World J. Surg. 10, 612–622, 1986

World Journal of Surgery

Current Results of Conservative Surgery for Differentiated Thyroid Carcinoma

Ricardo L. Rossi, M.D., Blake Cady, M.D., Mark L. Silverman, M.D., Marvin S. Wool, M.P.H., M.D., and Tia A. Horner

Departments of Surgery and Pathology and the Section of Endocrinology, Lahey Clinic Medical Center, Burlington, Massachusetts, Department of Surgery, New England Deaconess Hospital, Boston, Massachusetts, and Department of Surgery, Harvard Medical School, Boston, Massachusetts, U.S.A.

From 1961 to 1980 at the Lahey Clinic, 309 patients had initial surgical therapy for differentiated thyroid carcinoma. Review of this experience in comparison with previous decades revealed a progressive increase in the incidence of the disease in men, an increase in less extensive forms of the disease, an increase in use of bilateral subtotal thyroidectomy (77% of patients), the discontinuation of use of prophylactic nodal dissection, and the progressive replacement of radical neck dissections by modified and limited neck dissections. In this series, with a median follow-up period of 13 years, 11% of patients had recurrence, and 7% died of disease. Determinants of outcome were shown to be risk groups as defined by age and sex, extent of disease (size of tumor and extent of extraglandular involvement), capsular invasion, blood vessel invasion, ability to remove all tumor at operation, and, to a lesser extent, pathologic type. Presence of nodes affected recurrence rate but did not have any deleterious effects on survival. Multifocal involvement did not appear to be an adverse prognostic factor. Treatment was successful in 73% of patients with nodal recurrences, in 53% with local recurrences, and in 27% with distant recurrences. Recurrences more often were treated successfully in low-risk patients than in high-risk patients. None of the deaths from local recurrence could have been prevented by initial total thyroidectomy. Recurrent nerve paralysis and hypoparathyroidism each occurred in only 1 patient (0.4%) who underwent bilateral subtotal or near-total thyroidectomy. We conclude that a selective approach using lesser operations than total thyroidectomy is sufficient for management of patients with well-differentiated thyroid carcinoma and that total thyroidectomy is not required.

The extent of thyroid surgery for differentiated thyroid carcinoma remains controversial. The relative infrequency and chronic course of these malignancies make it unlikely that the disagreements will be resolved other than by a long-term prospective randomized multicenter trial. While some groups [1–3] have advocated total thyroidectomy for most patients with differentiated thyroid carcinoma, we have continued to use a selective and conservative surgical approach in the belief that the routine use of total thyroidectomy will increase operative morbidity but not necessarily improve outcome. The earlier Lahey Clinic experience with 792 cases of differentiated thyroid carcinoma has been reported [4, 5]. We review here our results with conservative thyroid surgery in patients who underwent operation for differentiated thyroid carcinoma at Lahey Clinic from 1961 to 1980.

Materials and Methods

We reviewed patients with differentiated thyroid carcinoma who had their initial operation at the Lahey Clinic from 1961 to 1980. Complete follow-up data were obtained by contact with patients, referring physicians, family members, and hospitals and from autopsy reports and municipal and state records. Determinant survival rates were calculated. No actuarial calculations or projected survival estimations were made. A patient who died with disease or was last seen with active disease was considered dead of disease. A death was de-

Presented at the International Association of Endocrine Surgeons in Paris, September 1985.

Reprint requests: Ricardo L. Rossi, M.D., Department of Surgery, Lahey Clinic Medical Center, 41 Mall Road, Burlington, Massachusetts 01805, U.S.A.

fined as operative if it occurred within 1 month after surgery. All other patients were categorized as dead of other causes or free of disease for at least 5 years after therapy.

Follicular carcinoma was the category used to describe pure follicular cancer without any papillary element. It included Hürthle cell carcinomas. If a tumor had any papillary element, it was defined as papillary carcinoma. Minor capsular invasion, i.e., minimal breaching of the capsule by tumor without appreciable pathologic evidence of disease outside the thyroid gland, was differentiated from major capsular invasion, i.e., widespread breaching of the tumor capsule or direct involvement of soft tissue outside the thyroid gland. In our analysis the size of the primary thyroid tumor was the largest diameter reported by the pathologist. Extraglandular invasion was considered to be present if either surgical or pathological findings showed perithyroidal involvement of trachea, muscle, recurrent nerves, or soft tissue.

