemical studies have supported the idea that aberrations in *p53* function are associated with a stepwise loss of differentiation in this neoplasm.³⁴ To date, knowledge regarding the participation of special oncogenes in PTC has not led to novel prognostic indicators applicable to present clinical practice.

Follicular Thyroid Carcinoma (FTC) Including Hürthle Cell Carcinoma

When more than 75% of cells in an FTC exhibit Hürthle cell or oncocytic features, the tumor is classified as a Hürthle cell cancer (HCC), oncocytic carcino-

ma, or oxyphilic variant FTC.²² A minority of patients (21% to 41%) with FTC or HCC present with pTNM stage I disease. Most patients (35% to 70%) have pTNM stage II disease. Patients aged 45 years or older with nodal metastases or extrathyroid extension (stage III) account for only approximately 4% to 7% of FTC and 8% to 10% of HCC.^{5,22} In contrast with PTC, in which only 1% to 3% present with stage IV disease, about 4% to 6% of HCC and 7% to 15% of nonoxyphilic FTC cases have distant metastases at the time of initial diagnosis.^{5,35} Fig 3 demonstrates cause-specific survival according to pTNM stage in a cohort of 153 patients with nonoxyphilic FTC surgically treated at our center from 1940 to 1990.²²

Using multivariate analysis, Brennan et al³⁶ identified age greater than 50 years, marked vascular invasion, and metastatic disease at the time of diagnosis to be the only independent predictors of cause-specific mortality using data from 100 patients with nonoxyphilic FTC treated surgically between 1946 and 1970. Low-risk patients (0 to 1 factor present) had survival rates of 99% and 86% at 5 and 20 years, respectively. High-risk patients having 2 or 3 of these factors had survival rates of 47% and 8% at 5 and 20 years, respectively (Fig 4). In a subsequent Mayo Clinic study, 65 patients with FTC were classified as either showing capsular invasion alone or vascular invasion with or without capsular invasion. In this review, the 10-year rates of cause-specific mortality and distant metastases were 28% and 19%, respectively, for patients with vascular invasion.³⁷ Comparable rates for patients with tumors with capsular invasion only were 0% and 0%, respectively. Microin-

vasion was classified as minimal in 37 patients (57%), moderate in 20 patients (31%), and marked in 8 patients (12%). Microinvasion was an estimate of the degree of histologic invasion and included both capsular invasion and vascular invasion. Vascular invasion was identifiable in 45 patients (69%). Evidence of capsular invasion in the absence of demonstrable vascular invasion was present in the remaining 20 cases. The 10-year mortality rates for minimal, moderate, and marked microinvasion were 10%, 34%, and 27%, respectively. The diagnosis of malignancy is seldom in question when widely invasive tumors are present with obvious vascular inva-

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sion. Problems arise with minimally invasive tumors. Although observed vascular invasion would appear to be straightforward, this is not necessarily so. Prominent vessels that lie in close apposition to the tumor but are not actually invaded are often present in the capsule. Spaces with tongues of tumor that are not lined by endothelium of a blood vessel but by attenuated thyroid epithelium may develop within the neoplasm, and therefore they simply represent infolding and convoluted patterns within the neoplasm.³⁷ Although the importance of microinvasion of blood vessel or thyroid capsule is widely accepted in diagnosing FTC and HCC, even in the beginning of the 21st century there remains confusion regarding the prognostic importance of angioinvasion and considerable controversy about the definition of minimal capsular invasion.

Sanders and Cady³⁸ recently reviewed 1,019 DTC patients treated between 1940 and 1990, with a median follow-up of 13 years overall. PTC comprised 76% of the cases; 20% were typical FTC and 4% had HCC. In the entire group, there were 78% low-risk and 22% high-risk patients by the AMES criteria. The AMES criteria remained highly discriminatory in predicting rates of recurrence and death. In the entire group of patients from 1940 through 1990, the adjusted survival rate at 20 years was 96% for low-risk patients and 50% for high-risk patients ($P=0.001$).

