Papillary Carcinoma of the Thyroid

A Clinicopathologic Study of 241 Cases Treated at the University of Florence, Italy

MARIA LUISA CARCANGIU, MD,* GIANCARLO ZAMPI, MD,† ALBERTO PUPI, MD,‡ ANTONIO CASTAGNOLI, MD,§ AND JUAN ROSAI, MD‖

A clinicopathologic study of 241 cases of papillary thyroid carcinoma treated at the University of Florence Medical School, Florence, Italy is presented. The features of greatest prognostic value were patient's age at presentation, small tumor size, total encapsulation, extrathyroid extension, multicentricity, and presence of distant metastases. The prognosis of the disease was not influenced by the pattern of tumor growth, presence of solid areas, initial presence or subsequent development of cervical lymph node metastases, type of initial thyroid operation, performance of neck dissection, or prophylactic administration of radioactive iodine. It is concluded that conservative thyroid surgery in the form of lobectomy, without neck dissection or prophylactic administration of iodine 131 (^{131}I), constitutes adequate therapy for most cases of papillary thyroid carcinoma. More extensive therapy should be considered for older patients and for those in whom the tumor exhibits extrathyroid extension or easily detectable multicentricity.

Cancer 55:805–828, 1985.

PAPILLARY THYROID CARCINOMA (PTC) is the most common form of thyroid malignancy. Numerous clinicopathologic studies have documented its generally indolent clinical course and excellent overall prognosis. However, controversy still exists about the prognostic significance of some morphologic parameters and over what is the best form of therapy for this tumor. Furthermore, a reevaluation in recent years of the cytoarchitectural features that characterize this tumor has led to a broader concept of PTC, and the inclusion within this category of a number of lesions that were formerly regarded either as separate tumor types or as belonging to some other major group of thyroid neoplasia. Some of these variants carry prognostic implications that are substantially different from those of garden variety PTC. Others do not, even if their morphologic departure from the classic type is so marked as to suggest to the pathologist that they should.

The existence of these changing and sometimes conflicting views about PTC that have been expressed in the literature have prompted us to review our personal experience, based on a relatively large number of cases that were treated and followed in a rather consistent fashion in a single institution, over a long period.

Material and Methods

All cases that were coded in the files of the Pathology Institute of the University of Florence, Italy as carcinoma of the thyroid gland were reviewed, and the microscopic slides were studied. All cases that were regarded by the authors as PTC were evaluated for adequacy of pathologic material, clinical information, and follow-up information.

Presented in part at the 9th European Congress of Pathology, Hamburg, West Germany, September 1983; and at the 73rd Annual Meeting of the International Academy of Pathology (United States-Canadian Division), San Francisco, California, March 1984.

From the Institutes of Anatomic Pathology and Nuclear Medicine, and the Nuclear Medicine Service of the Unitã Sanitasia Locale 10-D, Florence, Italy, and the Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota. A substantial amount of this work was done during a sabbatical furlough that one of the authors (J.R.) spent at the Institute of Anatomic Pathology of the University of Florence Medical School, Florence Italy.

* Associate Professor of Anatomic Pathology, University of Florence Medical School, Florence, Italy.

† Professor of Anatomic Pathology and Director of the Institute of Anatomic Pathology, University of Florence Medical School, Florence, Italy.

‡ Associate Professor of Nuclear Medicine, University of Florence Medical School, Florence, Italy.

§ Attending Physician, Nuclear Medicine Service of Unitã Sanitaria Locale 10-D, Florence, Italy.

‖ Professor of Laboratory Medicine and Pathology and Director of Anatomic Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

Address for reprints: Juan Rosai, MD, Box 76 Mayo, University of Minnesota Hospitals, Minneapolis, MN 55455.

The authors thank Dorothee Aeppli, PHD, Statistician, Division of Biometry, School of Public Health, University of Minnesota, for having performed the statistical evaluations contained in this article.

Accepted for publication February 10, 1984.

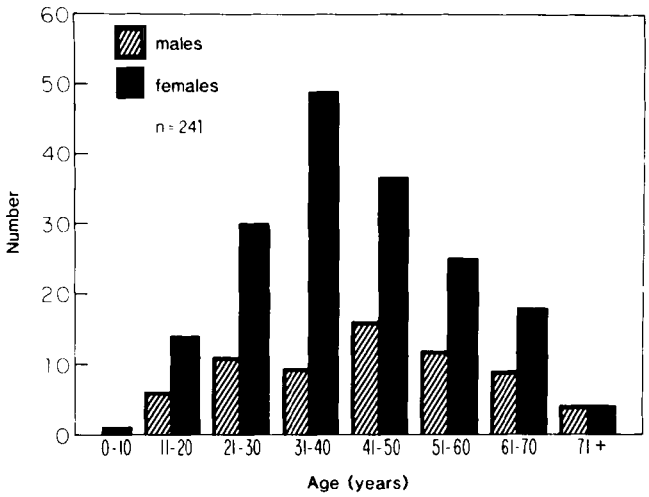


FIG. 1. Age and sex distribution of patients with PTC. The male:female ratio is 1:2.6.

Cases were included in the study only when microscopic slides and clinical information, and when follow-up data extended for a minimum of 3 years or until death. For the period stated, only 55 patients had to be eliminated because of lack of information about their evolution. The follow-up period ranged from 3 to 23 years, with a mean of 6.3 years. Follow-up information for a minimum of 10 years, or until death, was available in 70 patients (29% of the entire group). Excluded from this series were papillary carcinomas composed exclusively or predominantly of Hürthle cells (Hürthle cell carcinoma), water-clear cells (clear cell carcinoma),[1] and C-cells (papillary medullary carcinoma).[2] Also excluded were three cases of PTC accompanied by areas of anaplastic transformation[3] as well as a small group of poorly differentiated ("insular") carcinomas possibly linked with PTC, but having a distinct set of morphologic features.[4]

The cases finally selected for the study reported here numbered 241. All patients had been treated at one or another of the several surgery departments belonging to or affiliated with the University of Florence Medical School, and most cases were studied in consultation by the Department of Nuclear Medicine of the same university. After completion of therapy, all patients were followed indefinitely on a 1-year basis, or until death.

Microscopic slides were reexamined and, when necessary, new slides were prepared from the paraffin blocks. In most cases, only sections stained with hematoxylin and eosin were studied. In 22 cases, slides from the primary tumor were not available, only those of the nodal metastases. The following morphologic parameters were evaluated in the primary tumor: presence of ground-glass nuclei, tumor size, capsule, type of margins, pattern of growth (relative proportion of papillae and follicles), presence and type of fibrosis, presence and degree of cystic changes, presence and amount of solid areas, squamous metaplasia, psammoma bodies, lymphocytic infiltration of the tumor stroma, multicentricity, blood vessel invasion, extrathyroid extension, and morphologic appearance of the nonneoplastic thyroid. Some of these parameters were also evaluated in the nodal metastases. The correlations that these various morphologic features bore among themselves, with the incidence of metastases, and with the evolution of the disease, were studied by applying the chi-square formula to establish the statistical significance of the differences encountered. The Kaplan and Meier technique[5] was used to determine the estimated probabilities of recurrence/metastases and of survival, computed from the time of initial diagnosis. Differences between groups were tested by the method of Breslow.[6] The computer program used for this purpose was BMDP (June 1981), Department of Biomathematics, University of California at Los Angeles.

Results

Clinical Features

Sex: There were 67 male and 174 female patients, resulting in a male to female ratio of 1:2.6. This ratio remained fairly constant throughout the various age groups, except of the fourth decade, in which women greatly predominated (Fig. 1).

Age: The age distribution of the patients is shown in Figure 1. The range was from 10 to 88 years, and the mean was 41.3 years. The mean age of female patients was 39.6 years, and that of male patients 43.9 years.

Type of presentation: Two hundred thirty-eight patients (98.7%) presented initially with clinically evident disease in the neck. This was located within the thyroid gland in 160 (67.2%), in the thyroid gland plus cervical nodes in 31 (13%), and in the cervical nodes only in 47 (19.7%). Thus, clinically evident cervical lymphadenopathy at the time of presentation, with or without an accompanying thyroid mass, was noted in 78 patients (32.4%). Chest x-ray taken on admission or within the next 2 months showed evidence of lung metastases in 15 patients.

The three patients without clinical evidence of disease in the neck presented with lung metastases in two cases and with bone metastases in the other.

History of previous irradiation of the neck: This was obtained in 16 patients (6.6%), the mean interval between the irradiation and the diagnosis of the PTC being 22.7 years. The irradiation had been given for hyperthyroidism (three patients), "thymic hypertrophy" (two), tinea (three), acne (one), eczema (one), cutaneous hemangioma (one), otitis (one), cervical adenopathy (one), tonsillar

hypertrophy (one), vertebral collapse (one), and malignant lymphoma (one). No significant differences among the groups with and without history of previous irradiation were apparent.

Hyperthyroidism: A history of clinically evident hyperthyroidism before the diagnosis of PTC was present in eight patients (3.3%). In four of these, the diagnosis of carcinoma was made incidentally by the pathologist after a thyroidectomy had been performed because of the hyperthyroidism.

Pathologic Features

The two major criteria used for the recognition of papillary carcinoma were the presence of true papillary formation and a set of cytologic features, of which the ground-glass nucleus was the most important. True papillae had a central fibrovascular stalk and were usually lined by a single layer of cuboidal to low columnar tumor cells (Fig. 2). Special care was used in distinguishing these formations from follicular infoldings as seen in hyperplastic glands and from the "macropapillae" sometimes seen in benign nodules at the surface facing areas of cystic change. Thyroid tumors having true papillae, no matter how scanty, were regarded as papillary carcinomas and included in this study (even if the nuclei did not exhibit ground-glass features), unless they were composed throughout by one of the types listed in the "Material and Methods" section.

Ground-glass nuclei were identified by their relatively large size, round to slightly oval shape, frequent overlapping, generally inconspicuous and marginated nucleolus, irregularly thickened nuclear membrane, and optically clear appearance of the nucleoplasm, with few or no chromatin strands remaining (Fig. 2). Thyroid neoplasms having this combination of nuclear features were regarded as papillary carcinomas and included in the study even in the cases in which papillae could not be identified. Ground-glass nuclei were found in 88.2% of the cases. In some instances, this was a focal, inconspicuous phenomenon; in others, nearly all tumor cells exhibited this feature.

Tumor size: Division into several categories based on tumor size could not be done because this information was sometimes lacking from the gross description. Therefore, cases were simply divided into those measuring 1 cm or less and those larger than 1 cm based on the actual measurement of the greatest diameter of the tumor in the microscopic slides. Fourteen percent of the cases belonged to the first category. The prognosis for these patients was significantly better than for the rest: as many as 90% were free of disease at the time of the last follow-up examination, and none of the patients had died from the tumor. Only one instance of blood-borne metastasis had supervened, but there was a 64.5% incidence of cervical lymph node involvement in this group, as compared to 47.3% for the group with larger tumors (Table 1).

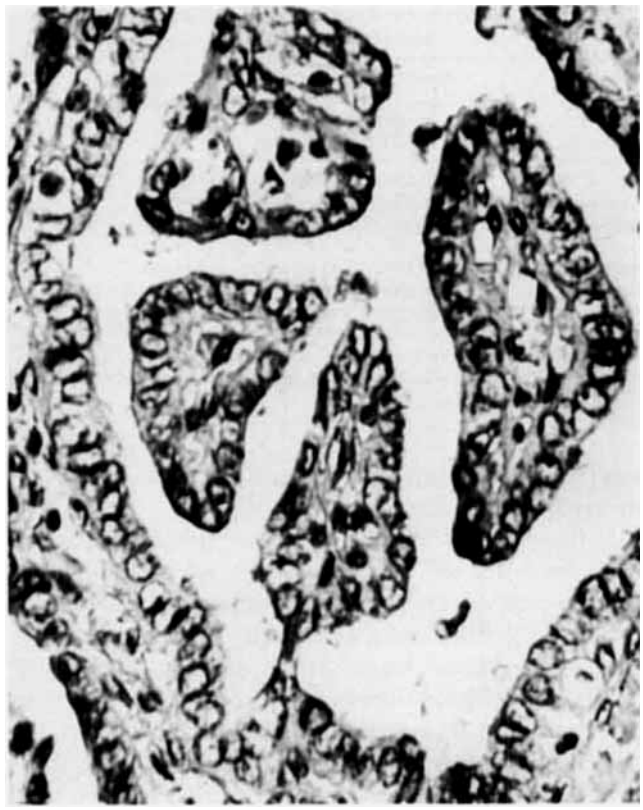


FIG. 2. Typical PTC, with well-formed papillae. Overlapping nuclei with so-called ground-glass appearance are present throughout.

Capsule: The presence of a capsule was determined at the microscopic level through the identification of a well-defined fibrous wall that separated the tumor from the adjacent tissues and which was distinct from the areas of fibrosis often present in PTC. On the basis of this feature, cases were divided into those with absent, partial, and total encapsulation. The structure in question

TABLE 1. Tumor Size and Its Influence on Prognosis and Metastatic Behavior

	Tumors ≤1 cm	Tumors >1 cm	
	31 (14.2%)	188 (85.8%)	
Alive & well	28 (90.3%)	144 (76.6%)	$P < 0.025$
Alive with tumor	3 (9.6%)	27 (14.4%)	
Dead of tumor	0 (0%)	9 (4.8%)	
Node metastases	20 (64.5%)	89 (47.3%)	$P < 0.10$
Distant metastases	1 (3.2%)	36 (19.1%)	$P < 0.05$

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 2. Tumor Encapsulation and Its Influence on Prognosis and Metastatic Behavior

	Absent Capsule	Partial Capsule	Total Capsule	
	92 (42.0%)	106 (48.4%)	21 (9.6%)	
Alive & well	67 (72.8%)	86 (81.1%)	19 (90.5%)	$P < 0.05$*
Alive with tumor	19 (20.6%)	9 (8.5%)	2 (9.5%)	
Dead of tumor	3 (3.3%)	6 (5.7%)	0 (0%)	
Node metastases	52 (56.5%)	49 (46.2%)	8 (38%)	
Lung metastases	13 (14.1%)	16 (15.1%)	0 (0%)	$P < 0.25$*

* The chi-square calculations were made between tumors with absent capsule and tumors with total capsule.

Patients who died of causes other than papillary carcinoma have been excluded.

was regarded as a capsule whether it was focally infiltrated by carcinoma or not.

Follow-up data showed that the number of patients who were free of disease was lowest in the tumors without capsule, and highest in those with total encapsulation, the differences among the three groups, however, being rather small. None of the patients with totally encapsulated tumors had blood-borne metastases, and none died from their tumors, but as many as 38% developed cervical lymph node metastases (Table 2).

Margins: Tumor margins were divided into pushing and infiltrating, depending on the nature of the interphase between tumor and adjacent tissue, independently from the presence or absence of a tumor capsule. The margins were pushing in 33.3% of the cases, and infiltrating in 66.7% (Table 3). There was a close correlation between the presence of a capsule and the type of margin, in the sense that 76.2% of the tumors with total capsule had pushing margins, whereas this was the case for only 27.2% of those without a capsule. However, these figures show that the opposite also occurred: 23.8% of the totally encapsulated tumors showed focal permeation of this capsule by an infiltrating pattern of growth, and 27.2% of the tumors without capsule still maintained a pushing type of margin all around (Table 4).

