Changing Clinical, Pathologic, Therapeutic, and Survival Patterns in Differentiated Thyroid Carcinoma

BLAKE CADY, M.D., CORNELIUS E. SEDGWICK, M.D., WILLIAM A. MEISSNER, M.D., JOHN R. BOOKWALTER, M.D.,*
VINCENTE ROMAGOSA, M.D.,† JOAN WERBER, A.B.

From the Department of Surgery,
Lahey Clinic Foundation and
Laboratory of Pathology,
New England Deaconess Hospital,
Boston, Massachusetts

Records of 792 patients with differentiated thyroid carcinoma seen at the Lahey Clinic Foundation over a 40-year period were analyzed; 631 patients had a minimum followup period of 15 years. Differentiated types currently constitute nearly 90% of thyroid carcinomas. The clinical presentation has improved substantially through the years, and the results of treatment generally have improved. The per cent of patients with primarily incurable and locally unresectable disease or distant metastases has decreased from 7% before 1950 to 1% currently, and this group resulted in almost one third of the total fatalities and one half of fatalities within the first 5 years after treatment. Clear relationships were demonstrated between older age, men, extraglandular extension, blood vessel invasion, major capsular involvement, multifocal disease, and higher mortality rates. Lymph node metastases were found to exert a protective effect in all categories of disease analyzed, and this effect was directly related to the number of lymph node metastases present such that no deaths occurred in those patients who had more than 10 node metastases. Surgical treatment recommended is subtotal thyroidectomy for patients at high risk of death from disease as defined by combinations of age, sex, and extraglandular extension. Patients at low risk or with small carcinomas can be treated satisfactorily by lobectomy. Lymph node resections should be of a limited type or a modified neck dissection and should be performed only therapeutically. No improvement, as judged by mortality or recurrence rates, could be demonstrated by the use of radiotherapy after surgery, and its use should be discouraged. Thyroid hormone administered for suppression of endogenous thyroid-stimulating hormone production improved mortality rates significantly in patients with papillary and mixed forms of carcinoma in all age groups but did not affect survival in patients with follicular carcinoma of the thyroid.

THE TREATMENT of thyroid carcinoma remains controversial with basic philosophies of treatment ranging from radical[2] to conservative[7] regarding resection of the thyroid gland, excision of regional lymphatics, and use of radiation therapy and thyroid feeding for suppression postoperatively. The biologic nature of the disease is also uncertain, with a few authorities[27] even suggesting that patients rarely, if ever, die of disease.

An intensive analysis of the entire Lahey Clinic Foundation material was undertaken to provide a statistical basis for updating concepts of biology and treatment.

Material and Method

Nine hundred and sixty-four patients had primary therapy at the Lahey Clinic Foundation and pathologic material available for classification[19] in 1975. Mixed forms of thyroid carcinoma, which contained elements of both papillary and follicular patterns, were classified separately. *Papillary predominant* indicated that 60% or more of the general pattern appeared papillary, *follicular predominant* indicated the same predominance of follicular features, and *predominance not stated* indicated that papillary and follicular features were approximately

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* Present address: 9 Belmont Avenue, Brattleboro, Vermont 05301.

† Resident in Pathology, New England Deaconess Hospital, Boston, Massachusetts.

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equivalent. The few patients with areas of giant or spindle cell metaplasia were considered to have papillary and mixed carcinomas unless an overall pattern of giant or spindle cell type was predominant, and these were classified as undifferentiated carcinoma. Oxyphil cell type (Hürthle cell) follicular carcinoma was included as a subgroup of follicular carcinoma.

Current followup information was achieved in 98% of all patients at 15 years and in 97% of all patients. In only 6 instances (0.6%) were patients lost to followup study before 5 years. To eliminate any favorable bias, patients were considered dead of disease if they had died or were last seen with active disease present. Thyroid carcinoma was the usual, but not invariable, direct cause of death in these patients. The three patients who died postoperatively (all had unresectable local disease) were considered dead of disease. All others were documented as living, disease free; dead, disease free; or lost to followup (29 patients).

Initial definitive surgery at the Lahey Clinic was classified as *biopsy only*, when the thyroid cancer was locally unresectable; *excision of nodule*, when only the prominent nodule was excised; *lobectomy*, when unilateral subtotal, near total, or total lobe removal was performed; *thyroidectomy for disease*, when disease grossly involved more than one lobe and both lobes were excised to ensure an adequate visceral margin of normal thyroid; and *thyroidectomy for suppression*, when gross disease was clearly confined to one lobe of the thyroid gland but the contralateral lobe was excised only for aid in achieving thyroid elimination for the eventual use of radioactive iodine or for concern regarding clinically inapparent multifocal disease. These definitions were chosen in the context of the surgical practice at the Lahey Clinic[3,24] where total thyroidectomy was almost never performed because of strong concerns about the risk of hypoparathyroidism. Only 19 instances (2%) of permanent hypoparathyroidism were produced.

In the 1930's, many patients were treated by nodule excision only because differentiation between adenoma and cancer was not clearly defined. Increasing sophistication in frozen section diagnosis of thyroid carcinoma has led to the virtual disappearance of nodule excision as the sole surgical treatment of thyroid carcinoma, although occasional disease with minimal capsular invasion may still be considered as adenoma until permanent sections are returned. Not all patients with such disease are returned to the operating room for further surgical procedures.

At operation, estimations of the extent of disease were: 1) *occult disease*, no gross diagnosis by the surgeon of thyroid cancer—these situations included microscopic, macroscopic, or small foci of carcinoma in glands excised for benign conditions, or solitary nodules where frozen section was either not performed or did not confirm minimal capsular invasion because of sampling limitations; 2) *intrathyroid disease*, thyroid cancer diagnosed but tumor completely confined within the thyroid gland capsule; and 3) *extrathyroid disease*, thyroid cancer grossly involved structures external to the thyroid gland capsule.