A carcinoma was defined as clinically occult if it was not suspected before the operation; these tumors were usually found in patients who did not have a thyroid nodule and were operated on for a benign thyroid condition, such as hyperthyroidism or diffuse goiter. Surgically occult carcinomas were those not suspected by the surgeon. The category included microscopic, macroscopic, and small malignancies. In these patients, glands were excised for one or both of the following: benign conditions and solitary nodules in which carcinoma was not discovered either because frozen section was not performed or because sampling limitations prevented confirmation of minimal capsular invasion.

Surgical therapies in the series consisted of biopsy only (in patients with locally unresectable thyroid carcinoma), excision of nodule (prominent nodule only), unilateral thyroidectomy (subtotal, near-total, or total thyroid lobectomy), bilateral thyroidectomy (subtotal or total thyroid lobectomy with contralateral subtotal lobectomy as no patients in our series had a true extracapsular total thyroidectomy), radical neck dissection (removal of the sternocleidomastoid muscle, jugular vein, and 11th cranial nerve), modified neck dissection (preservation of the 11th cranial nerve with or without preservation of the sternocleidomastoid muscle and the jugular vein), and limited nodal dissection (excision of isolated groups of enlarged nodes). Men up to 40 years of age and women 50 years of age and younger were considered to be in a low-risk group, and those over these ages were defined as high-risk patients based on the analysis presented in one of our previous reports [6].

Recurrences after initial therapy were defined as local if they occurred within the thyroid bed or soft tissues of the neck, nodal if they occurred in lymph nodes of the neck or mediastinum, and distant if they occurred in sites away from the neck. The significance of differences in recurrence and death rates was determined by Miettinen's modification of the Fisher exact test [7]. Tests involving $> 2 \times 2$ contingency tables were analyzed by chi-squared test with Yates correction. Linear trend analysis was carried out by the method of Rothman and Boice [7]. Correlation of recurrence and death rates with tumor size was analyzed by one-way analysis of variance. All p values are two-tailed. Significance was accepted for p values less than 0.05 with calculation of exact values to indicate possible approach to near significance.

Results

All 309 consecutive patients with differentiated thyroid carcinoma who had their initial thyroid operation at Lahey Clinic from 1961 to 1980 inclusively were followed up until death or for a minimum of 5 years. The median follow-up time was 13 years (range 5–24 years), and 65% of patients had follow-up for 10 years or more. Of the 309 patients, 211 (68%) were women, and 98 (32%) were men. Pure follicular tumors were present in 21% of patients, and 79% of subjects had papillary forms.

Initial clinical presentations in relation to patient outcome are shown in Table 1. Twenty patients had a clinically occult carcinoma, and the indication for operation was a diffuse thyroid condition, such as hyperthyroidism or diffuse goiter. In 16 of these 20 patients, the size of the tumor was recorded by the pathologist. In 11 (69%) of the 16 patients it measured less than 1 cm in diameter, in 3 (19%) it was between 1 cm and 1.9 cm, and in 2 (13%) it was between 2 cm and 2.9 cm. No patient had a larger tumor. None of the 20 patients had a recurrence or died of disease. One patient died of a cardiovascular cause 1 week after operation.

Of the remaining 289 patients who had clinically apparent disease, 33 (11%) had recurrence, and 20 (7%) died of disease. For the 309 patients in the series the overall recurrence rate was 11%, and the mortality rate was 7% including the operative death.

Two patients presented with distant metastatic disease to the lung and no palpable thyroid mass. They are alive with no evidence of disease at 20 years and 12 years, respectively, after treatment with bilateral subtotal thyroidectomy, radioactive iodine, and thyroid hormone therapy. Both patients had papillary carcinoma; 1 patient was 36 years of age, and the other patient was 53 years old at the time of presentation of the cancer.

Operative procedures performed in the series and the outcomes are shown in Table 2. Biopsy only

Table 1. Initial clinical presentation and outcome, 1961–1980.