Shaha et al⁹ performed a retrospective review of 228 consecutive previously untreated patients diagnosed with FTC who were seen and treated at Memorial Sloan-Kettering Cancer Center during a period of 55 years from 1930 to 1985. Ninety patients (39%) were younger than 45 years of age, and 138 (61%) patients were older than 45 years. Important factors associated with worse prognosis identified on multivariate analysis were age older than 45 years ($P<0.001$), Hürthle cell subtype ($P<0.05$), extrathyroidal extension, tumor size exceeding 4 cm, and the presence or absence of distant metastasis ($P<0.001$). Other prognostic factors such as gender, focality, and presence of nodal metastasis had no significant influence on prognosis. They grouped their patients into three distinct prognostic groups: low-, intermediate-, and high-risk. The 5-, 10-, and 20-year determinate survival rates for the entire series of patients with FTC were 85%, 80%, and 76%, respectively. The 10-year survival rates for the low-, intermediate-, and high-risk groups were 98%, 88%, and 56%, respectively, and the 20-year survival rates for the same groups were 97%, 87%, and 49%, respectively.

At present, HCC tumors are considered to be an aggressive subtype of FTC. Watson and colleagues³⁹ reported on outcome in 29 HCC patients treated at the Mayo Clinic between 1946 and 1971. The average

age of these patients was 55 years. Of the 29 patients, 24 had grade 1 lesions and 5 had grade 2 lesions. Patients with histologic grade 2 lesions had higher rates of metastatic disease and of deaths from thyroid cancer than patients with grade 1 lesions. Patients with adjacent tissue involvement at the time of the initial operation had moderately higher rates of local recurrence and metastatic disease than patients who did not have involvement in other neck structures. The presence or absence of nodal involvement was important and resulted in significant differences in the rates of local recurrence, metastatic disease, and death from thyroid cancer. The patients in this series were selected on the basis of strictly defined histologic criteria and accounted for only 2.5% of a total group of patients with thyroid cancer and approximately 20% of all patients with FTC. In a later Mayo study, flow cytometric analysis demonstrated that DNA aneuploidy was independently associated with tumor-related mortality. Of 30 patients with euploid HCC, no disease-specific mortality was observed after an average of 13 postoperative years.⁴⁰

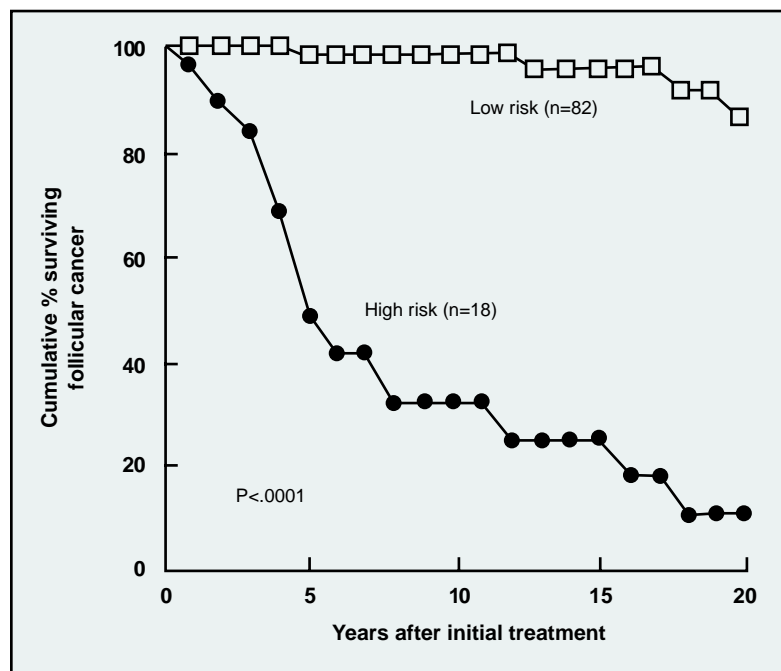


Fig 4. — Cause-specific survival among 100 patients with nonoxyphilic follicular thyroid cancer treated at the Mayo Clinic from 1946 to 1970 and plotted by high-risk and low-risk categories. High-risk = 2 or more of the following factors present: age greater than 50 years, marked vascular invasion, and metastatic disease at time of initial diagnosis. From Brennan MD, Bergstralh EJ, van Heerden JA, et al. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc.* 1991;66:11-22. Reprinted with permission.