Pathologic features have important correlations with biology. *Blood vessel invasion* was searched for in all patients, including the use of elastic tissue stains and required visualizing tumor involvement or attachment to vessel wall, as free floating cancer cells within a vessel lumen can be artifactual. *Multifocal disease* implied more than one defined focus of carcinoma which was discontinuous. Multifocal disease does not necessarily imply multifocal origin. *Minor capsular involvement* implied limited involvement or focal penetration of an otherwise intact capsule about the tumor, whereas *major capsular involvement* indicated the capsule was breached in multiple areas or in a major segment by carcinoma.

The maximum diameter of unifocal cancers was recorded. The number of lymph node metastases was noted and categorized as 1 to 3, 4 to 10, or more than 10 lymph node metastases present.

Radiation therapy was classified as *prophylactic* if all macroscopic tumor had been excised at operation or *therapeutic* if macroscopic tumor was left at the conclusion of the operation. Radiation therapy was by external beam in nearly all prophylactic as well as therapeutic instances. Radioactive iodine was used in occasional patients with gross residual disease but was usually reserved for therapy of distant metastases.

First disease recurrence was categorized as: 1) *local recurrence*, indicating disease in the thyroid bed, trachea, esophagus, or midline neck in the thyroid area; 2) *nodal metastases*, if lymph node metastases appeared in the neck area or in the unusual cases where disease appeared in the area of a previous neck dissection; or 3) *distant metastases*, if disease was defined outside the neck area. If disease appeared in more than one location simultaneously, it was defined as the most serious metastatic site (inverse order of these three criteria) for the purpose of analysis.

Determinate mortality and recurrence rates were based on patients at risk during the entire time period. Patients dead free of disease, lost to followup study, or alive free of disease less than the full time period were not included for calculation of determinate rates of survival or recurrence. All other tables cite 20 year gross rates of mortality.

An analysis of the variability between the determinate mortality rates and the gross mortality rates demonstrated negligible differences at 5, 10, and 15 years. However,

TABLE 1. *Lahey Clinic Foundation, Differentiated Thyroid Carcinoma, 1931–1960; Relation of Age to 20-Year Gross Mortality*

	Total No.	Age Groups							
		< 20		20 to 40		41 to 50		> 50	
		No.	%	No.	%	No.	%	No.	%
Papillary and mixed incidence	441	31	7%	201	46%	85	19%	124	28%
Dead of disease and mortality rate		0	0	9	5%	3	4%	36	29%
Follicular incidence	190	11	6%	63	33%	35	18%	81	43%
Dead of disease and mortality rate		1	9%	4	6%	7	20%	34	42%
Total cases (incidence)	631	42	(7%)	264	(42%)	120	(19%)	205	(33%)
Dead of disease and mortality rate		1	2%	13	5%	10	8%	70	34%

at 20 and 25 years there is substantial separation of gross and determinate rates (15% vs 27% and 18% vs 28% overall respectively) due to the decreasing number of patients at risk. Approximately 80% of all deaths occurred by 15 years, but more than 90% of deaths occurred by 20 years. For more accurate estimates of true risk of death to patients, the 15-year determinate mortality figures should be increased by 25% to approximate the 20- and 25-year mortality risk [since about 80% of total eventual deaths occurred by 15 years $(0.25 \times 80) + 80 = 100$] in the tables using determinate rates. A similar approximation of eventual risk of death can be achieved by increasing the 20-year gross figures by 25% in those tables where only gross survival figures are used.

Most of the survival, mortality, and recurrence calculations were based on the first three decades studied and, therefore, exhibited a *minimum* 15-year followup period; 75% of such patients had a minimum 20-year followup determination, and 214 patients (27%) had a minimum followup period of 30 years.

Statistical analysis of significance of differences was carried out using either chi square analysis or the Fisher exact test whenever appropriate. P values of significance are noted in the text or tables when performed.

Results

Twenty-five medullary carcinomas (3%), 147 undifferentiated carcinomas (15%), and 792 differentiated thyroid carcinomas (82%) were recorded. Through the four decades, undifferentiated forms became significantly less common and currently are found in 9% of patients.

The various types of papillary and mixed carcinomas are also changing subtly. The incidence of papillary and papillary predominant forms has decreased significantly ($P < 0.001$) from 57% to 34% of differentiated cancers. A commensurate significant rise was observed in the other mixed forms while the incidence of pure follicular carcinoma has remained unchanged. All aspects of the spectrum of papillary and mixed forms of thyroid carcinoma were similar and contrasted distinctly with the follicular forms regarding male incidence (22% vs 35%), size of primary, incidence of occult disease (34% vs 51%), node metastases (35% vs 13%), blood vessel invasion (40% vs 60%), and recurrence and mortality rates.

Before 1960, follicular carcinoma occurred in older patients, but in the last decade there has been a shift to younger ages in patients with follicular carcinomas and to older ages in patients with papillary and mixed forms so that currently the ages are the same.

Age at diagnosis and primary treatment is a crucial factor in results of treatment (Table 1). Only 1 of 42 (2%) patients less than 20 years of age died of disease, 13 of 264 (5%) betwen 20 and 40 years of age died of disease, and 10 of 120 (8%) between 41 and 50 years of age died. Patients more than 50 years of age had a markedly increased mortality rate with 70 of 205 (34%) actually dying of disease. The age of high risk began at 50 for patients with papillary and mixed forms but at 40 for patients with follicular carcinomas as 20% of such patients between 40 and 50 died of disease. Of the 94 total deaths in these three decades, 70 (75%) occurred in the 33% of patients more than 50 years of age, and 85% of deaths (80 of 94) occurred in the 50% of patients more than 40 years of age.