			Outcome			
			Recurred		Patient died of disease	
Presentation	No.	%	No.	%	No.	%
Clinically occult	20	6	0	0	0[a]	0
Palpable nodes	24	8	7	29	1	4
Thyroid mass and palpable nodes	22	7	8	36	5	23
Thyroid mass only	241	78	16	7	14	6
Distant metastasis	2	0.6	2	100	0	0
Total	309		33	11	20	6

[a]Excluding 1 patient who died of cardiovascular cause 1 week after operation, which was the only operative death in the series.

was performed in 2 patients with extensive unresectable disease; both patients died of disease. None of the 57 patients who underwent unilateral thyroidectomy had a recurrence or died of disease. Of the 239 patients who had bilateral subtotal thyroidectomy, 12% had recurrence, and 8% died of disease. These differences were statistically significant ($p = 0.001$ and $p = 0.02$, respectively). The patients in the group treated with unilateral thyroidectomy were compared with those treated with bilateral subtotal thyroidectomy in terms of extent of disease. Tumors less than 3 cm in diameter were found more often in patients treated with unilateral thyroidectomy than in those treated with bilateral subtotal thyroidectomy ($p = 0.02$). Two percent of patients who underwent a unilateral thyroidectomy had tumors larger than 4 cm whereas 11% of patients who underwent a bilateral subtotal thyroidectomy had tumors of that size ($p = 0.05$). Major capsular invasion was present in 18% of patients who underwent unilateral thyroidectomy as compared with 25% of patients who had bilateral subtotal thyroidectomy; extraglandular involvement was observed in 5% and 11% of each group, respectively. Surgically occult tumors were present in 28% of patients who had unilateral thyroidectomy and in 21% of patients who had bilateral subtotal thyroidectomy. These differences for major capsular invasion, extraglandular extension, and incidence of occult tumors did not reach statistical significance.

Ninety-five patients had removal of lymph nodes by a formal neck dissection. In 34 patients (11% of series) a radical neck dissection was performed, in 19 patients (6% of series) a modified neck dissection was undertaken, and 42 patients (15% of series) had limited neck dissection. Except in 5 patients, all radical neck dissections were performed before 1970. Since then, modified or limited nodal dissections have been used preferentially. For these 95 patients who had a nodal operation, the recurrence rate was 11% with 5 patients (5%) dying of disease. This recurrence rate is identical to that of the 214 patients who had thyroid operation only without nodal dissection. In the latter group 16 patients (7%) died of disease, a difference that was not significant ($p = 0.5$).

Of 269 patients with all macroscopic tumor removed at operation, 19 patients (7%) had recurrence, and of the 40 patients with macroscopic residual cancer, 14 patients (35%) had recurrence ($p = 0.0001$). Eleven (4%) of 269 patients with all macroscopic tumor removed at the time of initial operation died of disease whereas 10 (25%) of 40 patients with macroscopic residual cancer died of disease ($p < 0.0001$).

Some pathologic findings and patient outcomes are displayed in Table 3. Patients with major capsular invasion, larger tumors, and blood vessel invasion had higher recurrence and death rates with differences that were statistically significant. Incidences of recurrence and death correlated with tumor size exponentially ($p = 0.002$ and $p = 0.005$, respectively). The incidence of recurrence increased considerably in patients with tumors of 2 cm in diameter or larger. Blood vessel invasion affected the outcome in patients with papillary and with follicular tumors, but the effect was more severe in the latter group. Of the 18 patients with follicular carcinoma and blood vessel invasion, 8 (44%) had recurrence and 5 (28%) died of disease. Of 48 patients with follicular carcinoma with minor or no blood vessel invasion, only 1 patient (2%) had a recurrence ($p < 0.0001$) and died of disease ($p = 0.005$). Of the 57 patients with papillary carcinoma and blood vessel invasion, 10 patients (18%) had recurrence and 7 patients (12%) died of disease whereas for the 185 patients with papillary carcinoma and no blood vessel invasion, recurrence and death rates were 8% ($p = 0.04$) and 4% ($p = 0.03$), respectively. The course in patients with multifocality of tumor in the thyroid gland was similar to that in patients who had apparent unifocal disease. Patients with involved lymph nodes at pathologic examination of the original specimen had a higher recurrence rate ($p = 0.009$), but their survival was not affected by lymph node metastases.