Patients having tumors with pushing margins had a slightly better chance of remaining free of disease following therapy. They had a lesser probability of developing cervical nodal metastases, but no differences were found regarding the incidence of blood-borne metastases (Table 3). When the features of capsule and margins were combined, a sharper separation into prognostically different groups was obtained (Table 5).

TABLE 3. Type of Tumor Margins and Its Influence on Prognosis and Metastatic Behavior

	Pushing margins	Infiltrating margins	
	73 (33.3%)	146 (66.7%)	
Alive & well	63 (86.3%)	109 (74.6%)	$P < 0.25$
Alive with tumor	5 (6.8%)	25 (17.1%)	$P < 0.05$
Dead of tumor	4 (5.5%)	5 (3.4%)	
Node metastases	25 (34.2%)	84 (57.5%)	$P < 0.005$
Lung metastases	9 (12.3%)	20 (13.7%)	

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 4. Relation Between Tumor Encapsulation and Type of Margins

Total capsule		21
Pushing margins	16 (76.2%)	
Infiltrating margins	5 (23.8%)	
Partial capsule		106
Pushing margins	32 (30.2%)	
Infiltrating margins	74 (69.8%)	
Absent capsule		92
Pushing margins	25 (27.2%)	
Infiltrating margins	67 (72.8%)	

Pattern of growth: Cases were divided into three groups on the basis of the relative proportion of neoplastic papillae and follicles, independently from the presence of solid areas, sclerosis, or other secondary features. There were 122 cases (55.7%) in which papillae predominated, 21 (9.6%) in which the amount of papillae and follicles were roughly equivalent, and 76 (34.7%) in which the neoplastic follicles were the predominant element. Among the latter, there were 25 cases in which the growth was almost entirely of a follicular type; these were regarded as the "follicular variant" of PTC and will be discussed separately.

No marked differences were detected among the three major groups regarding probability of freedom from disease or incidence of cervical node metastases. Lung metastases, however, were more frequent among the tumors in which follicles predominated (Table 6).

Fibrosis: The presence of fibrosis was evaluated in the primary tumor, exclusive from that which could be found in the tumor capsule and in the stroma of the papillae. Thus defined, it usually manifested in the form of strands that separated the tumor incompletely into lobules. The fibrosis was arbitrarily divided into sclerohyaline and desmoplastic, the first referring to the deposition of wide bands of hyalinized collagen, and the second to a cellular proliferation of spindle cells admixed with thin connective tissue strands (Fig. 3). If a tumor contained areas of fibrosis of both types, it was considered desmoplastic. Fibrosis of one type or another was detected in 56.2% of the cases, the two morphologic types of fibrosis being roughly equivalent in frequency. Five of the 56 tumors with desmoplastic-type fibrosis were of the so-called occult sclerosing type. In 36 (64.3%) of the tumors having desmoplastic-type fibrosis, this change was accompanied by a lesser differentiated appearance of the tumor: instead of well-developed papillae or

TABLE 5. Tumor Encapsulation and Type of Margins, and Their Combined Influence on Prognosis and Metastatic Behavior

	Tumors with total capsule & pushing margins	Tumors with absent capsule & infiltrating margins
	16 (7.3%)	67 (30.6%)
Alive & well	15 (93.7%)	40 (59.7%)
Alive with tumor	1 (6.25%)	16 (23.9%)
Dead of tumor	0 (0%)	3 (4.5%)
Node metastases	7 (43.7%)	45 (67.2%)
Lung metastases	0 (0%)	10 (14.9%)
Other distant metastases	0 (0%)	3 (4.5%)

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 6. Pattern of Tumor Growth and Its Influence on Prognosis and Metastatic Behavior

	Predominantly papillary	"Mixed"	Predominantly follicular
	122 (55.7%)	21 (9.6%)	76 (34.7%)
Alive & well	91 (74.6%)	15 (71.4%)	66 (86.8%)
Alive with tumor	19 (15.6%)	4 (19.0%)	7 (9.2%)
Dead of tumor	5 (4%)	2 (9.5%)	2 (2.6%)
Node metastases	59 (48.4%)	14 (66.7%)	36 (47.4%)
Lung metastases	13 (10.6%)	0 (0%)	16 (21%)
Other distant metastases	5 (4%)	1 (4.8%)	2 (2.6%)

Patients who died of causes other than papillary carcinoma have been excluded.

follicles, there were small irregular clusters of tumor cells having irregular contours and often exhibiting squamous metaplasia. Presence or type of fibrosis, or occurrence of the lesser differentiated areas mentioned above, did not correlate with any statistically significant difference at the clinical or prognostic level (Table 7).

Cystic changes: Secondary cystic changes were seen in 52.5% of the primary tumors, but in only 9.1% of the cases were they marked (Table 8). Cervical lymph node metastases had cystic foci in 74.5% of the cases, 24.5% of these being marked. There was no correlation between the presence of cystic changes in the primary tumor and in the nodal metastases. Instead, an obvious relationship was evident between the predominant pattern of growth of the primary tumor and the presence of cystic foci within it: marked cystic changes were present in 13.1% of the cases having a predominantly papillary pattern of growth, but in only 5.3% of those in which follicles predominated (Table 9).

Of the tumors with marked cystic changes, 20% were totally encapsulated, and 55% had pushing margins (as compared with 9.6% and 33.3% for the whole group, respectively). Only three (15%) of these markedly cystic tumors exhibited extrathyroid extension.

No differences were found in evolution or incidence of metastases between tumors with no cystic changes and those that had them in mild degree. Instead, patients whose tumors had marked cystic changes had a significantly greater chance of being free of disease. Not a single patient in this category died of tumor (Table 8).

Solid areas: Foci of solid growth having a cytologic composition similar to that seen in the papillary or follicular areas were seen in 19.6% of the cases. In 15 instances they represented a focal phenomenon, and in 28 they were extensive and dominated the microscopic picture (Fig. 4). Of the tumors having solid foci, 46.4% showed elsewhere a predominance of papillae, and 53.6% of follicles. There were no statistical differences in the incidence of freedom of disease between the group with solid areas (no matter how extensive they were) and the one without them. Tumors with solid areas had a slightly higher incidence of nodal and blood-borne metastases, but the differences did not reach a statistically significant level (Table 10).

Squamous metaplasia: Foci of squamous metaplasia in the tumor, identified by the usual criteria of intercellular bridges and/or keratinization, were seen in 18.7%

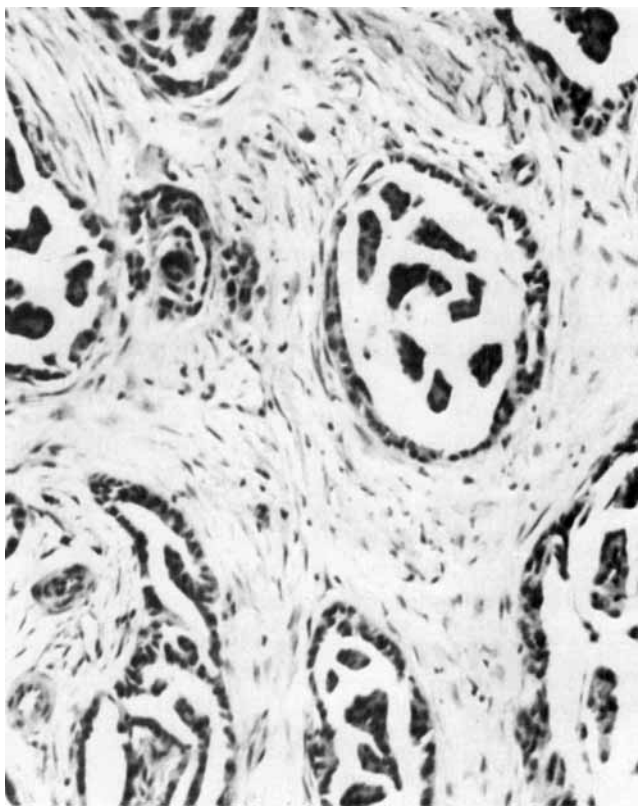


FIG. 3. Area of PTC with extensive fibrosis and irregular configuration of neoplastic foci (×200).

TABLE 7. Presence and Type of Tumor Fibrosis and Its Influence on Prognosis and Metastatic Behavior

	Fibrosis absent	Sclerohyaline fibrosis	Desmoplastic fibrosis	
	96 (43.8%)	67 (30.6%)	56 (25.6%)	
Alive & well	78 (81.2%)	53 (79.1%)	41 (73.2%)	$P < 0.50$
Alive with tumor	10 (10.4%)	10 (14.9%)	10 (17.8%)	
Dead of tumor	6 (6.2%)	2 (3.0%)	1 (1.8%)	
Node metastases	41 (42.7%)	36 (53.7%)	32 (57.1%)	$P < 0.25$
Lung metastases	10 (10.4%)	10 (14.9%)	9 (16.1%)	

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 8. Presence and Amount of Cystic Change in the Tumor and Its Influence on Prognosis and Metastatic Behavior

	Cystic changes absent or mild	Cystic changes marked	
	199 (90.9%)	20 (9.1%)	
Alive & well	153 (76.9%)	19 (95%)	$P < 0.05$
Alive with tumor	29 (14.6%)	1 (5%)	
Dead of tumor	9 (4.5%)	0 (0%)	
Node metastases	103 (51.7%)	6 (30%)	
Lung metastases	28 (14.1%)	1 (5%)	
Other distant metastases	7 (3.5%)	1 (5%)	

Patients who died of causes other than papillary carcinoma have been excluded.

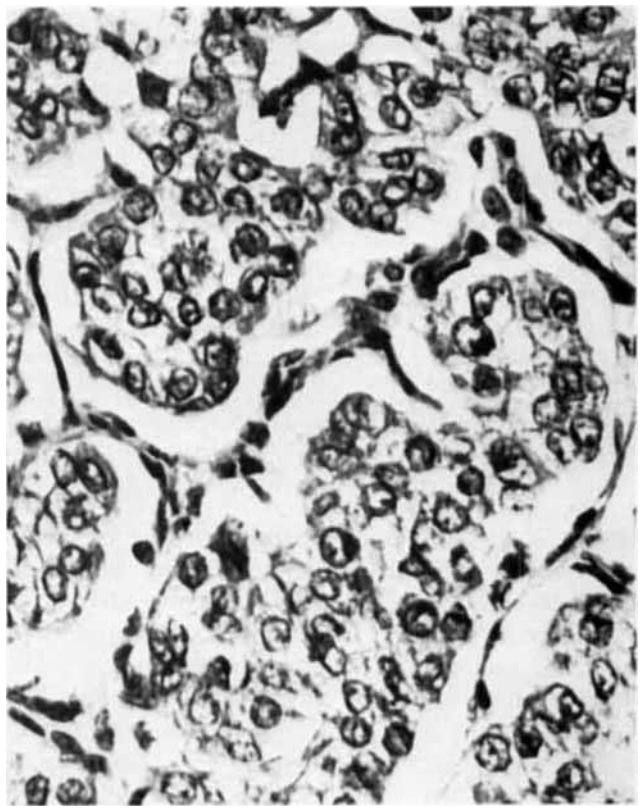


FIG. 4. Solid area of PTC, arranged in nests separated by delicate fibrovascular stroma. The appearance of the nuclei is similar to that of the typical PTC (compare with Fig. 2) (×500).

of the cases. They were seen 2.5 times more often in tumors with a predominantly papillary pattern of growth than in those that featured many follicles, and seemed to bear some topographic relationship with the solid areas just mentioned. Cases with squamous metaplasia were similar to the others regarding incidence of freedom of disease and frequency of metastases. Curiously, there was not a single death from tumor among the patients whose tumors had areas of squamous metaplasia (Table 11).

Psammoma bodies: Calcific concretions with a concentric laminated appearance were found in 51.6% of the cases. The usual locations in which they were found were within the fibrosed stroma, among epithelial islands with a solid appearance, and near the tip of the papillary fronds. Special care was taken to distinguish these formations from the variously sized coarse foci of calcification without concentric lamination that could be seen in the stroma, and from the round basophilic intrafollicular bodies formed as a result of condensation of the colloid material.

TABLE 9. Relation Between Pattern of Tumor Growth and Cystic Changes

Predominantly papillary pattern		122
Cystic changes absent	29 (23.8%)	
Cystic changes mild	77 (63.1%)	
Cystic changes marked	16 (13.1%)	
Predominantly follicular pattern		76
Cystic changes absent	61 (80.2%)	
Cystic changes mild	11 (14.5%)	
Cystic changes marked	4 (5.3%)	

Psammoma bodies were found in 54.4% of the tumors with a predominantly papillary pattern of growth, in 44% of the tumors in which follicles predominated, and in 61.3% of the tumors having solid areas. Psammoma bodies were seen in 53% of the nodal metastases. A rough correlation existed between the presence of psammoma bodies in the primary tumor and in the nodal metastases.

Patients whose thyroid tumors contained psammoma bodies were found to be affected more often by persistent disease on follow-up examination, and to have a higher incidence of nodal and pulmonary metastases, but the differences were not statistically significant (Table 12).

Lymphocytic infiltration: Infiltration of the tumor stroma by lymphocytes, sometimes accompanied by other mononuclear inflammatory cells, was seen in

TABLE 10. Presence and Amount of Solid Areas in the Tumor and Its Influence on Prognosis and Metastatic Behavior

	Tumors with no solid areas	Tumors with solid areas	Tumors with >50% solid areas
	176 (80.4%)	43 (19.6%)	28 (12.8%)
Alive & well	138 (78.4%)	34 (79.1%)	21 (75%)
Alive with tumor	22 (12.5%)	8 (18.6%)	7 (25%)
Dead of tumor	8 (4.5%)	1 (2.3%)	0 (0%)
Node metastases	83 (47.1%)	26 (60.5%)	16 (57.1%)
Lung metastases	22 (12.5%)	7 (16.3%)	4 (14.3%)
Other distant metastases	6 (3.4%)	2 (4.6%)	2 (7.1%)

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 11. Squamous Metaplasia and Its Influence on Prognosis and Metastatic Behavior

	Squamous metaplasia absent	Squamous metaplasia present
	178 (81.3%)	41 (18.7%)
Alive & well	139 (78.1%)	33 (80.5%)
Alive with tumor	24 (13.5%)	6 (14.6%)
Dead of tumor	9 (5%)	0 (0%)
Node metastases	87 (48.9%)	22 (53.6%)
Lung metastases	24 (13.5%)	5 (12.2%)
Other distant metastases	8 (4.5%)	0 (0%)

Patients who died of causes other than papillary carcinoma have been excluded.

26.7% of the cases; the feature was prominent in 8.2%. In most instances, the bulk of the lymphocytic outpouring was seen in the stalk of the papillae. Tumors with mild lymphocytic infiltration did not differ prognostically or otherwise from those without lymphocytes. Instead, of the 18 patients (8.2%) with tumors having a heavy lymphocytic infiltration, only 50% were found to be alive and well at the time of the last follow-up, whereas almost as many had persistent disease (Table 13). Nonneoplastic thyroid was available for microscopic examination in all of these 18 cases; it was normal in 6, affected by lymphocytic or Hashimoto's thyroiditis in 9, and was the seat of nodular hyperplasia in 3. The 50% incidence of thyroiditis in the group having heavy lymphocytic infiltration of the tumor is noteworthy, especially in view of the fact that the incidence of thyroiditis in the group with scanty or nil lymphocytic infiltration of the tumor was only 8.3%.