An increasing incidence of men with thyroid carcinoma in succeeding decades from 19% in the 1930's to 34% in the 1960's constituted a significant trend in both papillary and mixed and follicular carcinomas.

The combination of sex and age is significantly related to mortality (Table 2). The age of high risk for men begins at age 40 but for women at age 50. The overall risk of death for men is higher.

There was a decreasing size of carcinomas over the four

TABLE 2. *Lahey Clinic Foundation, Differentiated Thyroid Carcinoma, 1931–1960; Relationship Between Sex, Age, and Mortality*

	Men				Women			
	Incidence		Dead of Disease		Incidence		Dead of Disease	
Age	No.	%	No.	%	No.	%	No.	%
< 40	64	44	3	5	242	50	10	4
40 to 50	32	22	5	16	86	18	3	4
> 51	50	34	21	42	157	32	52	33
Total	146	100	29	20	485	100	65	13
				P < 0.001				P < 0.001

decades. Currently, 45% are less than 2 cm in maximum diameter and only 13% are more than 4 cm in maximum diameter. Both surgical and pathologic aspects have changed so that considerably more favorable case material was encountered in the 1960's (Table 3). One third of patients still present with surgically occult lesions, generally indicating a small, favorable lesion, and in only 12% of patients seen in the 1960's did carcinoma extend beyond the confines of the thyroid capsule. Although multifocal disease is becoming more frequent, blood vessel invasion has decreased by one-half to a 28% incidence. The extent of capsular invasion has decreased dramatically so that less than one half of patients have major involvement of the tumor capsule.

Despite these evidences of earlier disease noted through the four decades studied, the extent of operation performed for primary carcinoma of the thyroid gland has increased as a result of changes in attitude regarding the usefulness of radioactive iodine in the 1960's and the philosophy of radical surgery that persisted through the 1950's (Table 4). Currently, 60% have subtotal excision of the contralateral lobe primarily for aid in using later radioactive iodine. Table 4 also displays the changing philosophies regarding resection of regional lymphatics. Nodal dissections were performed in only 21% of patients in the 1930's but increased to 47% of all patients in the 1950's when 92% of resections were formal standard radical neck dissections. In the latter part of the 1960's, the overall incidence of nodal resection decreased to 38% of all patients, and the extent of nodal resections altered significantly so that only 43% are classified as radical neck dissections while 16% are classified as modified neck dissections with preservation of some combination of spinal accessory nerve, sternocleidomastoid muscle, and jugular vein, and frequently all three. The submaxillary triangle is usually not dissected during this procedure. Still more restricted limited nodal resections were performed in 41% of patients having lymphatic tissue excised and implied a deliberate attempt to resect lymph nodes in the immediate vicinity of the thyroid gland through the usual collar incision without sacrifice of either sternocleidomastoid muscle or jugular vein. The actual indicence of lymph node metastases was 11%, 28%, 35%, and 27% in the four decades and show a rough correlation with the number of nodal resections performed.

Table 5 demonstrates the correlation between lymph node pathology and age and sex in the decade 1951 to 1960. During this period 47% of all patients had neck dissections, 92% of which were formal radical neck dissections. There are increasing per cents of patients without lymph node metastases in the older ages, and this fraction is greater for men than for women. Conversely, patients with lymph node metastases were clearly younger in age and tended to be still younger as the number of lymph nodes increased.

The effect of lymph node metastases is analyzed in Table 6. Patients with pathologically confirmed lymph node metastases had a lower mortality rate than those without nodal metastases in every category analyzed. In

TABLE 3. *Lahey Clinic Foundation, Differentiated Thyroid Carcinoma, 1931–1970; Trends in Disease Presentation–Clinical and Pathologic*

	Surgical Evaluation						Pathologic Evaluation							
	Occult		Confined to Thyroid		Extra-thyroid		Multifocal Disease		Blood Vessel Invasion		Extent of Capsular Invasion			
											Minor		Major	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1931–1940	58	50	38	33	18	16	2	2	63	55	20	18	88	80
1941–1950	84	42	82	40	34	17	14	7	106	53	40	21	137	72
1951–1960	103	33	146	47	63	20	49	17	120	38	93	32	148	51
1961–1970	52	33	89	56	19	12	21	14	45	28	62	41	68	45

TABLE 4. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1931–1970; Trends in Clinical Disease and Treatment*

		Surgery for Primary Disease								Surgery for Nodal Metastases							
						Subtotal Thyroidectomy											
		Excision of Nodule		Lobectomy		For Disease		For Suppression		Node Dissection		Radical Neck		Modified Neck		Limited Dissection	
	No. of Cases	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1931–1940	114	38	36	2	2	43	41	23	22	24	21	9	38	3	13	12	50
1941–1950	201	33	18	7	4	87	47	60	32	65	32	57	88	3	6	5	8
1951–1960	316	20	7	52	17	126	41	107	35	148	47	136	92	3	2	9	6
1961–1970	161	3	2	23	15	36	23	93	60	61	38	26	43	10	16	25	41

the group with extraglandular disease and the highest potential mortality, the survival advantage of those with nodal metastases was significantly better statistically and generally improved as more nodes were involved. Most striking of all was that no patients with 10 or more nodes involved with metastases died.

Table 7 illustrates the determinate mortality and recurrence rates for all patients treated before 1961 with disease separated into follicular and papillary and mixed carcinomas. The general pattern of recurrence and mortality was essentially similar in the two groups. All recurrent disease documented in this study appeared by 25 years, but a few deaths occurred up to 30 years. One patient defined in this project as dead of disease is actually living with progressive advanced disease at 33 years and will undoubtedly die of disease shortly. The 30-year mortality and recurrence rates increase sharply over the 25-year figures despite the absence of more actual deaths accrued due to the decreasing size of the population at risk. Therefore, these final recurrences and mortality rates are not truly representative.