Cady and Rossi¹⁴ have applied their AMES risk-group categorization successfully to patients with either FTC or HCC and have found the scheme to be useful. Similarly, the AGES scheme,¹¹ originally developed for PTC, has been successfully applied to FTC.⁴¹ It would therefore appear that scoring systems that have been derived for PTC patients may be cautiously applied for predicting outcome in the rarer FTC.³⁵ However, certain unique features of this tumor, most notably vascular invasiveness³⁷ and the unique significance of DNA aneuploidy in oxyphilic FTC,⁴² also must be considered.

Medullary Thyroid Carcinoma

The TNM staging system is quite accurate for predicting cause-specific survival in MTC. In reported studies of treated MTC, the proportion of patients with intrathyroidal node-negative microcancers (stage I = T1 N0 M0) varies, depending on the number of familial cases detected by biochemical testing or DNA screening. The proportion of patients who present with stage I MTC varies from 5% to 25%, the lower numbers representing the older series. Most (25% to 50%) present with positive neck nodes (stage III), and approximately 30% to 45% present with stage II disease. The proportion of patients presenting with distant metastases usually exceeds PTC but is typically less than in FTC. Stage IV cases constitute 3% to 10% of most MTC series. Fig 5 illustrates cause-specific survival according to pTNM stage in a cohort of 181 patients with MTC surgically treated at the Mayo Clinic from 1940 to 1990.²²

TNM disease stage, inheritance pattern, and DNA ploidy pattern were independently significant prognostic variables in a study of 119 patients from the Mayo Clinic.⁴³ Worse outcome was found with sporadic MTC and pTNM stages III and IV. The 10-year cause-specific mortality was nearly 50% in nondiploid MTC vs 12% in diploid tumors. TNM stage, tumor resectability, and the presence or absence of amyloid staining of the tumor by Congo Red proved to be independently important prognostic variables in a subsequent study of 65 MTC patients.⁴⁴ A simple scoring system was devised by combining these factors. The adverse prognostic factors (TNM stages III or IV, incomplete surgical resection,

and negative amyloid staining) were each given 1 point. One point (adverse risk factor) indicated a low risk of mortality (22% at 10 years). Moderate risk was present with 2 points (74% 10-year mortality), and all patients with 3 points died within 1 year of surgery.

Other prognostic factors relevant to a worse outcome in MTC include age at diagnosis, male gender, vascular invasion, calcitonin immunoreactivity, and abnormal postoperative plasma calcitonin levels.⁴⁴⁻⁴⁶ In a recently published multivariate analysis,⁴⁶ only the presence of extrathyroid invasion and postoperative gross residual disease were significant in the prediction of cause-specific survival.

Tisell et al⁴⁷ reviewed 40 patients with MTC who had undergone total thyroidectomy and a variable amount of lymph node dissection at various hospitals in the United States. Nine of the patients had sporadic MTC, 26 patients had multiple endocrine neoplasia (MEN) type 2A, three patients had MEN 2B, and two patients had familial non-MEN MTC. All patients had persistent provoked hypercalcitoninemia (26 patients after one operation, 11 after two operations, and three after three operations). Serial determinations of plasma calcitonin levels were obtained before and after intravenous injection of calcium and pentagastrin. This study revealed that stimulated peak plasma calcitonin levels were more meaningful than basal levels in the serial postoperative evaluation of patients with persistent hypercalcitoninemia after thyroidectomy for MTC. Basal plasma calcitonin concentrations were normal in 63% of patients at the first postoperative test and in

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30% at the last test. Therefore, the fact that they had persistent and even progressive disease was not apparent until elevated plasma calcitonin levels were documented after provocative testing. In MEN 2A or familial MTC patients, long-term cure is almost guaranteed when total thyroidectomy is performed after detection by ret proto-oncogene screening and before the discovery of clinical disease.⁴⁸