Surgical findings as related to outcome are presented in Table 4. Surgically occult tumors were associated with recurrence and death in only 1% of cases. More than one-half of patients with extraglandular extension of tumor had recurrence ($p < 0.0001$), and about one-third died of disease ($p < 0.0001$).

Table 2. Surgical therapy and outcome, 1961–1980.

Surgical therapy	No.	%	Outcome: Recurred No.	Recurred %	Patient died of disease No.	Patient died of disease %
Biopsy only	2	0.6	2	100	2	100
Excision of thyroid nodule	11	3.6	2	18	1	9
Unilateral thyroidectomy	57	18	0	0	0[a]	0[b]
Bilateral subtotal thyroidectomy	239	77	29	12	18[a]	8[b]
Total	309		33	11	21	7
Without nodal dissection	214	69	23	11	16	7
With nodal dissection	95	31	10	11	5	5
				$p = 0.5$		
All macroscopic tumor removed	269	87	19	7	11	4
Residual disease	40	13	14	35	10	25
				$p < 0.0001$		$p < 0.0001$

[a]Difference in recurrence rate between patients treated with unilateral and bilateral thyroidectomy, $p = 0.001$.
[b]Difference in death rate between patients treated with unilateral and bilateral thyroidectomy, $p = 0.02$.

Table 3. Pathologic features and outcome, 1961–1980.

Pathologic finding	No.	Outcome: Recurred No.	Recurred %	Patient died of disease No.	Patient died of disease %
Follicular	66	9	14	7	11
Papillary	243	24	10	14	6
		$p = 0.39$		$p = 0.19$	
Blood vessel invasion	76	18	24	12	16
No blood vessel invasion	233	15	6	9	4
		$p = 0.0001$		$p = 0.001$	
Major capsular invasion	77	17	22	12	16
Minor or no capsular invasion	232	15	6	9	4
		$p = 0.0001$		$p = 0.001$	
Size (cm)[a]					
< 1	76	4	5	1	1
1–1.9	97	5	5	5	5
2–2.9	60	6	10	4	7
3–3.9	14	4	29	3	21
≧ 4	11	10	91	7	64
Unknown	51	4	8	1	2
Positive nodes	88	16	18	7	8
Negative nodes	221	17	8	14	6
		$p = 0.009$		$p = 0.85$	
Multifocal	33	5	15	2	6
Unifocal	276	28	10	19	7
		$p = 0.40$		$p = 0.92$	

[a]Incidences of recurrence and death correlated exponentially with tumor size to significance levels of $p = 0.002$ and $p = 0.005$, respectively.

Sex and age were major factors in determining patient outcome (Table 5), and the effects of these variables have been the subject of a separate report [7]. High-risk patients (men over 40 years of age and women over 50 years of age) had a worse prognosis than low-risk patients (men 40 years old or less and women of 50 years or less). Of 192 low-risk patients, only 2 (1%) died of disease whereas of 117 high-risk patients, 18 (15%) died of disease ($p < 0.0001$). Of 33 patients with recurrence, 2 of 10 (20%) in the low-risk group died of disease compared with 18 (78%) of 23 in the high-risk group. The effect of basic risk group on the biologic behavior of the tumor and patient outcome super-

Table 4. Extent of tumor at operation and outcome, 1961–1980.

		Outcome			
		Recurred		Patient died of disease	
Extent of tumor	No.	No.	%	No.	%
Occult	75	1	1	1	1
Apparent	234	32	14	20	9
		p = 0.0008		p = 0.02	
Intraglandular	276	16	6	8	3
Extraglandular	33	17	52	13	39
		$p < 0.0001$		$p < 0.0001$	

Table 5. Effect of risk group on outcome, 1961–1980.

		Outcome			
		Recurred		Patient died of disease	
Risk group	No.	No.	%	No.	%
Low-risk[a]	192	10	5	2	1
High-risk[b]	117	23	20	18	15
		p = 0.0001		$p < 0.0001$	

[a]Low-risk = men under age 40, and women under age 50.

[b]High-risk = men over age 40, and women over age 50.

seded the effect of pathologic type of tumor, extent of disease at presentation, and modalities of therapy used (Table 6).