More important in understanding the course of the varieties of differentiated thyroid carcinomas is the rate at which recurrences and deaths occur as noted on the lines entitled "Per cents of eventual total recurrences (mortality)." These demonstrate the periods of highest risk and the pattern of recurrence and death.

We have not yet observed a death from thyroid carcinoma after 30 years, although exceptional cases may certainly occur as illustrated by the case cited. Since no first recurrence was noted after 25 years, it can be concluded that deaths after 30 years would be very uncommon.

A preponderance of early deaths occurred in the few patients (37 or 6% of the series) presenting initially with inoperable or metastatic disease. Seventeen of the 37 patients were initially considered to have incurable disease because of the presence of distant metastases, (12 were follicular carcinoma) and 11 patients had near total thyroidectomy for suppression in attempts to treat the distant metastases by radioactive iodine. Fifteen of these 17 patients were dead of disease within 5 years, but 2 patients were alive and free of apparent disease 15 and 19 years after treatment. Twenty of the 37 patients had incurable disease when initially seen because of advanced unresectable local extension of disease; biopsy only was undertaken for pathology confirmation (18 were papillary and mixed carcinomas). Eleven patients died of disease, 8 within 5 years, 10 within 10 years, and all 11 by 15 years after treatment. Eight patients were living free of apparent disease from 17 to 26 years. The fate of one of these 20 patients was indeterminate, as the patient died of other causes, free of gross disease, at 6 years without an autopsy. Of these 37 patients with incurable car-

TABLE 5. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1951–1960; Relation Between Age and Lymph Node Metastases*

			Age					
			< 40		41 to 50		> 51	
Sex	Status of Lymph nodes	Total No.	No.	%	No.	%	No.	%
Men	Negative nodes	46	11	24	12	26	23	50
	1–10 pos	27	17	63	7	26	3	11
	> 10 pos	7	6	86	1	14	0	0
Women	Negative nodes	161	69	43	35	22	57	35
	1–10 pos	66	45	69	8	12	13	20
	> 10 pos	9	7	78	2	22	0	0

TABLE 6. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1941–1960; Relation of Lymph Node Metastases to Survival*

	Negative Nodes			1–3 Positive Nodes			4–10 Positive Nodes			> 10 Positive Nodes		
		Dead of Disease			Dead of Disease			Dead of Disease			Dead of Disease	
Pathology	No.	No.	%	No.	No.	%	No.	No.	%	No.	No.	%
Papillary and mixed	213	23	11	71	7	10	54	6	11	18	0	0
Intrathyroid disease	84	4	5	48	2	4	32	4	13	9	0	0
Extrathyroid disease	31	13	42	20	6	30	15	2	13	8	0	0
Follicular	136	37	27	11	2	18	9	1	11	4	0	0
Intrathyroid disease	47	13	28	8	0	0	3	0	0	2	0	0
Extrathyroid disease	13	9	69	3	2	67	6	1	17	2	0	0

cinoma, 26 patients died of disease constituting 28% of the 94 total deaths at 20 years. The mean age of the 26 patients who died was 55 years, whereas the mean age of the 10 patients who were living free of disease was 35 years. Seven of 12 (58%) patients with originally unresectable and incurable disease who were less than 41 years of age survived, but only 3 of 24 such patients (13%) 49 years of age or older survived.

Mortality rates of the 94% of patients originally classified as operable and curable were obtained by subtracting the 37 patients and 26 deaths of the incurable group to produce the mortality rates shown in Table 8. Only 34% of eventual deaths have occurred in the first 5 years, 57% by 10 years, 77% by 15 years, 88% by 20 years, 98% by 25 years, and 100% by 30 years. The rate of recurrence in patients with curable disease was not altered. The 15-year mortality rates are the most representative of the total risk to patients if increased by 25%, that is, 10% for papillary and mixed carcinomas and 28% for follicular carcinoma.

The pattern of first recurrences or metastases for the 143 patients in the first three decades in whom recurrences developed is shown in Table 9. In papillary and mixed forms, 20% presented with local recurrences alone, 34% presented with nodal metastases, while 45% presented initially with distant metastases. In contrast, 75%

TABLE 7. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1931–1970; Mortality and Recurrence Rates, 1931–1960; Papillary and Mixed and Follicular*

	5 Yr	10 Yr	15 Yr	20 Yr	25 Yr	30 Yr
Papillary and Mixed						
Number at risk	423	399	361	254	139	96
Recurrence						
Per cent	11	18	23	33	38	55
Per cent of eventual total recurrence	55	83	97	98	100	100
Mortality						
Per cent	6	8	12	19	19	29
Per cent of eventual total mortality	48	62	83	90	96	100
Follicular						
Number at risk	178	165	152	117	68	52
Recurrence						
Per cent of eventual total recurrences	61	85	94	94	100	100
Mortality						
Per cent	14	22	28	39	46	60
Per cent of eventual total mortality	49	76	86	94	100	100

* 1931–1950 only.

TABLE 8. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1931–1970; Determinate Mortality Rates–All Curable Cases, 1931–1960*

	5 Yr	10 Yr	15 Yr	20 Yr	25 Yr
Papillary and mixed, %	3	5	8	14*	16*
Follicular, %	7	17	22	33†	39†

Calculated long-term mortality: * (0.25 × 8%) + 8% = 10%; † (0.25 × 22%) + 22% = 28%.

of follicular carcinomas first reappeared as metastatic disease, while only 12% had isolated nodal and 12% isolated local recurrences. The pattern of reappearance of disease is not related to the time of reappearance after primary therapy.