Multicentricity: Microscopic multicentric involvement of the thyroid gland was detected in 21.9% of the cases. The mean age of these patients was 36.5 years, as opposed to 46 years for the entire group. Multicentricity carried an adverse prognostic significance: patients whose tumors exhibited this feature had a much higher incidence of nodal and pulmonary metastases and a decreased probability of being found free of disease on follow-up examination (Table 14).

Blood vessel invasion: This feature was recorded as present only when large size vessels (nearly always veins) contained tumor thrombi in their lumina, partially attached to the inner surface. Vessels of capillary size were not included in this evaluation because of the difficulty in distinguishing them from lymphatic vessels and sometimes even from areas of artifactual tissue shrinkage. Thus defined, blood vessel invasion was seen in 6.9% of the cases. None of the 21 totally encapsulated tumors exhibited this feature. Patients whose tumors

TABLE 12. Psammoma Bodies and Their Influence on Prognosis and Metastatic Behavior

	Psammoma bodies absent	Psammoma bodies present	
	106 (48.4%)	113 (51.6%)	
Alive & well	84 (79.2%)	88 (77.9%)	$P < 0.25$
Alive with tumor	10 (9.4%)	20 (17.7%)	
Dead of tumor	7 (6.6%)	2 (1.8%)	
Node metastases	50 (47.2%)	59 (52.2%)	
Lung metastases	10 (9.4%)	19 (16.8%)	$P < 0.25$
Other distant metastases	5 (4.7%)	3 (2.6%)	

Patients who died of causes other than papillary carcinoma have been excluded.

exhibited vessel invasion had a decreased chance to be free of disease on follow-up examination, but there was no statistically significant increase in the tumor death rate as compared with the group without blood vessel invasion (Table 15).

Extrathyroid extension: This was determined micro-

TABLE 13. Presence and Amount of Lymphocytic Infiltration and Its Influence on Prognosis and Metastatic Behavior

	Marked lymphocytic infiltration	Minimal or nil lymphocytic infiltration	
	18 (8.2%)	201 (91.8%)	
Alive & well	9 (50%)	163 (81.1%)	$P < 0.005$
Alive with tumor	7 (38.9%)	23 (11.4%)	$P < 0.001$
Dead of tumor	0	9 (4.5%)	$P < 0.5$
Node metastases	9 (50%)	100 (49.7%)	
Lung metastases	3 (16.7%)	26 (12.9%)	
Other distant metastases	0 (0%)	8 (4%)	

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 14. Tumor Multicentricity and Its Influence on Prognosis and Metastatic Behavior

	Multicentricity absent	Multicentricity present	
	171 (78.1%)	48 (21.9%)	
Alive & well	141 (82.4%)	31 (64.6%)	$P < 0.025$
Alive with tumor	16 (9.3%)	14 (29.2%)	$P < 0.01$
Dead of tumor	6 (3.5%)	3 (6.2%)	
Node metastases	74 (43.3%)	35 (72.9%)	$P < 0.001$
Lung metastases	16 (9.3%)	13 (27.1%)	$P < 0.001$
Other distant metastases	8 (4.7%)	0 (0%)	

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 15. Blood Vessel Invasion and Its Influence on Prognosis and Metastatic Behavior

	Blood vessel invasion absent	Blood vessel invasion present	
	204 (93.1%)	15 (6.8%)	
Alive & well	163 (79.9%)	9 (60%)	$P < 0.05$
Alive with tumor	26 (12.7%)	4 (26.7%)	
Dead of tumor	8 (3.9%)	1 (6.7%)	
Node metastases	102 (50%)	7 (46.7%)	
Lung metastases	28 (13.7%)	1 (6.7%)	

Patients who died of causes other than papillary carcinoma have been excluded.

scopically, based on the presence of neoplastic thyroid tissue intimately admixed with soft tissues (including skeletal muscle) of the neck. This feature was found in 23.3% of the cases. It was associated with a decreased chance for freedom from disease, and a markedly increased possibility of dying from the tumor. Six (11.8%) of the 51 patients whose tumors had spread beyond the thyroid died as a direct result of the neoplasm; of these, the death was due in most cases to locally uncontrollable tumor growth in the neck, with progressive encirclement of trachea and other vital structures. Presence of extrathyroid tumor did not correlate with a greater incidence of nodal or lung metastases, but other distant metastases (particularly to bone) were more frequent than in the cases in which the primary tumor was restricted to the thyroid (Table 16).

TABLE 16. Extrathyroid Extension and Its Influence on Prognosis and Metastatic Behavior

	Extrathyroid extension absent	Extrathyroid extension present	
	168 (76.7%)	51 (23.3%)	
Alive & well	138 (82.1%)	34 (66.7%)	$P < 0.01$
Alive with tumor	22 (13.1%)	8 (15.7%)	
Dead of tumor	3 (1.8%)	6 (11.8%)	$P < 0.001$
Node metastases	80 (47.6%)	29 (56.9%)	
Lung metastases	21 (12.5%)	8 (15.7%)	
Other distant metastases	4 (2.4%)	4 (7.8%)	

Patients who died of causes other than papillary carcinoma have been excluded.

A direct correlation existed between extrathyroid extension and vascular invasion. Among the cases with extrathyroid extension, 19.6% also had vascular invasion; this was true for only 3% of the others (Table 17). Tumors that exhibited extrathyroid growth and vascular invasion had a poor prognosis: only 50% of the patients were free of disease, and 10% had died of their tumor.

Nonneoplastic thyroid. Thyroid gland not involved by tumor was available for microscopic view in 172 patients. The changes observed, sometimes in combination, were the following: no detectable abnormalities, 72 (41.9%); nodular hyperplasia, 58 (33.7%); Hashimoto's or lymphocytic thyroiditis, 32 (18.6%); adenoma, 10 (5.8%). No prognostic differences were identified among the different groups.

Major Morphologic Variants of PTC

Occult sclerosing variant: Tumors were arbitrarily placed in this category when they measured 1 cm or less in diameter and were accompanied by a sclerohyaline and/or desmoplastic fibrous reaction. There were 14 tumors in this category, representing 6.4% of the total. The outcome for this group was excellent: 92.8% of the patients were free of disease on follow-up examination, and none of the patients had died from the tumor. A high percentage of cases (71.4%) was associated with cervical node metastases, but there was not a single instance of blood-borne metastasis in the group (Table 18).

Solid variant: Tumors were placed in this group when the solid areas present within them occupied 50% or more of the tumor surface examined. A major requirement for inclusion was for the tumor cells in the solid portion to have features roughly analogous to those seen in the papillary and/or follicular portions of the tumor, except for slightly increased variation in nuclear size and shape (Fig. 4). When thus defined, there were 28 cases of PTC that could be placed in this category. No differences in the prognosis or in the incidence of metastases were found between this group, the group having only focal solid areas, and the larger group having no solid foci at all (Table 10).

Follicular variant: This type was defined as a PTC with the characteristic nuclear features of this tumor type but exhibiting an exclusively or nearly exclusively follicular pattern of growth, sometimes admixed with solid foci (Fig. 5). Papillae, if present at all, were very scanty and, in most instances, poorly developed. Other morphologic features of this well-defined variety of PTC have been described elsewhere.[7,8] There were 25 tumors

in this category, representing 11.4% of the total. These cases were compared with the entire group of PTC cases and also with a subgroup of 122 cases in which the pattern of growth was predominantly papillary. There was an almost total identity among these groups as far as other morphologic features and the clinical data are concerned, except for the fact that the follicular variant of PTC tended to be smaller and had a somewhat higher incidence of lung metastases. The incidence of cervical node metastases was statistically similar for both groups; interestingly, when nodal metastases developed in the follicular variant of PTC, these deposits exhibited easily identifiable papillary formations in 66.6% of the cases.

Metastases

Lymph nodes: The cervical lymph nodes were, by far, the most common site of metastatic tumor. Microscopically confirmed positive nodes were found at some time during the evolution of the disease in 54.3% of the cases. There were no statistically significant differences among the sexes.

The incidence of cervical lymph node metastases was very high for the patients seen during the first two decades of life, and remained at a rather constant lower level thereafter (Fig. 6). As already mentioned, in 78 cases (32.4%), clinically enlarged nodes were present at the time of the initial diagnosis, and in 47 (19.5%), they constituted the only positive physical sign. Mediastinal lymph node metastases were seen in 11 patients (4.6%); they were always accompanied by disease in the cervical nodes. Metastases in other lymph node groups were not found. There were no prognostic differences among the patients who had cervical adenopathy at presentation and those who did not (Table 19). Also, there was no difference in the rate of cervical node involvement among the tumors having a predominantly papillary pattern of growth and those made up primarily of follicles (Table 6). When the primary tumor was predominantly papillary, this was also the case for 78.5% of the nodal metastases; when the primary tumors had a predominantly follicular pattern of growth, the lymph node metastases were still composed mainly of papillae in 45% of the cases. Lymph node metastases had cystic changes within them in 74.5% of the cases, and these changes were marked in 24.5%. Psammoma bodies were identified in 53% of the cases; interestingly, they were found in 36.1% of the cases in which they could not be located in the primary thyroid tumor.

A scintigraphic study with ^{131}I was performed in most patients with cervical adenopathy. The nodal metastases were classified as "hot" in the majority of the cases, and as "cold" in 20 (Figs. 7A and 7B). Biopsy was performed on five of these 20 cold enlarged lymph nodes. All of them showed metastatic PTC exhibiting a moderate to extensive degree of cystic degeneration, so that the neoplastic epithelium was reduced to an inconspicuous peripheral lining; none showed areas of anaplasia or dedifferentiation.

TABLE 17. Relation Between Extrathyroid Extension and Blood Vessel Invasion

Extrathyroid extension absent		168
Blood vessel invasion absent	163 (97.0%)	
Blood vessel invasion present	5 (3%)	
Extrathyroid extension present		51
Blood vessel invasion absent	41 (80.4%)	
Blood vessel invasion present	10 (19.6%)	

TABLE 18. Prognosis and Metastatic Behavior of the Occult Sclerosing Variant of PTC as Compared to the Other Types of PTC

	Occult sclerosing variant	Others
	14 (6.4%)	205 (93.6%)
Alive & well	13 (92.8%)	159 (77.6%)
Alive with tumor	1 (7.1%)	29 (14.1%)
Dead of tumor	0 (0%)	9 (4.4%)
Node metastases	10 (71.4%)	99 (48.3%)
Lung metastases	0 (0%)	29 (14.1%)
Other distant metastases	0 (0%)	8 (3.9%)

Patients who died of causes other than papillary carcinoma have been excluded.

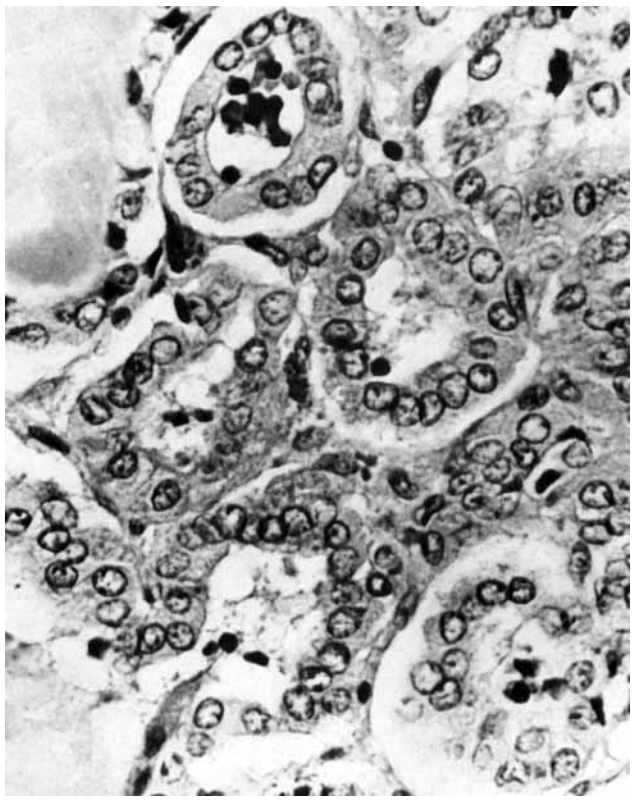


FIG. 5. PTC with follicular pattern of growth. Notice the optically clear quality of the overlapping nuclei. Papillae are not present (×500).

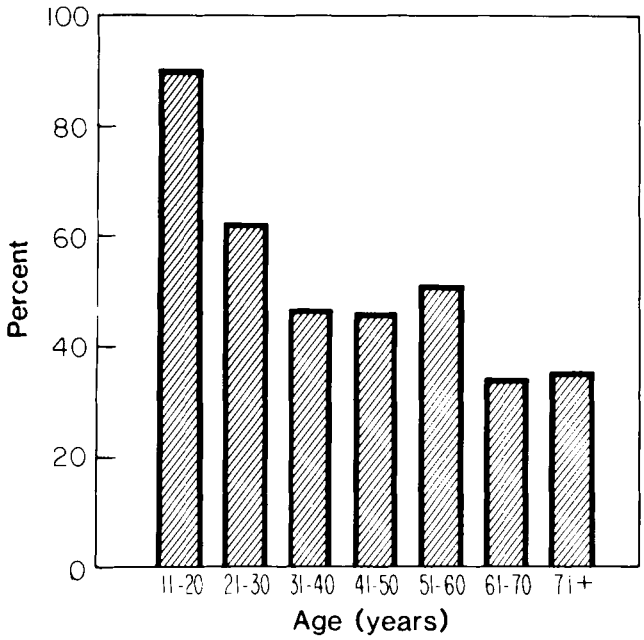


FIG. 6. Incidence of cervical lymph node metastases according to age.

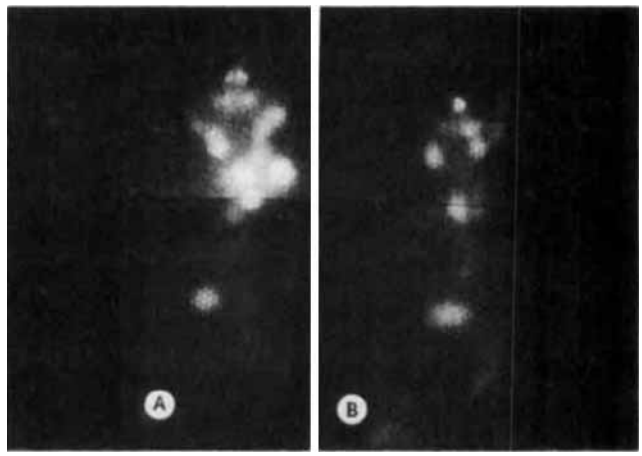
Lung: Pulmonary metastases were detected by plain chest x-rays and/or iodine 131 (^{131}I) scintigram in 34 of the patients (14.1%). The incidence was higher in the younger age group, particularly in the decade from 11 to 20 years, in whom it reached 50% (Fig. 8). There was no difference in the frequency of lung metastases between male and female patients. In 15 cases, these metastases were present at the time of initial diagnosis or within the next 2 months. All but three of the patients with lung metastases also had cervical lymph node involvement. Two of the patients also had metastases to the skeletal system, and one to the central nervous system.