Bergholm et al⁴⁹ identified all patients with MTC diagnosed in Sweden during 1959 through 1981. The cohort was followed with regard to survival to identify prognostic factors. In a follow-up report, Bergholm and colleagues⁵⁰ then examined to what extent those prognostic factors found in their previous analyses remained independent prognostic factors for survival 10 years or longer after diagnosis. The follow-up period was extended an additional 5 years and ranged between 11 and 32 years. The relative survival rate was 69.2% and 64.7% at 10 and 15 years, respectively, after diagnosis. The survival rate was worse after excluding those patients with a family history of MTC (60.8% and 53.7% at 10 and 15 years after diagnosis, respectively). In multivariate analyses, age, tumor size, stage of the disease at diagnosis, tumor amyloid content, and a euploid DNA pattern were found to be independent prognostic factors.^{49,51} However, in analyses of survival 10 years or longer after diagnosis, only stage, tumor size, and age remained independent prognostic factors. The authors concluded that there is still an excess mortality 10 years or longer after a diagnosis of MTC. However, they identified three groups of patients in whom the survival 10 years or longer after diagnosis did not differ from that of the general population: patients with a family history of MTC detected by screening, those with tumor size less than 1 cm, or those with early-stage disease at diagnosis.

Modigliani et al⁵² evaluated factors involved in the prognosis of MTC by reviewing clinical, biological, surgical, and epidemiological data on 899 MTC patients diagnosed between 1952 and 1996. Data were collected by the French Calcitonin Tumors Study Group with a standardized questionnaire and processed in a national database. Adjusted survival was $85.7 \pm 1.5\%$ at 5 years and $78.4 \pm 2.1\%$ at 10 years. Multivariate analysis showed that age and stage were independent predictive factors of survival. Gender, type of surgery, and type of familial form were predictive only in univariate analysis. Biochemical cure predicts a survival rate of 97.7% at 10 years. Authentic recurrence, ie, subsequent elevation of calcitonin after postoperative normalization, was found in 4.9%. In noncured patients (57%), survival was still good: 80.2% and 70.3% at 5 and 10 years, respectively. Similarly, prediction of biochemical cure was solely dependent on stage.

Therapeutic Implications

The primary surgical procedures employed in treating DTC vary from unilateral lobectomy with isthmectomy through bilateral subtotal lobar resection to near-total or total thyroidectomy.⁵³ In low-risk DTC, Shaha and colleagues⁵⁴ found no statistical difference in the overall failure rate between unilateral total lobectomy and total thyroidectomy. Cady⁸ has suggested that the vast majority of low-risk DTC patients "require only thyroid lobectomy without adjuvant therapy," and he strongly advised that the "removal of the contralateral lobe of the thyroid for arbitrary and doctrinaire reasons should be avoided." However, recent studies from Mayo of 1,913 AMES low-risk PTC patients have demonstrated that, even in this setting, unilateral total lobectomy leads to more locoregional recurrences when compared to bilateral lobar resection.⁵⁵ Thus, in our institution, near-total thyroidectomy is the usual primary procedure for patients with PTC, FTC, or HCC, whereas total thyroidectomy is typically employed in MTC, especially familial cases.

If only a unilateral lobectomy has been performed initially for a follicular cell-derived cancer, it is often prudent to consider completion thyroidectomy for lesions that are anticipated to have an aggressive behavior, because large thyroid remnants are difficult to ablate with iodine-131.⁵⁶ Radioiodine remnant ablation (RRA) has often been used after near-total or total thyroidectomy to "complete" initial therapy in follicular cell-derived cancer, but it should be used selectively.⁵⁷ Presently at our center, RRA is not usually recommended for low-risk PTC cases (with AGES scores <4 or MACIS scores <6), but it is regularly employed as postoperative therapy in patients with FTC (including the oxyphilic variant tumors) or high-risk PTC patients with MACIS scores of 6 or more. It should be noted that even in the early 21st century, there continues to be a lack of international consensus regarding the extent of initial surgery and whether radioactive iodine should be routinely administered for postoperative remnant ablation.⁵⁸

Conclusions

It would appear that for patients with DTC, it is possible at the time of initial treatment to accurately predict survival and future recurrence risk. Increased use of the TNM staging system and the prognostic scoring systems described in this paper, coupled with a better understanding of other independently important prognostic variables, should result in improved patient care and treatment. Such considerations may in future years permit the realization of the recently

much-discussed concept of "a selective approach to therapy that avoids unnecessarily aggressive treatment for tumors that are likely to follow a benign course, and inadequate therapy for others anticipated to display aggressive behavior."⁵⁹

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