Of patients with recurrent papillary and mixed cancer, 39% are apparently cured after treatment but only 16% of patients with follicular carcinoma are eventually cured. Specifically, 42% of patients with local recurrences, 69% with nodal metastases, but only 15% with distant metastases from papillary and mixed carcinomas are cured. In patients with follicular carcinoma, the respective figures are 29%, 43%, and 9%. Thus, not only is the primary follicular carcinoma more lethal than papillary and mixed carcinoma, but the recurrences are also inherently more lethal. In patients with papillary and mixed carcinomas, 7 of 10 (70%) who had simultaneous develpoment of nodal metastasis and local recurrence survived, whereas only 8 of 19 (42%) with local recurrence alone survived. Although this difference is not at the level of statistical significance ($P < 0.20$) because of small numbers, the data are again suggestive of a protective effect from nodal metastasis, as previously noted with primary disease (Table 6).

The changing incidence of recurrence and mortality in time for papillary and mixed carcinoma and follicular carcinoma is displayed in Table 10. In this table only patients with initially curable disease are considered to make comparisons truly valid. The numbers and per cents of patients with initially incurable carcinoma by the succeeding decades beginning in 1931 were 8 of 114 (7%), 13 of 201 (7%), 16 of 316 (5%), and 2 of 161 (1.2%). Thus, currently, patients presenting with primary incurable disease are unusual. Because a large fraction of total mortality (28%) and especially early mortality (47% of 5-year deaths) was displayed by this small group of primary incurable cancers which are essentially no longer seen, a more realistic analysis of progress in treating the usual operable thyroid carcinoma is achieved by this restriction of analysis to initially curable patients. Because of essentially identical figures, the first two decades were combined and the contrasts are between three time periods—before 1951, 1951 to 1960, and 1961 to 1970. For the latter two periods, mortality and recurrence rates are only valid at 15 years and 10 years for one half of the cases.

Clear stepwise gains are noted in recurrence and mortality rates of follicular carcinoma consistent with the improving case material. In papillary carcinoma, however, remarkably little change is noted in either recurrence or mortality rates, and, in fact, slight, but not significant, worsening of the recurrence rates is noted in the 1960's.

The effects of age, sex, decade studied, and nodal metastases on mortality have been displayed, but there are other significant determinants of mortality. Blood vessel invasion has no implication in prognosis with papillary and mixed carcinomas, but its presence doubles the mortality of follicular carcinomas, 63% of which display this feature. Major capsular invasion connotes a somewhat worse prognosis than minor capsular invasion. Multifocal compared to unifocal carcinoma also produces a modest worsening in mortality in papillary and mixed forms (19% vs 9%) but not in follicular carcinoma (23% vs 23%).

Of note in the papillary and mixed carcinomas is a significant ($P < 0.001$) decrease in mortality in follicular predominant forms (2%) in contrast to the other three varieties combined (12%) or separately. Careful analysis of many factors of this follicular predominant type shows no differences from the remainder of the papillary and

TABLE 9. *Lahey Clinic Foundation; Differentiated Thyroid Carcinoma, 1931–1960; Patterns of First Recurrence and Metastasis*

	Cases		Local Recurrences		Nodal Metastasis		Distant Metastasis	
Pathology	No.	%	No.	%	No.	%	No.	%
Papillary and mixed								
Dead of disease	52	61	11	58	9	31	33	85
Free of disease	33	39	8	42	20	69	5	15
Total (incidence)	86		19	(20)	29	(34)	38	(45)
Follicular								
Dead of disease	48	84	5	71	4	51	39	91
Free of disease	9	16	2	29	3	43	4	9
Total (incidence)	57		7	(12)	7	(12)	43	(75)

TABLE 10. *Differentiated Thyroid Carcinoma, 1931–1970; Changing Recurrence and Mortality Rates; Curable Cases; Papillary and Mixed and Follicular*

	5 Yr			10 Yr			15 Yr		
	No. at Risk	No.	%	No. at Risk	No.	%	No. at Risk	No.	%
Papillary and Mixed									
Recurrence rates									
1931–1950	198	23	12	186	37	20	168	44	26
1951–1960	202	10	5	190	20	11	180	25	14
1961–1970	113	8	7	55	8	15			
Mortality rates									
1931–1950	198	6	3	186	9	5	168	14	8
1951–1960	202	5	3	190	9	5	180	15	8
1961–1970	113	1	0.8	55	2	4			
Follicular									
Recurrence rates									
1931–1950	79	16	20	71	21	30	68	25	37
1951–1960	85	8	9	80	17	21	70	18	26
1961–1970	39	3	8	23	4	17			
Mortality rates									
1931–1950	79	10	13	71	16	23	68	18	27
1951–1960	85	2	2	80	9	11	70	12	17
1961–1970	39	0	0	23	2	9			

mixed forms except the incidence of lymph node metastases. Twenty of 43 (47%) patients with follicular predominant carcinoma and 136 of 398 (34%) with other papillary and mixed forms display pathologically proved lymph node metastases. Statistical analysis shows this difference not at the level of significance ($P > 0.10$) but the data are consistent and suggestive of a protective effect of nodal metastases.

Surgical estimation that a thyroid carcinoma is extraglandular and invading local soft tissue or visceral structures implies a serious prognosis in both papillary (35% mortality) and follicular (54% mortality) carcinoma. When carcinoma is surgically occult, the prognosis is best (3% mortality, papillary and mixed; 17% mortality, follicular).

The maximal diameter of the primary carcinoma when measured and unifocal in origin is directly related to mortality in follicular carcinoma where the ratio of mortality rates from smallest to largest carcinoma is 1 to 6. In papillary and mixed carcinoma, this ratio is only slightly more than 1 to 2 and shows no statistical significance.

A comparison between nodule excision and lobectomy versus thyroidectomy for suppression was designed to help answer the question of whether excision of the uninvolved contralateral thyroid lobe protects the patient in any way against recurrences when carcinomas are limited to one lobe. Although there are numerous biases in presenting and analyzing such data, there was no apparent impairment or statistically significant difference in survival resulting from the more limited surgery, considering comparable sizes for either pathologic variety.