All 34 cases of lung metastases were studied with ^{131}I scintigram. In 30 (88.2%) cases there was uptake of the radioactive iodine, whereas the other 4 cases were described as cold (Figs. 9A and 9B).

TABLE 19. Incidence of Cervical Adenopathy at the Time of Initial Presentation and Its Influence on Prognosis and Metastases to Other Sites

	Patients with clinically positive cervical nodes	Patients with clinically negative cervical nodes
	78 (32.4%)	163 (67.6%)
Alive & well	59 (75.6%)	128 (78.5%)
Alive with tumor	13 (16.7%)	22 (13.5%)
Dead of tumor	2 (2.6%)	9 (5.5%)
Lung metastases	17 (21.8%)	17 (10.4%)
Other distant metastases	3 (3.8%)	10 (6.1%)

Patients who died of causes other than papillary carcinoma have been excluded.



FIGS. 7A AND 7B. ^{131}I scans in a patient with PTC with lymph node and bone metastases. (A) Postoperative scan showing uptake in thyroid gland remnant, in several cervical nodes, and in D10 vertebra. (B) Scan taken 2 years later, after therapy with 200 mCi of ^{131}I. A marked diminution of uptake in the neck is evident, but bone metastasis remains unchanged.

The presence of lung metastases had a very detrimental effect on survival. When they were present, the possibility of the patient having persistent disease or dying of the tumor was significantly increased (Table 20). This was particularly the case when the metastases were cold; of these four patients, three died of tumor and one is alive with persistent disease.

Other distant organs: Thirteen patients had metastases to other distant organs. Their clinicopathologic features are summarized in Table 21, and the scintigraphic appearances of two of these cases are shown in Figures 7A and 7B and 10A and 10B.

Therapy

Patients were divided into two major groups depending on the type of the initial surgical procedure in the thyroid gland.

Nodulectomy/lobectomy group: Sixty-six cases, representing 27.4% of the total belonged to the nodulectomy/lobectomy group (NLG). None of the patients had radical neck dissection as part of the initial procedure, and none were administered radioactive iodine immediately following the operation. In 20 cases (30.3% of the group), a total or near total thyroidectomy was carried out later because of tumor recurrence, the mean interval between the two operations being 6.5 years. The recurrence (microscopically confirmed) was in the thyroid gland in 15 patients (22.7%); 3 patients had recurrence only in the cervical nodes; 2 others had developed distant metastases, and the thyroidectomy was done in order to administer ^{131}I therapy.

Total or near-total thyroidectomy group: One hundred seventy-five patients (72.6%), belong to the total or near-

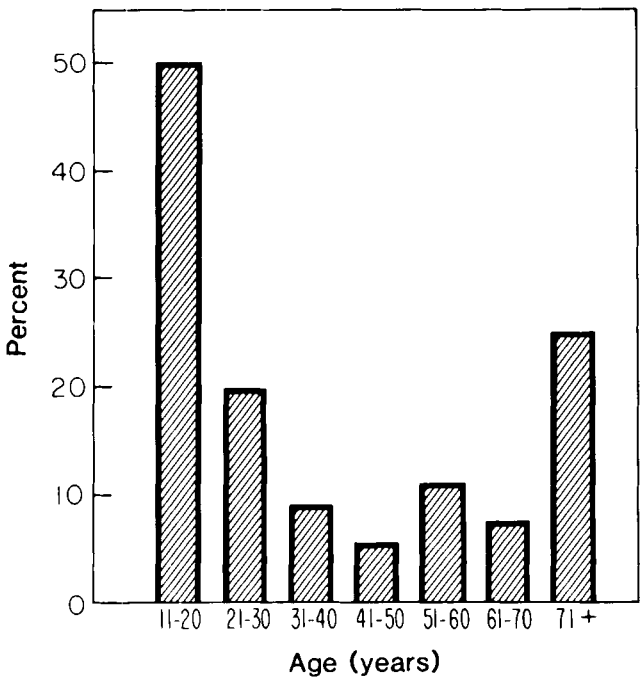


FIG. 8. Incidence of lung metastases according to age.

total thyroidectomy group (TTG). Included in this group were those patients in whom the thyroidectomy was done within 2 months after the performance of a nodulectomy or lobectomy. In 42 cases (24% of the group), the removal of the thyroid was accompanied by a radical neck dissection on the side of the lesion. Data on postoperative complications were not available.

Radioactive iodine (^{131}I) was administered 6 weeks after the operation in 72 patients (41.1% of the group). The doses given ranged from 80 to 150 mCi.

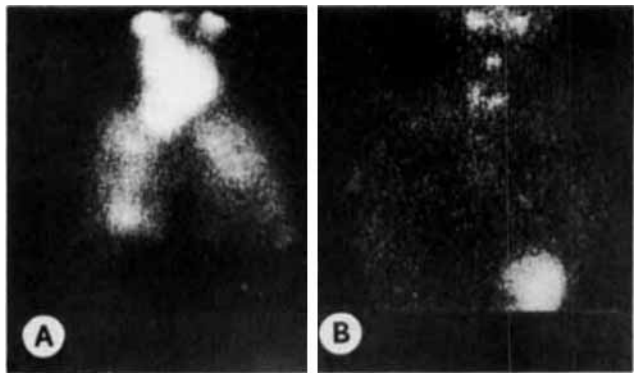
When nodal or blood-borne metastases were detected in patients who had had a thyroidectomy (either initially or after a nodulectomy/lobectomy), the patients were usually treated with radioactive iodine, in doses averaging 150 mCi.

Following the operation, all patients in both surgical groups received thyroid replacement therapy for life (0.2 μg/kg/day), in order to suppress thyroid-stimulating hormone activity.

Evolution

The evolution of the disease and overall metastatic behavior for the entire patient population are shown in Table 22. A steep rise in the probability of developing recurrences or metastases was noted in the first 2 years after initial surgery, followed by a slower but continuous increase in subsequent years (Fig. 11). This probability was not statistically different among the sexes (Fig. 12) or age groups (Fig. 13).

The estimated probabilities of survival for the whole patient population, counting deaths from all causes and



FIGS. 9A AND 9B (A) Postoperative ^{131}I scan, taken 1 week after administering a therapeutic dose (160 mCi) of radioactive iodine. Marked uptake is seen in the thyroid remnant, cervical lymph nodes, and both lung fields. (B) Scan taken several months after ^{131}I therapy, showing disappearance of all lung foci. The positive area in the lower right corner represents stomach.

deaths from PTC, are shown in Figure 14. A higher percentage of women (81.2%) than men (64.7%) were found to be free of disease on follow-up examination, but there were no statistically significant differences in the probability of survival, whether evaluated for all age groups (Fig. 15) or in patients older than 40 years (Fig. 16). Instead, a striking correlation was found between the patients' age and the probability of dying from tumor (Fig. 17). There were no tumor deaths in the patients younger than 41 years, but the incidence rose steeply in older patients, to reach the high figure of 37.5% in patients 71 years old or older (Fig. 18). The adverse effect of increasing age in the prognosis of PTC was apparent both for male and female patients (Fig. 19).

When patients were divided into a "low-risk" group (men 40 years of age or younger, and women 50 years of age or younger) and a "high-risk" group (older patients), as proposed by Cady *et al.*,[9,10] a marked difference between the two emerged, outlining the utility

TABLE 20. Frequency of Lung Metastases and Their Influence on Prognosis and Other Metastatic Behavior of the Tumors

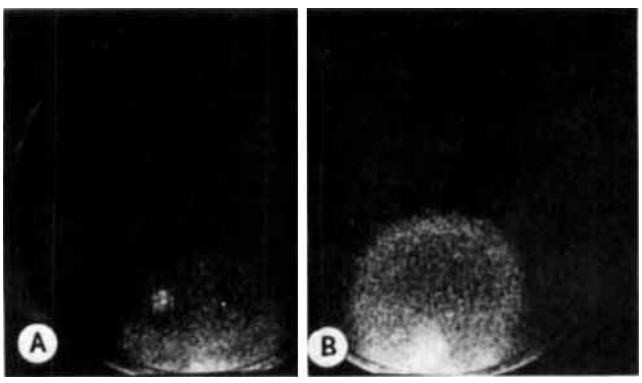
	Patients with lung metastases	Patients without lung metastases
	34 (14.1%)	207 (85.9%)
Alive & well	16 (47%)	171 (82.6%)
Alive with tumor	13 (38.2%)	22 (10.6%)
Dead of tumor	4 (11.8%)	7 (3.4%)
Node metastases	31 (91.2%)	100 (48.3%)
Distant metastases (other than lung)	3 (8.8%)	10 (4.8%)

Patients who died of causes other than papillary carcinoma have been excluded.

TABLE 21. Clinicopathologic Features of Patients With Distant Metastases Other Than Lung

Site	Age/sex	Presentation	Pattern	Initial therapy	Site of metastases	Scan	Other metastases	Treatment	Evolution
Bone	34/F	Thyroid nodule for 11 yr	Pred pap	Lobectomy + LN + ^{131}I (1977)	Cervical area around occipital foramen (probably occipital bone) (1981)	Positive	Cervical nodes	^{131}I	Alive with disease (1983)
Bone	45/F	Invasive thyroid nodule	Pred pap	TT + ^{131}I (1978)	Vertebra (L4) (1982)	Positive	Cervical nodes	^{131}I Ext x-rays	Alive with disease (1983)
Bone	34/M	Thyroid nodule	Pred pap	TT + LN (1978)	Skull (frontal and occipital bones) (1978, present at time of operation)	Negative	Cervical nodes	^{131}I	Alive with disease (1983)
Bone	51/M	Invasive thyroid nodule	Pred pap	TT + LN (1978)	Ribs (left 5th & 6th) and femur (1982)	Negative	Cervical and mediastinal nodes	^{131}I Ext x-rays chemotherapy	Dead of tumor (1983)
Bone	72/M	Invasive thyroid nodule	Pred solid	TT (1980)	Vertebra (D10) (1982)	Positive (Fig. 7)	Cervical nodes	^{131}I Ext x-rays	Alive with disease (1983)
Bone	35/M	Thyroid nodule	Pred foll	TT + LN + ^{131}I (1967)	Skull (occipital bone) (1982)	Positive	Cervical nodes	^{131}I	Alive with disease (1983)
Bone	61/M	Pathologic fracture humerus (1970)	Pred foll	TT + ^{131}I (1975)	Humerus (1970)	Not done	None	^{131}I	Alive and well (1983)
Bone	25/F	Thyroid nodule	Pred foll	ST (1966)	Vertebra (C8) and rib (6th) (1979)	Positive	Cervical nodes and lung	^{131}I	Alive with disease (1983)
Bone	48/M	Thyroid nodule	Pred foll	TT + LN + ^{131}I (1973)	Skull (occipital bone) (1974)	Negative	Cervical nodes and lung	^{131}I	Dead of tumor (1978)
Central nervous system	32/F	Multinodular goiter	Pred pap	TT + ^{131}I (1980)	Cerebrum (right parietal lobe) (1980)	Positive (Fig. 10)	Cervical nodes and lung	^{131}I	Alive with disease (1983)
	50/F	Thyroid nodule	Pred foll	TT + ^{131}I (1975)	Cerebellopontine angle (1980)	Not done	None	^{131}I	Alive with disease (1983)
Soft tissues	44/F	Thyroid nodule	Pred pap	Nodulectomy (1967) TT + ^{131}I (1969)	Arm, chest wall, deltoid muscle (1971–1980)	Negative	Cervical nodes	Ext x-rays	Alive with disease (1983)
Liver	66/F	Thyroid nodule	Pred pap	Lobectomy (1967)	Liver (1974)	Negative	Cervical nodes	—	Dead of tumor (1974)

Pred: predominantly; pap: papillary; foll: follicular; LN: cervical lymph node dissection; TT: total thyroidectomy; Ext: external; ST: subtotal thyroidectomy.



FIGS. 10A AND 10B. The ^{131}I scan shows an area of uptake representing a cerebral metastasis in right parietal lobe. The patient also had lung metastases. (B) After therapy, the area of cerebral uptake has disappeared. The lung metastases, however, were still evident (not shown).

of this simple distinction. An even sharper separation was obtained when the low-risk group was defined as comprised of men 40 years of age or younger, and women 60 years of age or younger (Fig. 20).

Among the patients in the NLG, three died in the immediate postoperative period. Forty-three (65.1%) were found to be free of tumor on a follow-up that ranged from 3 to 23 years (mean, 8.7 years), and did not need a reoperation in the thyroid gland. Of these, 40 patients did not have any tumor recurrence after the original operation, whereas 3 patients developed cervical adenopathies that were treated with simple removal. Two of these patients subsequently died of other causes, both of them 7 years after the initial thyroid operation. Of the remaining 20 patients, all of whom had had a thyroidectomy because of tumor recurrence after the

TABLE 22. Evolution of the Disease and Metastatic Behavior in the Entire Patient Population, and Divided by Sex

	All patients	M	F
	(241)	(67)	(174)
Alive & well	187 (77.6%)	44 (65.7%)	143 (82.2%)
Alive with tumor	35 (14.5%)	16 (23.8%)	19 (10.9%)
Dead of tumor	11 (4.6%)	5 (7.5%)	6 (3.4%)
Dead of other causes	8 (3.3%)	2 (3%)	6 (3.4%)
Node metastases	131 (54.3%)	42 (62.7%)	89 (51.1%)
Lung metastases	34 (14.1%)	8 (11.9%)	26 (14.9%)
Other distant metastases	13 (5.4%)	6 (8.9%)	7 (4.0%)

initial operation, 13 were alive and well, 5 were alive with disease, 1 had died from tumor, and 1 had died of an unrelated disease 9 years after surgery. Thus, the total number of patients found free of disease in the NLG was 57 (86.4%) (Fig. 21).

In the TTG, there were no postoperative deaths. One hundred-thirty-six patients (77.7%) were free of disease at the time of the last follow-up, which ranged from 3 to 17 years (mean, 7.4 years). Of these, 90 (51.4% of the group) never had recurrence of the tumor after the thyroidectomy, whereas 44 others had developed metastases (29 to cervical nodes, 8 to lung, and 7 to cervical nodes and lung) that were successfully treated with surgical removal (in the cases of the cervical nodes) and/or radioactive iodine therapy. The remaining two patients in this group died of causes other than thyroid carcinoma, 7 and 8 years after the thyroid operation, respectively. Twenty-nine patients (16.6%) were alive with persistent disease and ten patients (5.7%) had died of tumor (Fig. 22).

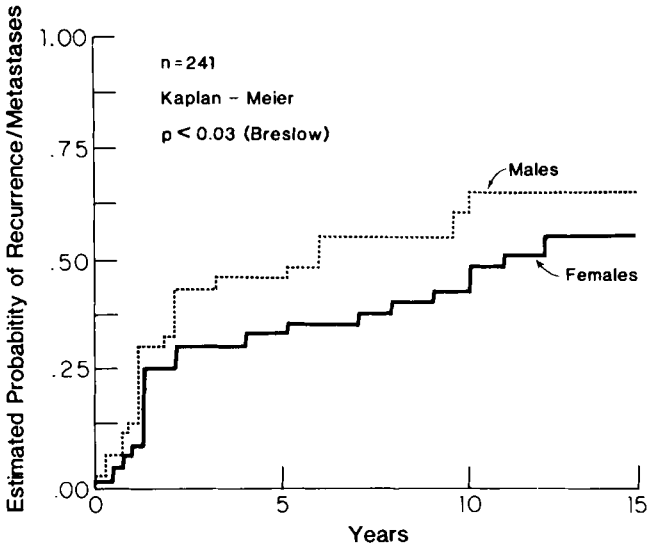


FIG. 12. Estimated probability of recurrence/metastases according to sex. The difference is not statistically significant.