Thirty-three patients (11%) presented with 1 or more recurrences in 1 or more sites (Table 7). Treatment was successful for nodal recurrence in 73% of patients, for local recurrence in 53% of patients, and for recurrence in distant sites in only 25% of patients. The difference in death rate between patients who had recurrence in nodes and those who had recurrence in distant sites was significant (p = 0.03). For patients who had recurrence, the result of therapy and the survival rate were better in the low-risk group than in the high-risk group (Table 8).

Recurrences were treated with surgery in 9 patients, external radiotherapy in 9 patients, radioactive iodine in 10 patients, and thyroid hormone in 31 patients. In 8 (47%) of 17 patients who had recurrence and pathologic nodal involvement at the time of original tumor presentation and operation, the site of recurrence was in nodes. Recurrences in 17 (84%) of 20 patients without original nodal involvement were in extranodal locations (thyroid bed, soft tissue, distant sites). Eight (9%) of 88 patients with originally positive pathologic nodes had recurrence in nodes whereas only 3 (1%) of 221 patients with negative nodes had such recurrence (p = 0.003).

The 16 patients (5%) who presented with a local recurrence were reviewed in detail to assess if a more extensive initial thyroid operation could have altered the outcome. Fifteen of these patients had undergone a bilateral subtotal thyroidectomy, and 1 patient had biopsy only. Two patients presented originally with lung metastases and thyroid mass; 9 patients originally had extensive invasion of soft tissue, trachea, or recurrent nerves. Eight patients had macroscopic residual tumor after their initial operation. In only 2 patients (0.6% of the series) could we postulate that perhaps a total thyroidectomy would have prevented local recurrence. Nevertheless, both of these patients are alive with no evidence of disease at 13 years and 20 years after management of their recurrence; one was treated with radioactive iodine and the other with surgery and external radiotherapy. The first patient was a 57-year-old man with a follicular carcinoma of less than 1 cm in diameter with nodal metastases, blood vessel invasion, and major capsular invasion. He presented with a local recurrence 15 months after the initial operation. The other patient, 34 years old, with papillary carcinoma of unknown size, major capsular invasion, and positive lymph nodes had local recurrence 2¼ years after initial treatment. None of the 8 deaths in these 16 patients with local recurrence could have been prevented by total thyroidectomy since all of them occurred in patients who presented originally with extensive local disease or in whom all tumor could not be removed or distant metastatic disease was present at the original operation. Local recurrences in these 16 patients were managed with thyroid hormone (14 patients), radioactive iodine (8 patients), external radiotherapy (8 patients), and operation (4 patients).

Of the 9 recurrences in patients with follicular carcinoma, only 1 (11%) was in nodes, 4 (44%) were local, and 4 (44%) were in distant sites. Of the 24 recurrences in patients with papillary carcinoma, 11 (46%) were in nodes, 12 (50%) were local, and only 6 (25%) were in distant sites. Death was caused by disease in 7 patients (78%) with recurrences of follicular carcinoma and in 14 patients (58%) with papillary recurrences.

External beam radiotherapy and radioactive iodine used therapeutically were associated with cure in 58% and 72% of patients, respectively. The recurrence rates in patients who received prophylactic therapy with radioactive iodine and those who did not receive radioactive iodine were 16% (14 of 90 patients) and 5% (10 of 182 patients), respectively (p = 0.007). The percentages of patients in these groups who died of disease were 8% and 2%,

Table 6. Extent of disease and outcome according to risk group, 1961–1980.

	Extraglandular					Major capsular invasion					Residual tumor				
		Recurred		Patient died of disease			Recurred		Patient died of disease			Recurred		Patient died of disease	
Risk group	No.	No.	%	No.	%	No.	No.	%	No.	%	No.	No.	%	No.	%
Low-risk[a]	17	4	24	1	6	49	7	14	2	4	23	5	22	2	9
High-risk[b]	24	12	50	12	50	30	11	37	10	33	17	9	53	8	47
		$p = 0.1$		$p = 0.03$			$p = 0.03$		$p = 0.0008$			$p = 0.05$		$p = 0.009$	

[a]Low-risk = men under age 40, and women under age 50.
[b]High-risk = men over age 40, and women over age 50.