There was no statistically significant difference in survival in either pathologic type between those receiving and those not receiving therapeutic radiotherapy or prophylactic radiotherapy. There was no difference in the time of appearance of recurrent disease or death between those receiving and those not receiving prophylactic radiation therapy. No evidence of a statistically significant difference in survival was demonstrable in patients receiving supravoltage contrasted to patients receiving orthovoltage radiotherapy.

Results comparing patients who actually took thyroid hormone regularly postoperatively and those who did not was determined. With papillary and mixed carcinomas, there was a distinct and statistically significant ($P < 0.01$) decrease in mortality among those taking thyroid hormone for suppression both overall and in all the subgroups studied. For instance, in patients below the age of 50, 2 of 121 patients (2%) died who had thyroid suppression, while 13 of 196 patients (7%) without thyroid feeding died ($P < 0.001$). Among follicular carcinomas, however, no detectable differences in survival were noted. Thus, in low-risk patients less than 40 years of age, 2 of 25 patients (8%) died who took thyroid, while 4 of 50 patients (8%) died who did not take thyroid hormone. In high-risk patients over the age of 40, 11 of 26 patients (42%) with thyroid feeding died of disease, while 31 of 80 patients (35%) without thyroid feeding died.

Comment

The decreasing incidence of undifferentiated forms of thyroid carcinoma over the four decades studied undoubtedly reflects a variety of influences, one of which

may be the more frequent surgical excision of thyroid nodules, since some reports suggest that indolent papillary and mixed carcinomas, if left untreated, may convert to aggressive undifferentiated forms.[15] The fact that 78% of undifferentiated carcinomas in our series were in patients more than 50 years of age but only 42% of follicular and 29% of papillary and mixed forms were in patients more than 50 years of age may be consistent with this assumption. Although some treated differentiated thyroid carcinomas may convert to undifferentiated forms as the disease recurs,[14] perhaps as a differential regrowth of areas of metaplasia originally noted in differentiated carcinoma, in our experience this happens rarely.

It might be expected that, if conversions to more aggressive forms of undifferentiated carcinoma in longstanding papillary and mixed thyroid carcinomas were common, the incidence of late deaths from thyroid cancer would continue at a steady rate as long as patients were followed. In fact, this did not occur, the most remote first recurrence appearing before 25 years after operation, and the most delayed death occurring before 30 years.

The subtle shift in succeeding decades within the papillary and mixed thyroid carcinomas toward those with more follicular elements has not been commented on in the literature and represents the influence of several factors, one of which certainly is the cessation of childhood radiation. Papillary and mixed carcinoma subgroups have no discernible distinguishing features among them except two: the uniquely favorable prognosis and the greater incidence of lymph node metastases encountered among the cases categorized as follicular predominant. However, several features clearly contrast the entire group of papillary and mixed carcinomas to follicular carcinoma. Sex, age, size, various pathologic features, incidence of lymph node metastases, surgical evaluation, recurrence and mortality rates and patterns, sensitivity to thyroid feeding, and lethality of recurrences all show differences between these two pathologic types. The aspects of these features that occur in follicular carcinoma generally imply a worse prognosis, that is, more men, older age, larger size, and fewer lymph node metastases. No adequate explanation exists for the shift in age during the past decade to a younger range that is similar to that of patients with papillary carcinoma. Since age bears such a key role in prognosis, a decrease in future mortality figures may result in patients with follicular carcinoma.

Although many human cancers have a worse prognosis in older age groups, none shows such a striking increase in age-related recurrence and mortality figures or such a sharply defined age separation between high and low mortality groups. Speculation as to the nature of a survival impairment beginning at age 50 in a disease that largely affects women must center about the role of sex hormone changes that occur at menopause.[22] The relationship between age and mortality in men is more linear and without such a sharp age-related break in the death rate. If endogenous estrogen production ameliorates the effects of the disease, there must be other reasons why men less than the age of 40 have a prognosis comparable to that of women of the same age. Certainly a major clue in understanding the biology of thyroid carcinoma would derive from knowledge of the relationships of age, sex, and risk of death. Pincus et al.[21] demonstrated urinary steroid changes that would provide a basis for these relationships. Only one brief experimental trial of estrogen administration in recurrent and metastatic thyroid carcinoma was reported by Rawson and Leeper,[22] although some animal studies have been conducted.[22]

The significantly increasing incidence of male patients with differentiated thyroid carcinoma is of unknown etiology and may create a worsening of overall prognosis in the disease in the future. This trend seems to be accelerating, and in four decades the male to female ratio has changed from 1:4 to 1:2.

One clear factor in the cause of differentiated thyroid carcinoma is the history of prior radiation therapy, generally in low doses, for benign conditions in the head and neck area in children.[10] Forty-six patients (6%) with such a history were found in this study, but this is a minimum figure as histories of such exposure were not sought for or recorded in early years. The usual latent period after such radiation to the induction or discovery of thyroid carcinoma is 10 to 20 years,[9,28] and the patients tend to be young, female, and have papillary carcinoma.[28] Some of the trends noted in this series may reflect the decreased use of childhood radiation therapy beginning in the 1940's; as the age of patients with papillary and mixed forms of disease seems to have increased in the last decade, there was a shift toward the pathologic variants with more follicular elements, and the ratio of men and women increased.

Other trends in disease presentation noted in this series clearly indicate earlier disease in the later decades. Thus, smaller nodules were excised, and fewer patients had extraglandular extension, blood vessel invasion, and major capsular involvement in each succeeding decade. These trends may relate to a greater acceptance of surgery of the thyroid gland and a generally more sophisticated view regarding thyroid masses. This can be implied also by the virtual disappearance of patients initially presenting with locally inoperable or metastatic disease. The surgery performed on differentiated thyroid carcinomas has changed also but not always in the direction one might expect from the increasing appearance of earlier disease. Thus, the shift toward more radical excision in the 1940's and 1950's reflected the zenith of radical surgical attitudes toward carcinoma generally.