A statistical comparison was made among these groups. There was no difference in the estimated probability of survival (Fig. 22), but patients who had nodulectomy or lobectomy as the initial procedure (plus thyroidectomy if needed) had statistically higher disease-free survival rates (Fig. 21). The patients in the NLG were compared with those in the TTG for a variety of prognostically significant parameters in an attempt to determine whether there were differences among the two populations that might have biased the results (Table 23). TTG patients tended to have tumors that were larger, with a higher incidence of extrathyroid extension, multicentricity, and vascular invasion, whereas the tumors of NLG patients were more likely to be encapsu-

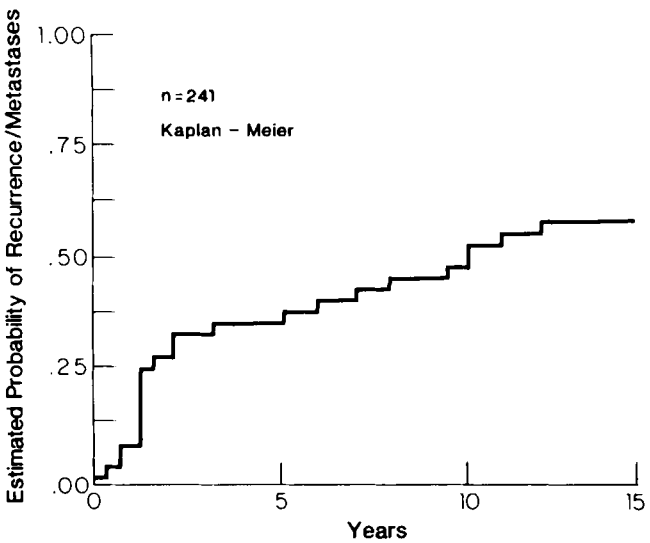


FIG. 11. Estimated probability of recurrence and/or metastases for the entire patient population.

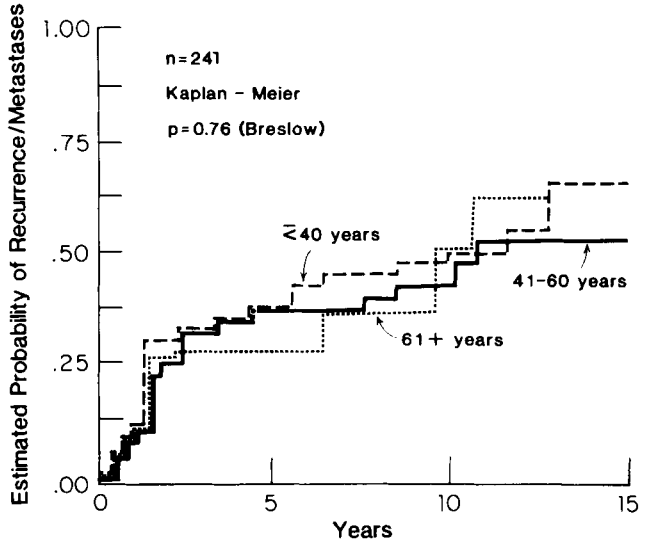


FIG. 13. Estimated probability of recurrence/metastases according to age. The differences are not statistically significant.

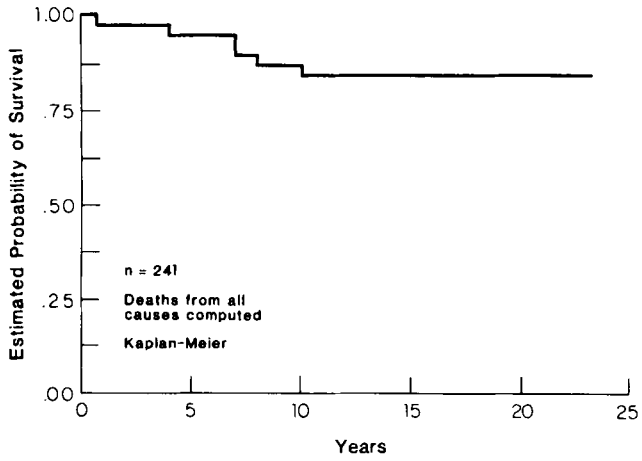


FIG. 14. Estimated probability of survival for the entire patient population, computing deaths from PTC and from other causes.

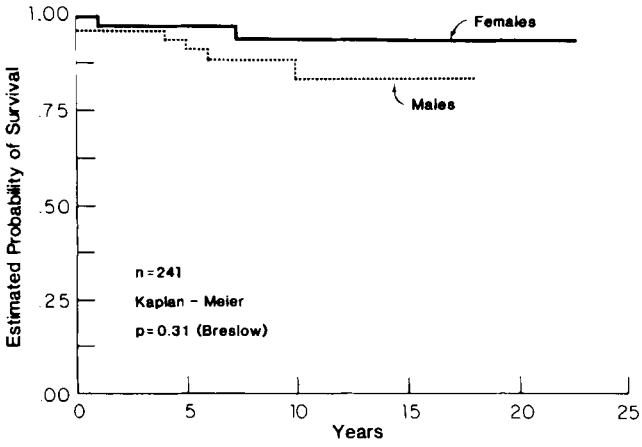


FIG. 15. Estimated probability of survival according to sex. The difference is not statistically significant.

lated, with pushing margins and marked cystic changes. The same set of parameters was used to compare, among the NLG patients, those who needed a thyroidectomy

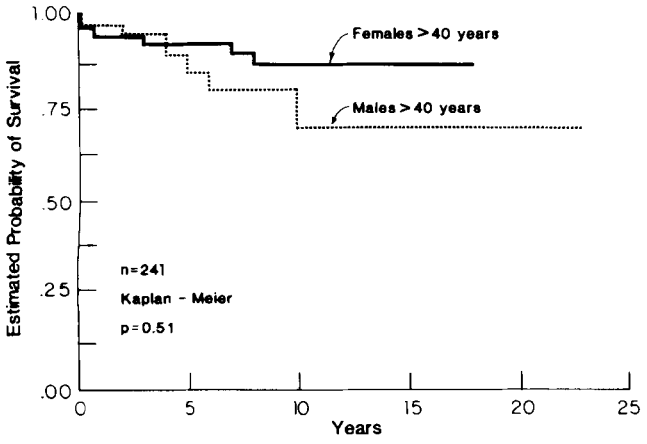


FIG. 16. Estimated probability of survival in patients older than 40 years according to sex. The difference is not statistically significant.

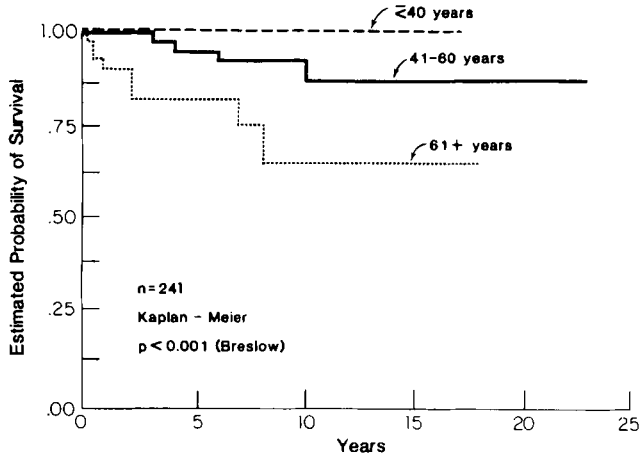


FIG. 17. Estimated probability of survival according to age. The differences are highly significant.

later and those who did not. Patients in the former subgroup had tumors with a higher incidence of extrathyroid extension and multicentricity, whereas tumors in the latter category were more likely to be encapsulated and/or have pushing margins.

In the TTG, patients who had a radical neck dissection at the time of the thyroidectomy were compared with those who did not (Table 24). There were no statistical differences in disease-free survival between the two subgroups. Interestingly, the presence of clinically apparent cervical adenopathy was not the only factor that led to the performance of the neck dissection, as this feature was recorded as absent in 35.7% of the patients who had the node dissection and present in 33.6% of those who did not.

Patients in the TTG were also divided among those who received radioactive iodine following the operation and those who did not. The two subgroups were comparable in terms of prognostically significant parameters (Table 25), and no differences were observed among them regarding the probability of cure from disease (Fig. 23).

Thirty patients with lung metastases of PTC were treated with radioactive iodine. In 53.5% of the cases, this led to a total and permanent disappearance of these deposits (Fig. 9).

Fatal cases: Fourteen patients in this series died as a direct or indirect result of the thyroid carcinoma, resulting in an incidence of tumor death of 5.8%. Three of these patients died of postoperative complications. The clinical and pathologic features of the other 11 cases are summarized in Table 26.

Analysis of these 11 fatal cases of PTC showed the following features: (1) all but one of the patients were women older than 60 years or men older than 40 years; (2) none of the patients had received previous external radiation therapy; (3) all of the tumors were larger than 1 cm in diameter; (4) none of the tumors were totally

encapsulated; (5) four of the tumors showed extrathyroid extension at the time of surgery; (6) in all but one of the tumors, uncontrollable tumor growth in the soft tissues of the neck was the determining or contributing cause of death; and (7) the initial surgical therapy had consisted of nodulectomy or lobectomy in three patients, and subtotal or total thyroidectomy in eight patients.

Discussion

The study of a relatively large number of cases of PTC treated in a single institution has shown a clinical and pathologic picture generally comparable to that of other large series on the subject, but which in some aspects departs considerably from them. The preponderance of PTC in female patients was confirmed, as well as the fact that in female patients the disease-free survival figures are higher than they are in male patients. The mean age of our patients (41.3 years) is similar to that of other large European series, such as those of Franssila[11,12] (49 years) and Tscholl-Ducommun and Hedinger[13] (48.3 years). Interestingly, this corresponds very closely to the median age reported in an American series by Crile[14] for patients seen in the period between 1926 and 1935 (45 years), whereas patients seen in the same institution between 1955 and 1964 had a median age of 31 years. Cady *et al.*,[9] from the Lahey Clinic, also remark on a shift in age to a younger range. In the series of Mazzaferri *et al.*[15] of patients under the care of US Air Force physicians, the mean age was 31.7 years

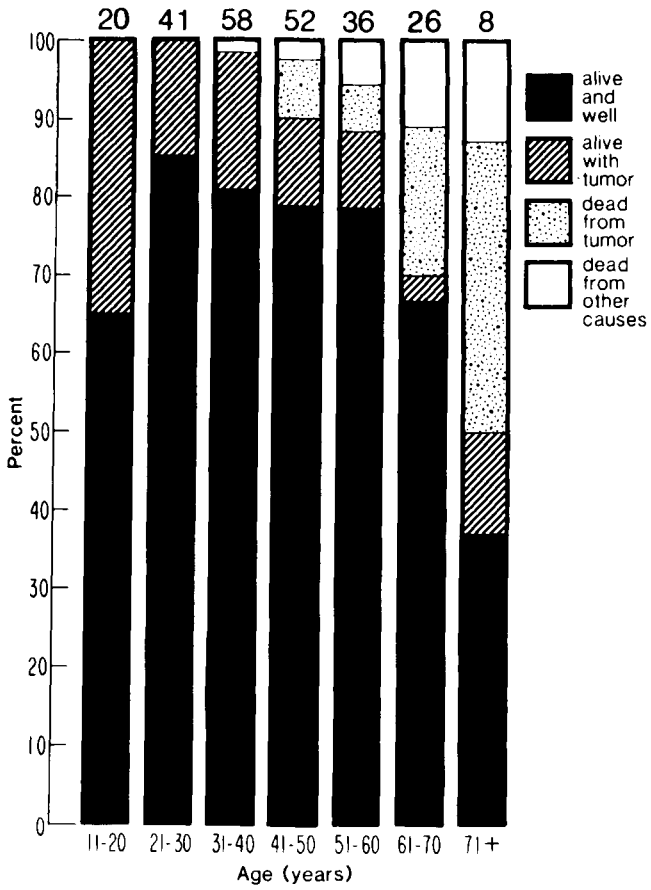


FIG. 18. Evolution of the disease in the entire patient population.

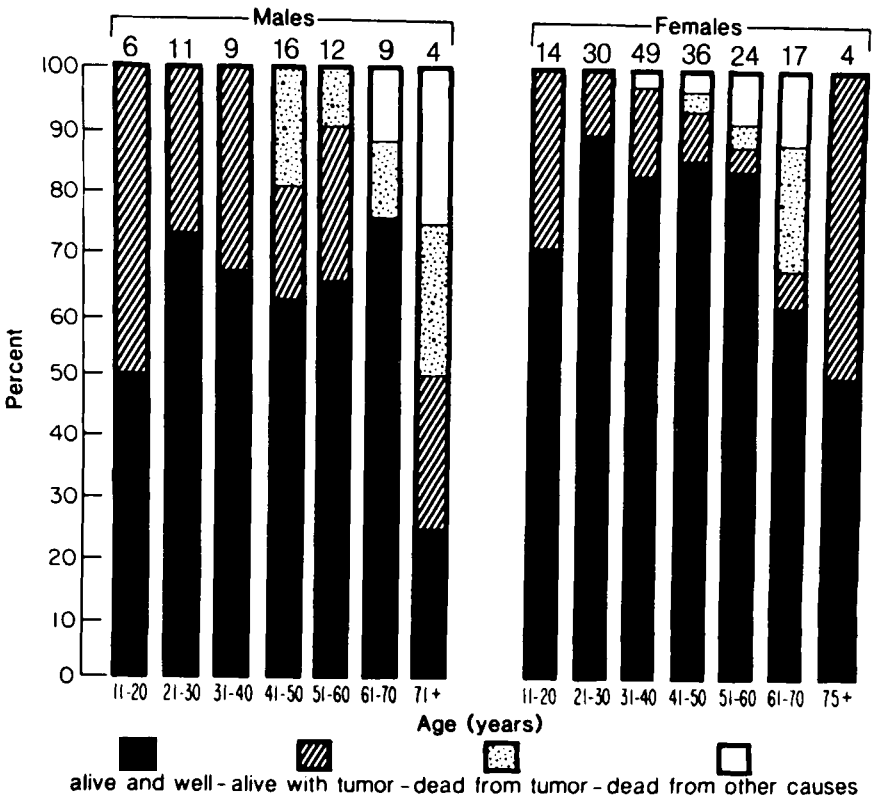


FIG. 19. Evolution of the disease according to sex and age.