Despite this more radical surgical attack on the primary

cancer site, clear-cut evidence of a favorable effect on prognosis was not obtained. When prognostic features are matched and local excision plus lobectomy compared to thyroidectomy for suppression, no advantage to the more extensive thyroid tissue removal was noted. This does not imply that standard surgical precepts should be abandoned but only that many of the arguments put forward for the use of total thyroidectomy as standard treatment[2,6] need to be viewed with caution.

The implied benefits of excision of uninvolved thyroid gland do not make sense anatomically as can be noted by inspection of anatomic cross-sectional views of the neck, but are rational for only two reasons: to remove multifocal disease that may occur in the nonpresenting thyroid lobe and for aid in thyroid ablation to simplify management at a later stage with radioactive iodine. The presumed lethality of the micrometastases or microscopic areas of multifocal disease is by no means certain, for studies show that despite the high incidence of such findings on serial sectioning of thyroid glands,[6] the defined recurrence rate of unresected thyroid lobes remains very low.[26] Certainly if there is reasonable risk of future recurrent or metastatic disease as judged by age, sex, and extraglandular extension of the primary cancer, even in lesions which are primarily papillary, surgical thyroid ablation should be undertaken, as frequently radioactive iodine uptake can be induced and its use is immeasurably simplified by surgical thyroid removal.

Surgery of the nodal catchment areas surrounding the thyroid gland has varied through the years also, again less as a response to disease as it presented than as a result of a changing philosophy of cancer surgery. Thus, the incidence of primary nodal resections increased greatly from the 1940's (32%) to the 1950's (47%) despite the decreasing incidence of grossly palpable lymph nodes on preoperative physical examination from 24% to 20%. This trend was accentuated by the increased use of standard radical neck dissection during the 1950's so that more than 90% of nodal dissections performed were of this type. In the 1960's, a sharp decrease in the incidence (from 47% to 38%) and radicalness of nodal resections as part of the primary surgical attack occurred with increasing use of modified or limited nodal resections. The incidence of patients presenting with palpable nodal enlargement preoperatively fell still further to 14%, and the incidence of patients who had nodes detected pathologically decreased from 35% to 27% in the 1960's. This decreased incidence of nodal metastases was largely the result of more favorable disease presentations but may also have resulted from performing fewer nodal resections of a more limited type with resultant fewer opportunities for the pathologist to discover occult lymph node metastases. Another facet of lymph node metastases in thyroid carcinoma illustrates the difficulty in analyzing the role of lymphatic metastases and lymph node resections. Mediastinal lymph nodes are one of the principal drainage routes of the thyroid gland,[23] and undoubtedly harbor many occult lymph node metastases,[20] yet they are seldom resected[20] despite the zeal to remove the upper jugular chain of lymph nodes which lie considerably farther from the thyroid gland.

The most interesting relationship detected during the present study concerned the presence of lymph node metastases and mortality. Follicular carcinoma generally has fewer lymph node metastases and a higher overall mortality. The small subgroup of follicular predominant papillary and mixed carcinoma displayed the opposite features—a higher incidence of nodal metastases and a favorable prognosis. In the sub-categories of both primary intraglandular carcinoma with a good overall prognosis and primary extraglandular carcinoma with a much worse prognosis (45 of 115 patients died; 45 patients of the 94 total deaths had extraglandular disease), the presence of pathologically defined lymph nodes ameliorated the prognosis. Furthermore, the greater the number of lymph nodes metastases, the lesser the mortality. In fact, of the 22 patients in this entire series who displayed more than 10 node metastases, not one patient died of the disease. Patients with papillary and mixed carcinomas that recurred locally had a better prognosis if nodal metastases were also present at the time of first recurrence. When age, sex, and lymph node metastases were analyzed, patients of older ages in both sexes had fewer nodal metastases and a markedly worse prognosis, while patients of younger ages had more nodal metastases and a far better prognosis. Thus, 127 of 161 patients (79%) more than 40 years of age did not have lymph node metastases while 75 of 155 (48%) less than 40 did have node metastases.

Such a favorable relationship between lymph node metastases and mortality or risk groups has been reported previously but twice in thyroid (or any other human) cancers.[4,12] The history of thyroid cancer is replete with confusion about the role of nodal metastases, however. The concept of lateral aberrant thyroid[5] in lymph nodes was merely one manifestation of this confusion.

Totally new concepts are implied if the data noted here relating lymph node metastases to a more favorable prognosis are confirmed in other studies. Clark et al.[4] and Hirabayashi and Lindsay[12] indicated in tables displaying their data that patients with lymph node metastases in differentiated thyroid cancer had a statistically significant improved survival whether carcinoma was primary or recurrent but failed to comment on this unusual finding or speculate as to the cause.

Because of the extremely high incidence of lymph node metastases seen in many patients with papillary carcinoma, it is entirely possible that even radical neck dissections fail to excise all nodal metastases, especially

considering the largely untouched substernal and upper mediastinal routes. Speculation about the role of lymphatic resections in thyroid carcinoma is implied by the figures presented. It is difficult to formulate a concise surgical protocol, but it is reasonable to resect lymph nodes that are grossly palpable either preoperatively or when discovered at operation, by means of the least destructive surgical approach feasible—limited nodal resection through the thyroid collar incision or by means of a modified neck dissection[16] preserving spinal accessory nerve, jugular vein, and sternocleidomastoid muscle. Certainly, there is no evidence that prophylactic nodal resections in the absence of gross nodal enlargement play any role whatsoever in management despite the high incidence of occult nodal metastases. Such an approach was implied by Woolner et al.[29] who pointed out that not a single patient with occult papillary carcinoma died whether initial or subsequent lymph node metastases appeared or not.