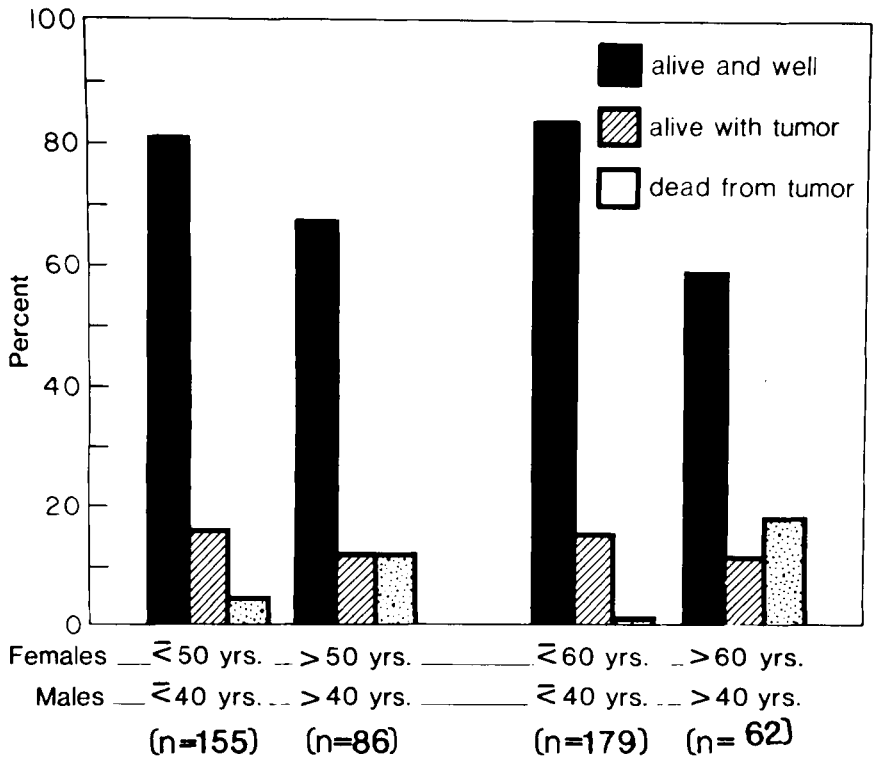


FIG. 20. Evolution of the disease according to the distinction into two risk groups, as proposed by Cady *et al.*[10] (left) and according to a slight modification of that system (right).

for women, and 33.4 years for men. This fact may be partially responsible for some of the differences in survival rates between certain American and European series. An adverse effect on prognosis was evident with increasing age, despite the paradoxical fact that metastases to cervical nodes and lung were comparatively more common in the younger age groups. This adverse effect became evident after the fifth decade in women and the sixth decade in men. When patients were divided into low-risk (men 40 years of age or younger, and women 50 years of age or younger) and high-risk (older patients) groups,[10] a definite difference in survival rates was observed; this difference was even more striking when the first group was made up of men 40 years of age or younger and women 60 years of age or younger.

Nearly all of our patients presented with the classic complaint of a thyroid mass and/or cervical adenopathy, the only three exceptions presenting with pulmonary (two patients) and osseous metastases (one patient). The number of patients who had a history of previous irradiation to the neck (6.6%) was similar to that reported in the series of Mazzaferri *et al.*[15] (6%). Probably both of these figures are underestimations, because a good number of cases might have gone unrecorded. The patients who had a previous history of hyperthyroidism were few, probably not more than those that could be expected from chance alone, and no convincing areas of transitions were seen morphologically between the hyperplastic and the neoplastic areas. Whereas some authors[16] have suggested a possible causal relationship between the two disorders, it is our impression and that of others[17] that they are not related.

The microscopic criteria that were used for placing the tumors in the PTC category were analogous to those employed in other recent studies,[11,13,18-20] and less restrictive than those used in older publications. The two major differences with the latter consisted in a greater reliance on cytologic features (particularly the ground-glass nucleus) for the diagnosis of PTC even when papillae were inconspicuous or absent, and the inclusion in the PTC group of all well-differentiated tumors having true papillary formations, even if they constituted only a scanty proportion of the growth.[21]

The good prognostic significance traditionally attached to a small primary tumor was confirmed in our series. We used 1 cm as the dividing line, whereas most other authors have used the figure of 1.5 cm, but the findings were comparable both in terms of frequency and evolution. Fourteen percent of our patients were in this group, a figure close to the 13.7% reported by Tscholl-Ducommun and Hedinger,[13] and the 19% reported by Franssila,[11] but lower than the 29% reported by Woolner *et al.*[22] and the remarkable 64% reported by Frauenhoffer *et al.*[23] Whether these differences are due to a delay in diagnosis in some patient populations or to some other selecting factor is not clear. The finding that these small tumors had a higher incidence of cervical nodal metastases than their larger counterparts is in all likelihood a

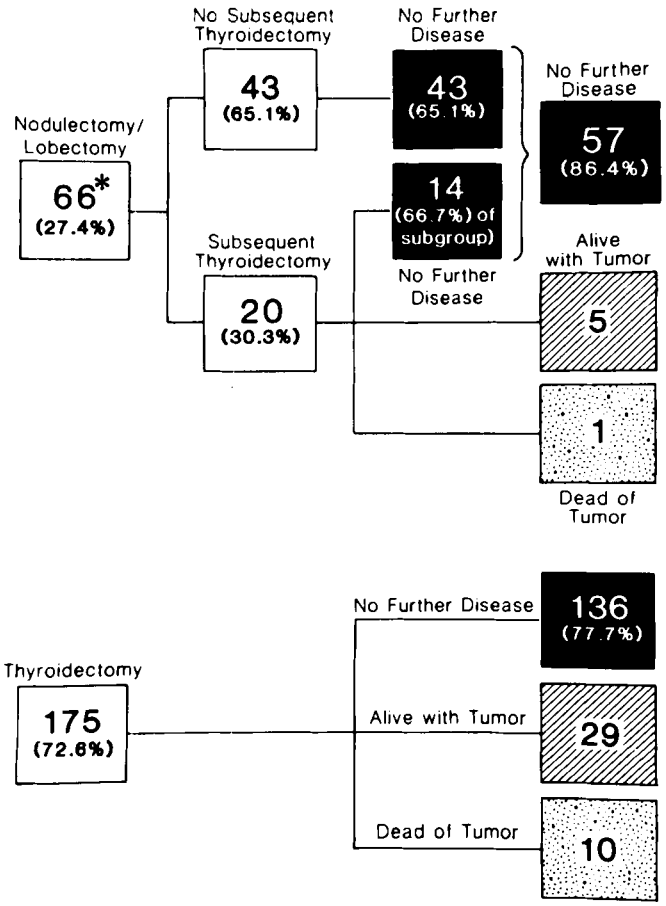


FIG. 21. Evolution of PTC according to the type of initial surgery. *Three patients in the NLG died postoperatively.

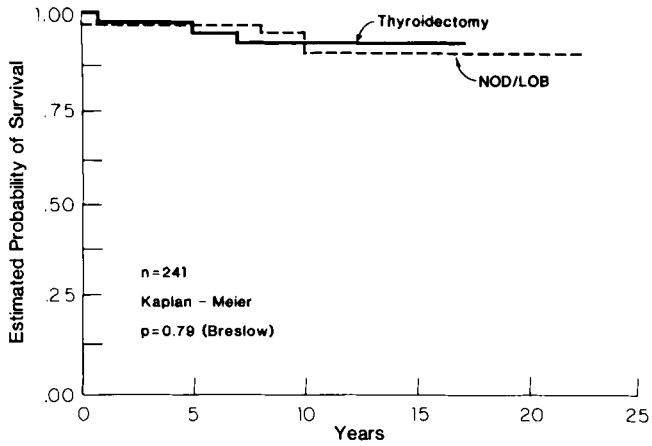


FIG. 22. Estimated probability of survival depending on the type of initial surgery. There are no statistically significant differences between the two groups.

statistical artifact, due to the fact that it was the nodal metastasis that was responsible for its detection. Blood-borne metastases, on the other hand, are extremely rare in this group, and death from tumor practically nonexistent. The remarkably good prognosis of these small-sized PTC, to which the adjective "occult" is often applied, has been commented upon by several authors.[13,24,25]

Similarly favorable prognostic connotations can be attached to the presence of total encapsulation of the tumor, a feature seen in approximately 10% of our cases. High probability of freedom of disease, lack of blood-borne metastases, and absence of tumor deaths were the hallmarks of this group in our series, as well as in the series of others.[11,26] On the other hand, the fact that 38% of these tumors led to cervical nodal metastases leaves little doubt that papillary thyroid neoplasms endowed with a total capsule should still be regarded as carcinomas, as other authors have remarked.[27] The concept of the existence of a papillary adenoma, as proposed by some,[28] seems to us tenuous at best, as we have been totally unable to identify any differential features between the encapsulated papillary tumors that metastasized and those that did not. Nomenclature issues notwithstanding, the favorable clinical significance of a total capsule is obvious. This does not seem to apply to the feature of partial encapsulation, since in our series tumors with this feature did not differ in terms of blood-borne metastases or tumor deaths from those lacking a capsule altogether.

The type of tumor margin, *i.e.*, whether pushing or infiltrating, that PTC can exhibit, and its influence on prognosis, is a feature that very few authors[23] have evaluated, perhaps because most have regarded it as analogous to the presence or absence of encapsulation, respectively. Although an undeniable relationship between these two morphologic parameters exists, they are not totally dependent on each other. Thus, some totally

TABLE 23. Comparison of Clinical and Pathologic Features Between the Various Surgical Groups

	TTG	NLG	NLG without subsequent thyroidectomy*	NLG with subsequent thyroidectomy
	(175 pts.)	(66 pts.)	(43 pts.)	(20 pts.)
Sex (M:F)	1:2.8	1:2.2	1:2	1:2.5
Age ≤ 40 years	47.4%	59.4%	41.9%	61.9%
Size ≤ 1 cm	16.3%	8.2%	9.5%	5.5%
Total encapsulation	6.9%	16.4%	19%	11.1%
Pushing margins	26.4%	49%	54.7%	44.4%
Predominantly papillary pattern	54.7%	59%	57.1%	66.6%
Marked cystic changes	6.9%	14.7%	14.2%	16.6%
Multicentricity	25.8%	11.5%	9.5%	16.6%
Blood vessel invasion	7.5%	1.6%	2.3%	0%
Extrathyroid extension	27.0%	14.7%	11.9%	22.2%

* Excluding three postoperative deaths.
TTG: total or near-total thyroidectomy; NLG: nodulectomy/lobectomy group.

TABLE 24. Influence of the Performance of a Radical Neck Dissection as Part of the Initial Surgical Procedure in the Prognosis and Subsequent Metastatic Behavior to Distant Organs in TTG Who Had Radical Neck Dissection as Part of Initial Surgical Therapy

	Radical neck dissection performed	Radical neck dissection not performed
	42 (24%)	133 (76%)
Alive & well	28 (66.7%)	106 (79.7%)
Alive with tumor	12 (28.6%)	17 (12.8%)
Dead of tumor	1 (2.4%)	9 (6.8%)
Lung metastases	12 (28.6%)	18 (13.5%)
Other distant metastases	2 (4.8%)	7 (5.3%)

TTG: total or near-total thyroidectomy group.
Patients who died of causes other than papillary carcinoma have been excluded.

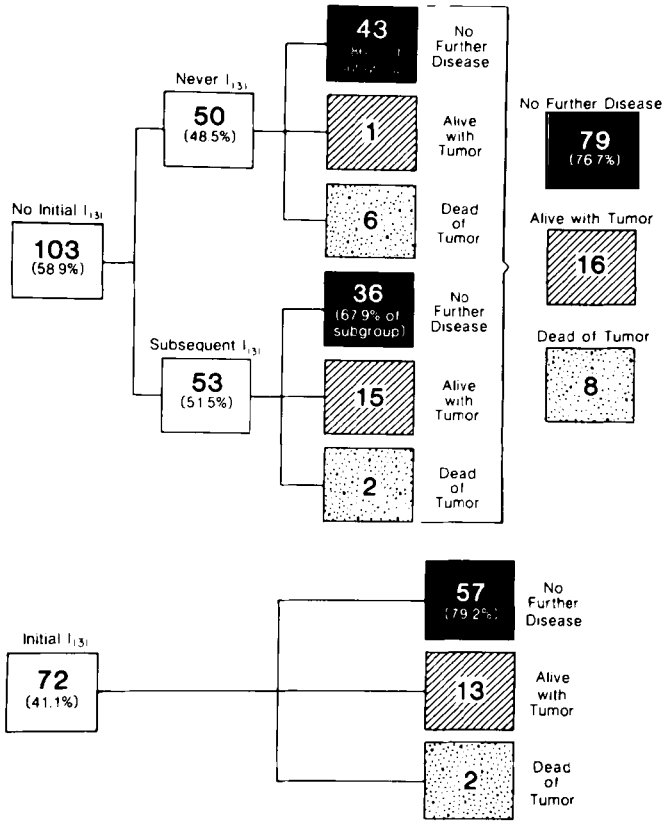


FIG. 23. Evolution of PTC in the group of patients treated initially with thyroidectomy according to whether prophylactic ^{131}I therapy was administered.

encapsulated tumors may show focally infiltrative margins, whereas the margins of a tumor that is totally devoid of a capsule may still be of the pushing type. Tumors with pushing margins, taken as a whole, were not significantly different from those with infiltrating margins as far as evolution was concerned, except for a higher incidence of cervical lymph node metastases seen in the latter group. Our findings were therefore substantially different from those of Frauenhoffer *et al.*[23]; in their material, lack of circumscription was associated with more advanced clinical stage at presentation and a greater incidence of subsequent distant metastases and deaths from tumor.

The pattern of growth of the tumor, specifically, the formation of papillae and follicles and their relative proportions, has been a subject of endless debate both in terms of tumor classification and prognostic implications. Currently, few would agree with a former proposal that thyroid tumors should be named according to their predominant patterns and, therefore, that only tumors in which papillae made up over 50% of the mass should be called papillary. There is now general agreement that if a well-differentiated thyroid carcinoma makes papillae, it should be placed in the category of PTC no matter how scanty these papillary formations might be.[29] We followed this practice in the current study. The second issue concerns the prognostic importance that the relative amount of papillae and follicles may carry. In this regard, our results agree with those of most other authors[11,24,30] in the sense that this morphologic feature seems to carry little if any prognostic significance. The only difference we noted was a higher incidence of lung metastases in the group in which follicles predominated, but this was not reflected in a poorer outcome for these patients.

The presence of fibrosis within the tumor and the quality of this fibrosis also proved to be of insignificant prognostic value. This we found somewhat surprising for the desmoplastic type of fibrosis, which was often associated with a distorted pattern of growth of the

TABLE 25. Comparison of Clinical and Pathologic Features of TTG Patients Between Those Who Received Iodine Therapy After Surgery and Those Who did Not

	^{131}I— therapy after surgery	No ^{131}I therapy after surgery
	72 (41.1%)	103 (58.9%)
Sex (M:F)	1:1.6	1:4.6
Age ≤ 40 years	50%	41.6%
Cervical adenopathy at presentation	47.2%	37.6%
Size ≤ 1 cm	14.5%	18.3%
Total encapsulation	8%	6.4%
Pushing margins	19.3%	31.1%
Predominantly papillary pattern	51.6%	58%
Marked cystic changes	6.4%	7.5%
Multicentricity	32%	20.4%
Blood vessel invasion	9.7%	6.4%
Extrathyroid extension	29%	22.5%

TTG: total or near-total thyroidectomy group.

TABLE 26. Clinical and Pathologic Features of Fatal Cases of Papillary Thyroid Carcinoma*

Age/Sex	Presentation	Initial therapy	Site of recurrence or metastases	Survival after initial therapy	Probable cause of death	Salient pathologic features
66/F	Thyroid nodule; previous hx of hyperthyroidism	Lobectomy	Soft tissues neck, nodes, liver	7 yr	Local extension and distant tumor	Extrathyroid extension
44/F	Thyroid nodule	TT + LN + Ext x-rays	Soft tissues neck, nodes, lung	4 yr	Local extension and distant tumor	None
61/F	Thyroid nodule, cervical and mediastinal nodes, lung metastases	TT	Nodes, lung	4 mo	Respiratory insufficiency	Classic appearance, but with areas of necrosis; multicentric
73/F	Thyroid nodule	TT	Thyroid remnant, Soft tissues neck, nodes, lung	23 yr	Local extension and distant tumor	Multicentric in the thy recurrence; slides of original tumor not available
88/M	Thyroid nodule	Nodulectomy	Soft tissues neck	2 yr	Local extension	Extrathyroid extension
71/F	Thyroid nodule	TT	Soft tissues neck, lung	3 mo	Local extension and distant tumor	Multicentric
51/M	Invasive thyroid nodule and cervical nodes	TT + LN	Nodes, mediastinum, bone	5 yr	Asphyxia due to local and mediastinal extension	Extrathyroid extension
41/M	Invasive thyroid nodule	TT + tracheostomy + ^{131}I + Ext x-rays	Soft tissues neck, nodes	6 yr	Local extension	Extrathyroid extension
41/M	Thyroid nodule	Nodulectomy	Soft tissues neck	9 yr	Cardiorespiratory insufficiency	None
70/F	Thyroid nodule	ST	Soft tissues neck, nodes	7 yr	Local extension, with spread into trachea	None
48/M	Thyroid nodule	TT + LN + ^{131}I	Nodes, lung, bone	5 yr	Widespread distant tumor	Slides of original tumor not available

* Excluding three postoperative deaths.
TT: total thyroidectomy; ST: subtotal thyroidectomy; LN: cervical lymph node dissection; Ext: external.

tumor cells so as to give the neoplasm a lesser differentiated appearance. In this context, our results are at variance with those of Tscholl-Ducommun and Hedinger[13]; these authors reported a slightly decreased survival for these "moderately differentiated papillary carcinomas," a feature that we failed to appreciate in our material.

Cystic changes, when of marked degree, proved to be indicative of an excellent outlook. It seems likely, though, that it is not the cystic change itself that is responsible for this improved prognosis, but rather the fact that it usually supervenes in tumors that are endowed with other favorable morphologic features, such as total encapsulation, pushing margins, and lack of extrathyroid extension.

The fact that a certain proportion of PTC contain areas with a solid pattern of growth has been commented upon by several authors, but the clinical implication of this finding has not been agreed upon. As a matter of fact, it has been our experience in consultation material that the presence of such areas is often taken as evidence that the tumor is less differentiated and that it will therefore behave in a more aggressive fashion. We have found that this is not at all the case, regardless of the extent of this change, as long as certain criteria are followed for their identification and especially for their separation from two highly aggressive forms of PTC, to be discussed later, *i.e.*, poorly differentiated ("insular") carcinoma, and PTC having areas of anaplastic carcinoma. The formations we accepted as solid foci in PTC could be focal or extensive (although we never found a totally solid PTC), diffuse, lobular, or trabecular, and could arise in the context of papillary or follicular areas. Most important, the cellular features in these solid areas were basically the same as those in the papillary or follicular areas, except for a slightly higher variability in nuclear size. When thus defined, solid foci in PTC did not modify any of the clinical parameters we investigated

nor did they result in a significantly increased rate of distant metastases.

Somewhat similar considerations can be made for the phenomenon of squamous metaplasia, which we believe is pathogenetically related to the development of solid areas. Neither we nor others have found that this feature correlates with any important clinical or prognostic parameter. The latter also applies to the presence of psammoma bodies, whose extreme importance resides elsewhere. We are referring, of course, to the diagnostic value of these formations in the thyroid gland. It has been stated by several authors[29,31] and it has been our experience that the presence of typical psammoma bodies in a tumor of this organ is a nearly specific indicator that this particular neoplasm belongs to the papillary group of carcinomas, regardless of its pattern of growth. It has been further stated that the presence of psammoma bodies in the thyroid gland or even in cervical lymph nodes in the absence of obvious tumor in that particular section should be regarded, until proven otherwise, as evidence that there is a papillary carcinoma nearby. The extremely rare exceptions that have been reported[31,32] serve only to outline this fact.

Heavy lymphocytic infiltration of the tumor showed an obvious correlation with the presence of Hashimoto's or lymphocytic thyroiditis in the nonneoplastic gland. In these cases, it almost seemed as if the tumor was recapitulating the events that had led to the lymphocytic outpouring in the remainder of the organ. Thus, our impression is at variance with that of others,[33] who regard the thyroiditis sometimes seen in glands harboring a PTC as a reaction to the neoplasm. A finding of some interest is the fact that although no tumor deaths had occurred in the group with heavy lymphocytic infiltration in the tumor, a very high percentage of these patients had persistent disease at the time of their last follow-up examination. To the best of our knowledge, this fact has not been previously pointed out. We did not find that the presence of lymphocytic or Hashimoto's thyroiditis in the nonneoplastic gland had any bearing on prognosis.

Microscopic multicentric involvement of the thyroid gland is a well-recognized feature of papillary carcinoma, the wide variations in its reported frequency being probably due to the extent of the sampling and the liberality of the pathologist.[34] When a "customary" number of samples away from the tumor are taken, *i.e.*, between three and five, the number of cases that will show evidence of multicentricity is about 20%, as we have observed in our material. There was an obvious relationship between the presence of multicentricity in the gland and development of nodal and pulmonary metastases; also, the disease-free survival rate of patients with multicentric tumor growth was significantly decreased.

In our material, presence of blood vessel invasion carried with it only a modest prognostic difference, which was barely significant; most surprisingly, there was no increase in the incidence of blood-borne metastases among the tumors with blood vessel invasion. This relative lack of importance of blood vessel invasion of PTC was also noted by Hawk and Hazard,[35] Cady *et al.*,[9] and Hofstadter and Unterkircher.[36] This is in striking contrast to the experience of Franssila,[11,12] who found that all but one of his six patients having a tumor with this feature died from distant metastases.

A much greater significance could be attached to the feature of extrathyroid extension, as seen in about 23% of the cases in our series and those of others.[11,13] Particularly impressive was the over sixfold increase in the number of tumor deaths that we observed. This was due almost entirely to the development of uncontrollable recurrence in the neck, as the incidence of blood-borne metastases was not significantly increased. The fact that extrathyroid extension is one of the worst prognostic signs in PTC was also noted by Woolner *et al.*,[22] who found a 54% 10-year survival rate in this group as compared to an overall figure of 82%. Cady *et al.*[9] recorded a 35% mortality for "extraglandular" PTC. Tscholl-Ducommun and Hedinger[13] found, as we did, a higher incidence of recurrent disease and a lower cure rate for their patients with extrathyroid extension, but also found a higher incidence of distant metastases. The close correlation that we found between extrathyroid extension and vascular invasion was, to a certain extent, predictable, as was the fact that patients whose tumors exhibited both of these features had a very low cure rate. We agree with Woolner *et al.*[22] that, of the pathologic features of PTC not exhibiting dedifferentiation, the presence of extrathyroid disease has the most significant bearing on prognosis.

Among the morphologic variants of PTC, that which we have called "occult sclerosing" on the basis of the heavy sclerosing pattern and small size roughly corresponds to the "occult papillary carcinoma,"[22] "occult sclerosing carcinoma,"[37] and "nonencapsulated sclerosing tumor"[38] of other authors. Our results confirmed the three most important facts about this particular lesion: that it belongs by cell type and behavior to the group of papillary tumors despite its scarcity of papillary formations; that it is a malignant neoplasm, as evidenced by the high incidence of cervical lymph node involvement; and that it is associated with a very good prognosis, significantly better than that for PTC as a whole. It should be realized, though, that occasionally it may metastasize through the blood stream and cause death.[39]

The solid variant of PTC, arbitrarily defined as a tumor in which over 50% of it has a solid pattern of growth, did not differ from the others prognostically. It would be unnecessary to retain it in a separate category were it not for the fact that these tumors are sometimes confused with more aggressive forms of thyroid carcinoma, particularly those with anaplastic transformation of PTC.[25]

Our findings with the follicular variant of PTC amply confirm our previous results[7] and the belief expressed by several authors[11,27] that this tumor belongs to the papillary group. Its clinical behavior and the cohort of morphologic features that accompanied it were clearly those of PTC. It is true that there were proportionally more lung metastases in this group than in the predominantly papillary neoplasms, but this was also the case, as already indicated, for the predominantly follicular tumors in which papillae were clearly evident.

Not included in this series were papillary carcinomas with anaplastic transformation[3] and a group of poorly differentiated ("insular") carcinomas, some of which are histogenetically related to PTC.[4] Briefly, they were characterized by a compact pattern of growth with a lobular arrangement, formation of microfollicles and occasional papillae, small cells with scanty cytoplasm and round hyperchromatic nuclei, frequent mitotic activity, areas of necrosis, and an aggressive clinical course. They may correspond, at least in part, to the "poorly differentiated papillary carcinomas" of Tscholl-Ducommun and Hedinger.[13]

The marked tendency of PTC for metastatic involvement of the regional lymph nodes (particularly in the younger age groups) was shown once again in this study, as well as the remarkable fact that this feature does not influence the long-term prognosis of these patients. We did not find improved survival figures in the patients with metastatic cervical nodes, as Cady *et al.*[9] did, but neither did we find the opposite. Our microscopic findings in the involved nodes that were cold on scintigraphic examination were of interest; they showed that the lack of function was not the result of dedifferentiation of the tumor, as initially feared by the clinicians, but rather to the development within them of degenerative cystic changes that had no bearing on the prognosis.

We recorded an incidence of pulmonary metastases in our population that was somewhat higher than the 4% reported by Woolner *et al.*,[22] the 8.6% reported by Frazell and Foote,[40] and the 10% quoted by Franssila,[11] but lower than the 16.7% encountered by Wilson and Block.[41] Since no microscopic documentation of these metastases was obtained, the possibility exists that some of these pulmonary nodules were of a different nature. Incidentally, this applies to most other series in the literature. However, the fact that most of them were detected through the use of ^{131}I scintigram and that in 50% of the cases they regressed completely after ^{131}I therapy would seem to attest to their thyroid neoplastic nature. Nearly 50% of these lung metastases were present at the time of initial diagnosis, resulting in a 6.5% incidence of initial distant metastases for the entire series. This high figure, which is identical to that reported by Tscholl-Ducommun and Hedinger,[13] may be indicative of a significant delay in the diagnosis of PTC in some populations. The moderate but obvious deleterious effect on prognosis of lung metastases that we found agrees with the experience of previous authors. The incidence of osseous metastases (3.7%) was similar to the 3% recorded by Franssila,[11] but lower than the remarkably high figure of 9.5% quoted by Wilson and Black[41]; this feature carried with it an ominous prognostic significance, as other series have already indicated.[42]

The long-term results of the surgical therapy were most interesting in view of the lingering controversy about how much thyroid tissue should be removed and whether a radical neck dissection on the side of the lesion is indicated. In our series, patients who had a limited surgical procedure, *i.e.*, nodulectomy or lobectomy, did as well as those having a more extensive procedure. Two thirds of them were permanently cured of their disease without the necessity of a reoperation in the thyroid gland. Close to 25% of the patients developed a recurrence in the residual gland. This figure is similar to the results reported by Buckwalter and Thomas[43] and Rose *et al.*,[44] and higher than those observed by Lindsay[33] (12%), Tollefsen *et al.*[45] (5.7%), and Woolner *et al.*[22] (5.5%). Some of these differences are probably due to the variability in the extent of the "conservative" operation,[46] which ranged from a nodulectomy (as in several of our earlier cases) to a subtotal thyroidectomy, as in many of the cases reported by Woolner *et al.*[22] The important fact is that, in our series, of those patients who developed local recurrence that required the removal of the residual gland, two thirds were permanently cured, leading to a total cure rate of 86%, as opposed to a figure of 78% in the group that had a thyroidectomy as the initial procedure. Since this is a retrospective study, it could be argued that the two populations are not strictly comparable. Indeed, in the thyroidectomy group there was a somewhat higher percentage of tumors having unfavorable morphologic features, such as multicentricity and extrathyroid extension. These figures, however, were quite comparable to those in the subset of NLG patients who later required a thyroidectomy because of tumor recurrence.

Two considerations arise from these results. The first is that a limited surgical procedure seems a very adequate

form of therapy for most cases of PTC, at least those occurring in the usual age group and not displaying easily detectable multicentricity and/or extrathyroid extension. The second is that, even if the latter cases are included, the probability of cure is not diminished by performing the thyroidectomy only if and when recurrence develops. Rose *et al.*[44] also found that allowing the contralateral lobe to remain had no influence on the subsequent development of distant metastases. This being the case, lobectomy would appear as a procedure generally preferable to total thyroidectomy, since it usually avoids two major complications of the latter, *i.e.*, permanent hypoparathyroidism and recurrent laryngeal nerve injury. In various series, the incidence of the former ranges from 10% to 29% and that of the latter from 5% to 20%.[45-49] These complications are said to be particularly frequent when a conservative operation is "converted" to a total thyroidectomy some days or weeks after the initial procedure because of a microscopic diagnosis of cancer.[50]

The long-term results in the TTG, depending on whether an elective ("prophylactic") lymph node dissection was done at the time of the thyroidectomy, agrees with the conclusions reached by other authors,[7,14,22,51] in the sense that no benefit results from performing this involved, disfiguring, and disabling surgical procedure, which increases significantly the possibility of accidental injury of the recurrent laryngeal nerve.[49] To quote Cady *et al.*,[9] "there is no evidence that prophylactic node resection in the absence of gross nodal enlargement plays any role whatsoever in management despite the high incidence of occult nodal metastases." Woolner *et al.*[22] took an even stronger stand by stating that "radical dissection of the neck is unnecessary and certainly constitutes gross overtreatment in cases in which no palpable nodes are found."