The immunology of thyroid cancer has been addressed by only a few workers.[1,11,22] Implications of better prognosis in thyroid carcinoma with lymphoid infiltrate have been reported clinically in the past.[13,18] Amino et al.[1] noted increased levels of IgG and serum complement but did not detect cell-mediated immunity frequently. However, they were able to produce a short, partial, clinical remission in one thyroid cancer by immunization with tumor homogenate. Perhaps the explanation of improved survival with lymph node metastases lies in the area of lymph node function and immunology.

Recurrence and mortality rates recorded here indicate the pattern of slowly progressive disease and prolonged expression of mortality that has come to be recognized as characteristic of differentiated thyroid carcinoma. The pattern of recurrent or metastatic disease is clearly different in papillary and mixed forms in contrast to follicular carcinoma, however. Papillary and mixed cancers manifest distant metastases in 45% of instances in contrast to the follicular type with a 75% incidence. Nodal metastases constitute one-third of recurrent disease in papillary carcinoma and are highly curable (69%). Nodal metastases are much less common in follicular carcinoma (12%), but such patients are curable in a significant proportion of cases (43%). Local recurrences are least common in both groups but can be cured by further treatment in nearly 40% of cases. This pattern and curability of first recrudescence is not altered by the time of appearance of the recurrence or metastasis.

Analysis of the recurrence and mortality rates by time, as seen in Table 10, is of interest. The 1950's were characterized by a more radical surgical approach regarding both local thyroid resection and lymph node resection compared to the 1930's and 1940's, but this enthusiasm for radical surgery abated somewhat in the 1960's. Thus it is seen that recurrence rates decreased for both follicular and papillary and mixed carcinomas in the 1950's, but there was no appreciable change thereafter in follicular carcinoma. There is the suggestion of increasing recurrence rates in papillary and mixed carcinomas in the 1960's, which reflects largely nodal metastases (5 of 8 recurrences or 63% in contrast to a 34% nodal recurrence rate in previous decades). The less aggressive approach to regional nodal tissue may have precipitated a higher nodal relapse rate. However, it was demonstrated that nodal recurrences and primary nodal metastases do not lessen the curability in any stage of disease. Therefore, this modification of the primary surgical attack on thyroid carcinoma seems a reasonable compromise considering the better cosmetic and functional results from the more limited nodal surgery,[22] particularly with preservation of the spinal accessory nerve.

Mortality rates, as distinguished from recurrence rates, display interesting features. Follicular carcinoma has demonstrated a progressive reduction in mortality commensurate with the degree of improvement in recurrence rates. However, papillary and mixed carcinomas have demonstrated no alteration in mortality rates of consequence despite the earlier disease encountered clinically, the decade of more aggressive surgical treatment and the more recent increase in recurrence rates. Perhaps the combined effects of increasing age and increasing incidence in men and the decreasing proportion of highly curable radiation-induced carcinomas counterbalance the earlier clinical presentation of disease.

External beam radiotherapy was used extensively in thyroid carcinoma in both prophylactic and therapeutic fashion.[25] Analysis of data relating to the effect on mortality of radiation therapy demonstrates no significant reduction. This fact has to be tempered with the realization that, generally, patients believed to have more advanced disease by the operating surgeon were more likely to be referred for radiotherapy. Yet, no difference in survival was noted within any of the many subcategories analyzed. Thus, there is no demonstrable role for the use of prophylactic radiotherapy, particularly in those patients with lymph node metastases as a criteria for treatment, a not uncommon reason for recommending adjunctive radiotherapy.

Thyroid feeding postoperatively to block TSH production was maintained by less than one half of the patients contacted in followup study. The ability of a patient to avoid taking thyroid hormone is clearly related to how much residual thyroid gland was left at the conclusion of surgery; the results reported conceivably could be biased by the fact that patients subjected to subtotal thyroidectomy might be forced to maintain thyroid feeding to avoid myxedema, while those patients with sub-

stantial residual thyroid gland have more of an option as myxedema might not develop despite cessation of hormone ingestion. However, it has been pointed out that the extent of surgery for similar stages of disease seems not to be a major determinant of survival.

With the recognition of this possible bias, it was demonstrated that in papillary and mixed carcinomas, a statistically significant reduction in mortality was achieved by thyroid suppression in each of the categories analyzed and at all ages. This protective effect was not achieved in follicular carcinoma, however, again highlighting the substantial differences between papillary and mixed carcinomas and follicular carcinoma. Crile[8] has described this differential response to thyroid feeding. Thus, permanent thyroid feeding should be a standard part of the management of patients with papillary and mixed differentiated thyroid carcinomas.

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Discussion

Dr. Elliott Strong (New York, New York): Dr. Cady has emphasized in this study the experience of our own group, as well as the experience of others; that is, the deleterious effects on prognosis of well-differentiated thyroid cancer of advancing age, size of the primary tumor, and extension beyond the thyroid capsule, and also the relative benignity of certain aspects of this disease. I recently saw a patient who had originally been examined by Dr. Frazell 18 years ago. At that time her clinical presentation was identical to what you see today. (Slide): a stony-hard mass occupied the right lobe of her thyroid gland, with bilateral cervical lymphnode metastases, proven by biopsy, X-rays (slide) demonstrating bilateral pulmonary nodular metastases, and when I saw her, significant compression of the trachea due to the disease at the primary site. For various reasons, this patient had been followed for 18 years, having had absolutely no treatment whatsoever. We must remember such patients when we consider the treatment of well-differentiated thyroid cancer and postulate the long survival after such treatment to be the result of the treatment.