An evaluation among the TTG patients of the value of prophylactic administration of radioactive iodine also failed to demonstrate a beneficial effect for this therapy. Among the patients who did not receive ^{131}I initially, 50% needed it later because of the development of metastases, but the overall disease-free survival rate for the group was statistically no different from the group that had ^{131}I as part of the initial treatment. There were more tumor deaths in the group that did not receive prophylactic ^{131}I therapy, but most of these patients were not candidates for ^{131}I treatment even after metastases developed because of their lack of uptake on the scan. Here again it would seem that administration of radioactive iodine can safely be withheld until the time that metastases from the PTC become evident, if that is the case. Our results in this regard are similar to those of Wanebo *et al.*,[52] who concluded that postoperative treatment with ^{131}I did not appear beneficial in staged patients. It is interesting that even those authors who recommend the routine postoperative use of ^{131}I therapy show no statistical differences in survival for tumors that are small[53] or for those that occur in patients 39 years of age or younger.[54] Also to be noted is the fact that, in this series, the differences among the two groups are mainly on recurrence rates. We do not argue this point, since our results were similar. We only want to emphasize the fact that reserving the use of ^{131}I (coupled with thyroidectomy) for those patients who develop metastases, and delaying administration until these metastases become manifest, does not seem to compromise these patients' outlook. The marked effectiveness of ^{131}I in proved distant metastases can hardly be argued.[55,56] It is also acknowledged, and our series confirmed, that there is a poor response to radioiodine of metastases to the skeletal system and to those that are cold on scintiscan.[56,57,58]

The total incidence of tumor deaths in our series (4.6%) was nearly identical to that found by Woolner *et al.*[22] Crile[14] reported an incidence of 2% after excluding the dedifferentiated tumors. Conversely, Franssila[12] recorded a death incidence of 21%, but he included in this figure deaths that were probably from thyroid cancer, and deaths from other causes. Evaluation of our fatal cases showed, as in several other series,[59] that the majority of the patients were elderly and that several of the tumors had extrathyroid extension at the time of diagnosis. The death was usually due to uncontrollable local disease. This is in contrast with the findings reported by Silverberg *et al.*[60] in their autopsy series of fatal thyroid carcinoma; in their experience, the majority of the patients with well-differentiated carcinoma died from distant metastases. Evaluation of the initial surgical therapy in our cases strongly suggests that the demise of these patients was not due to the choice of operative procedure but rather to the presence of an intrinsically more aggressive neoplasm.

The incidence of distant metastases in the fatal cases was over 50%; Silliphant *et al.*[61] also recorded a 50% incidence of lung metastases among their fatal papillary carcinoma. It is well to point out, however, that in the majority of these cases it is the local disease rather than the distant tumor that is primarily responsible for the patient's death. It is rare for a patient with PTC to die from distant metastases without having recurrent tumor in the neck; this happened only in two of our cases and in 13% of those reported by Silliphant *et al.*[61]

Conclusions

The general conclusions we reached from this study regarding the therapy of PTC are the following:

A limited initial surgical procedure to the thyroid gland is a safe and preferable approach in the majority of the cases, unless the tumor is shown to have spread

to the opposite lobe or beyond the thyroid at the time of surgery. Although this study did not address this particular point, it is generally agreed that a lobectomy with isthmusectomy is preferable to nodulectomy.[43,46] Actually, the former operation has now become standard for many surgeons in the handling of solitary thyroid nodules.

Those patients having lobectomy in whom the tumor is shown on pathologic examination to exhibit extrathyroid extension and/or easily detectable multicentricity are at a higher risk of developing a local recurrence that may necessitate the completion of the thyroidectomy. For this subgroup of patients, two options could be considered:

1. To complete the thyroidectomy at the time of the initial procedure if the pathologist detects one or both of these morphologic features. This could be done as a frozen section procedure, so as to avoid the performance of a second operation. Examination of three random samples of thyroid tissue away from the main tumor mass would seem to us adequate to search for the presence of multicentricity. When looking for extrathyroid extension, it should be obvious that the sample should be taken from the tumor edge that is grossly closer to the thyroid capsule.
2. Not to perform any additional surgery at the time, but rather follow the patient at 6-month intervals, and perform the thyroidectomy or whatever other therapy might be necessary only in case of tumor recurrence. The evidence here presented suggests that the patient is not placed at an undue risk by adopting this policy.

Older patients, especially older men, are at an increased risk of recurrence, and they do not respond as well to thyroid feeding. For them, the possibility of initial thyroidectomy should therefore be considered.

Thyroid replacement therapy should be given for life, in a sufficient amount to suppress thyroid-stimulating hormone activity. There is general agreement among the authors on this point.[7,49]

Elective radical neck dissection does not improve the prognosis of these patients, and its performance can hardly be justified. If the nodes are grossly regarded as positive, either clinically or intraoperatively, those can be removed without carrying out a radical procedure.

Prophylactic administration of radioactive iodine does not seem to improve the outlook of these patients beyond what is achieved by suppression with thyroid hormone. The use of ^{131}I is better reserved as a therapeutic measure at the time that metastases become evident. Our data suggests that patients are not subjected to an increased risk by adopting this expectant attitude.

For the patients who develop recurrent disease after conservative surgical therapy, we suggest the following:

1. If the recurrence is in the cervical lymph nodes, these can be removed surgically, but this need not be done through a formal radical neck dissection.
2. If the recurrence is in the residual thyroid gland, the thyroidectomy should be completed if technically feasible, to remove the tumor and to facilitate the use of radioactive iodine, if that were to become necessary later.
3. If the recurrence is in the form of blood-borne metastases, thyroid hormone should certainly be administered if it was not already. Otherwise, treatment with radioactive iodine is indicated. For this therapy to be successful, the ablation of residual normal thyroid tissue becomes necessary, or at least very useful. This is best done surgically. For blood-borne metastases that appear isolated, surgical excision would seem justified.

All of the above considerations are made with the full realization that they are based on a retrospective series, with all the inherent limitations of this type of study. Alas, this applies to all other articles on the subject. A properly conducted prospective study would seem the best way to test the validity of these therapeutic suggestions.

REFERENCES

1. Variakojis D, Getz ML, Paloyan E, Straus FH. Papillary clear cell carcinoma of the thyroid gland. *Hum Pathol* 1975; 6:384–390.
2. Kakudo K, Miyauchi A, Toaki S, Katayama S, Kuma K, Kitamura H. C cell carcinoma of the thyroid: Papillary type. *Acta Pathol Jpn.* 1979; 29:653–659.
3. Hutter RVP, Tollefsen HR, DeCosse JJ, Foote FW Jr, Frazell EL. Spindle and giant cell metaplasia in papillary carcinoma of the thyroid. *Am J Surg* 1965; 110:660–668.
4. Carcangiu ML, Zampi G, Rosai J. Poorly differentiated ("insular") thyroid carcinoma: A reinterpretation of Langhans' "wuchernde struma." *Am J Surg Pathol* 1984; 8:655–668.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc J* 1958; 53:457–481.
6. Breslow N. A generalized Kruskel-Wallis test for comparing K samples subject to unequal patterns of censorship. *Biometrika* 1970; 57:579–594.
7. Chen KTK, Rosai J. Follicular variant of thyroid papillary carcinoma: A clinicopathologic study of six cases. *Am J Surg Pathol* 1977; 1:123–130.
8. Rosai J, Zampi G, Carcangiu ML. Papillary carcinoma of the thyroid: A discussion of its several morphologic expressions, with particular emphasis on the follicular variant. *Am J Surg Pathol* 1983; 7:809–817.
9. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg* 1976; 184:541–553.
10. Cady B, Sedgwick CE, Meissner WA, Wool MS, Salzman FA, Werver J. Risk factor analysis in differentiated thyroid cancer. *Cancer* 1979; 43:810–820.
11. Franssila KO. Is the differentiation between papillary and follicular thyroid carcinoma valid? *Cancer* 1973; 32:853–864.
12. Franssila KO. Prognosis in thyroid carcinoma. *Cancer* 1975; 36:1138–1146.
13. Tscholl-Ducommun J, Hedinger CE. Papillary thyroid carcinomas: Morphology and prognosis. *Virchows Arch [Pathol Anat]* 1982; 396:19–39.
14. Crile G Jr. Changing end results in patients with papillary carcinoma of the thyroid. *Surg Gynecol Obstet* 1971; 132:460–468.

15. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: The impact of therapy in 576 patients. *Medicine* 1977; 56:171–196.

16. Meissner WA, Adler A. Papillary carcinoma of the thyroid: A study of the pathology of two hundred twenty-six cases. *Arch Pathol* 1958; 66:518–525.

17. Doniach I. Aetiologic consideration of thyroid carcinoma. In: Smithers D, ed. Tumours of the Thyroid Gland. Edinburgh and London: E. and S. Livingstone, 1970; 66–67.

18. Hedinger C. Histological typing of thyroid tumours. International Histological Classification of Tumours N° 11. Geneva: World Health Organization, 1974.

19. Beaugie JM, Brown CL, Doniach I, Richardson JE. Primary malignant tumours of the thyroid: The relationship between histological classification and clinical behavior. *Br J Surg* 1976; 63:173–181.

20. Mazzaferri EL, Oertel JE. The pathology and prognosis of thyroid cancer. In: Kaplan EL, ed. Surgery of the Thyroid and Parathyroid Gland (Clinical Surgery International, vol. 6). Edinburgh: Churchill Livingstone, 1983; 18–39.

21. Carcangiu ML, Zampi G, Rosai J. Papillary thyroid carcinoma: A study of its many morphologic expressions and clinical correlates. *Pathol Annu* (in press).

22. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR Jr. Classification and prognosis of thyroid carcinoma: A study of 885 cases observed in a thirty year period. *Am J Surg* 1981; 102:354–387.

23. Frauenhoffer CM, Patchefsky AS, Cobanoglu A. Thyroid carcinoma: A clinical and pathologic study of 125 cases. *Cancer* 1979; 43:2414–2421.

24. Ito J, Noguchi S, Murakami N, Noguchi A. Factors affecting the prognosis of patients with carcinoma of the thyroid. *Surg Gynecol Obstet* 1980; 150:539–544.

25. Woolner LB. Thyroid carcinoma: Pathologic classification with data on prognosis. *Semin Nucl Med* 1971; 1:481–502.

26. Schroder S, Bocker W, Dralle H, Kortman K-B, Stern C. The encapsulated papillary carcinoma of the thyroid: A morphologic subtype of the papillary thyroid carcinoma. *Cancer* 1984; 54:90–93.

27. Doniach I. The thyroid gland. In: Symmers W St C, ed. Systemic Pathology, ed. 2, vol. 4. Edinburgh: Churchill Livingstone, 1976; 2021.

28. Meissner WA, Warren S. Tumors of the thyroid gland. In: Atlas of Tumor Pathology, series 2, fascicle 4. Washington DC: Armed Forces Institute of Pathology, 1969.

29. Underwood CR, Ackerman LV, Eckert C. Papillary carcinoma of the thyroid: An evaluation of surgical therapy. *Surgery* 1958; 43:610–621.

30. Russell MA, Gilbert EF, Jaeschke WF. Prognostic features of thyroid cancer: A long-term follow-up of 68 cases. *Cancer* 1975; 36:553–559.

31. Klinck GH, Winship T. Psammoma bodies and thyroid cancer. *Cancer* 1959; 12:656–662.

32. Patchefsky AS, Hoch WS. Psammoma bodies in diffuse toxic goiter. *Am J Clin Pathol* 1972; 57:551–556.

33. Lindsay S. Carcinoma of the Thyroid Gland. A clinical and pathologic study of 293 patients at the University of California Hospital. Springfield, IL: Charles C. Thomas, 1960.

34. Russell WO, Ibanez ML, Clark RL, White EF. Thyroid carcinoma: Classification, intraglandular dissemination, and clinicopathological study based upon whole organ sections of 80 glands. *Cancer* 1963; 11:1425–1460.

35. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. *Cleve Clin Q* 1976; 43:207–216.

36. Hofstadter F, Unterkircher S. Histologische Kriterien zur Prognose der Struma maligna. *Pathologe* 1980; 1:79–85.

37. Klinck GH, Winship T. Occult sclerosing carcinoma of the thyroid. *Cancer* 1955; 8:701–766.

38. Hazard JB. Small papillary carcinoma of the thyroid: A study with special reference to so-called non-encapsulated sclerosing tumor. *Lab Invest* 1960; 9:86–97.

39. Patchefsky AS, Keller IB, Mansfield CM. Solitary vertebral column metastases from occult sclerosing carcinoma of the thyroid gland: Report of a case. *Am J Clin Pathol* 1970; 53:596–601.

40. Frazell EL, Foote FW Jr. Papillary cancer of the thyroid: A review of 25 years of experience. *Cancer* 1958; 11:895–922.

41. Wilson SM, Block GE. Carcinoma of the thyroid metastatic to lymph nodes of the neck. *Arch Surg* 1971; 102:285–291.

42. McCormack KR. Bone metastases from thyroid carcinoma. *Cancer* 1966; 19:181–184.

43. Buckwalter JA, Thomas CG Jr. Selection of surgical treatment for well differentiated thyroid carcinomas. *Ann Surg* 1972; 176:565–578.

44. Rose RG, Kelsey MP, Russell WO, Ibanez ML, White EC, Clark RL. Follow-up study of thyroid cancer treated by unilateral lobectomy. *Am J Surg* 1963; 106:494–500.

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

46. Block MA. Management of carcinoma of the thyroid. *Ann Surg* 1977; 185:133–144.

47. Farrar WB, Cooperman M, James AG. Surgical management of papillary and follicular carcinoma of the thyroid. *Ann Surg* 1980; 192:701–704.

48. Rustad WH, Lindsay S, Dailey ME. Comparison of the incidence of complications following total and subtotal thyroidectomy for thyroid carcinoma. *Surg Gynecol Obstet* 1963; 116:109.

49. Thompson NW, Harness JK. Complications of total thyroidectomy for carcinoma. *Surg Gynecol Obstet* 1970; 131:861–868.

50. Duffield, RGM, Lowe D, Burnand KG. Treatment of well-differentiated carcinoma of the thyroid based on initial staging. *Br J Surg* 1982; 69:426–428.

51. Hutter RVP, Frazell EL, Foote FW Jr. Elective radical neck dissection: An assessment of its use in the management of papillary thyroid cancer. *Ca* 1970; 20:87–93.

52. Wanebo HJ, Andrews W, Kaiser DL. Thyroid cancer: Some basic considerations. *Am J Surg* 1981; 142:474–479.

53. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: A 10 year follow-up report of the impact of therapy in 576 patients. *Am J Med* 1980; 70:511–518.

54. Varma VM, Veierwaltes WH, Nofal MM, Nishiyama RH, Copp JE. Treatment of thyroid cancer: Death rates after surgery and after surgery followed by sodium iodide ^{131}I. *JAMA* 1970; 214:1437–1442.

55. Harness JK, Thompson NW, Sisson JC, Beierwaltes WH. Differentiated thyroid carcinomas: Treatment of distant metastases. *Arch Surg* 1974; 108:410–419.

56. Leeper RD. The effect of ^{131}I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma. *J Clin Endocrinol Metab* 1973; 36:1143–1152.

57. Maheshwari YK, Hill CR Jr, Haynie TP III, Hickey RC, Samaan NA. ^{131}I therapy in differentiated thyroid carcinoma: M.D. Anderson Hospital experience. *Cancer* 1981; 47:664–671.

58. Tubiana M, Lacour J, Monnier JP *et al.* External radiotherapy and radioiodine in the treatment of 359 thyroid cancers. *Br J Radiol* 1975; 48:894–907.

59. Tollefsen HR, DeCosse JJ, Hutter RV. Papillary carcinoma of the thyroid: A clinical and pathologic study of 70 fatal cases. *Cancer* 1964; 17:1035–1044.

60. Silverberg SG, Hutter RVP, Foote FW Jr. Fatal carcinoma of the thyroid: Histology, metastases, and causes of death. *Cancer* 1970; 25:792–802.

61. Silliphant WM, Klinck GH, Levitin MS. Thyroid carcinoma and death: A clinicopathological study of 193 autopsies. *Cancer* 1964; 17:513–525.