Table 7. Site of recurrence and outcome in 33 patients with 40 recurrences, 1961–1980.

Site of recurrence	No.	%	Patient died of disease[a] No.	%
Nodal	11	4	3	27
Local	17	6	8	47
Distant	12	4	9	75

[a]Difference in mortality rate between nodal and local recurrence, $p = 0.33$; difference in mortality rate between nodal and distant recurrence, $p = 0.03$.

Table 8. Site of recurrence and outcome according to risk group, 1961–1980.

	Low-risk		High-risk	
Site of recurrence	No.	Patient died of disease	No.	Patient died of disease
Nodal	5	0	6	3
Local	5	1	12	7
Distant	3	1	8	8

respectively ($p = 0.04$) (Table 9). However, patients who did not receive radioactive iodine probably had less extensive disease since 36% had surgically occult lesions, only 8% had extraglandular involvement, and only 10% had major capsular invasion. Among patients who received anticipatory radioactive iodine therapy for prophylaxis, only 8% had occult lesions ($p < 0.0001$), 13% had extraglandular involvement ($p = 0.17$), and 27% had major capsular invasion ($p = 0.0006$).

Review of 251 patients who received thyroid hormone preparations and 58 patients who were not given this therapy demonstrated recurrence rates of 10% and 9% and disease-related mortality rates of 6% and 9%, respectively. These differences were not significant. Analysis of pathologic features, major capsular invasion, extraglandular extension, and type of surgical procedure showed similarities between the 2 groups. The only difference observed

Table 9. Radiation therapy and outcome, 1961–1980.

Therapy	No.	Patient died of disease No.	%
External therapeutic radiation	12	5	42
Radioactive iodine			
Therapeutic	26	7	27
Prophylactic	90	7	8
None	182	4	2

was a higher percentage of surgically occult lesions in patients who did not receive thyroid medications (47%) than in those who were given this treatment (19%) ($p = 0.005$). When only patients with major capsular invasion are compared between these 2 groups, the 66 patients who received thyroid hormone and the 11 patients who were not given the therapy had similar rates of recurrence (25% and 27%, respectively) whereas 9% in the first group and 18% in the latter group died of disease. However, the differences were not significant.

Complications of conservative surgical procedures occurred in 12 patients (Table 10). Permanent hypoparathyroidism occurred in only 1 patient (0.3%) corresponding to 0.4% of patients who underwent bilateral thyroidectomy, and permanent vocal cord paralysis developed in only 1 patient (0.3%).

Discussion

The median follow-up period in the present series is 13 years. This is a limited time for long-term assessment of patients with differentiated thyroid carcinoma but sufficient to identify the majority of recurrences. Analysis of the previous Lahey Clinic experience, in which the maximum follow-up time was 45 years [4, 8], shows that over 80% of the recurrences were within 10 years, more than 95% were within 15 years, and all occurred within 25 years. Of the eventual deaths, 80% occurred within 15 years,

Table 10. Complications of conservative therapy, 1961–1980.

Complication	No.	%
Bleeding	2	0.6
Unilateral vocal cord paralysis		
Permanent	1	0.3
Transient	1	0.3
Hypoparathyroidism		
Permanent	1	0.3
Transient	4	1.3
Thoracic duct fistula	1	0.3
Unilateral superior laryngeal nerve paralysis	1	0.3
Postoperative pancreatitis	1	0.3
Operative death[a]	1	0.3

[a]Death of cardiovascular cause occurred 1 week postoperatively.

and all occurred within 30 years after initial therapy. In the present series the median follow-up time of patients who had recurrence and lived exceeded the median survival time of patients who eventually died of disease in both low- and high-risk groups [8]. The purpose of this series was to analyze patterns of disease and trends in well-differentiated thyroid carcinoma, to determine prognostic clinical and pathologic factors, and to assess the early results of our conservative therapy.

Comparing this series with previous studies from our institution [4, 6], we identified several trends in disease presentation. The proportion of men increased from 19% between 1931 and 1950 to 24% between 1951 and 1960 to 32% between 1961 and 1980. These increases were in the high-risk group of patients in which there is now a male predominance; in the low-risk group the female predominance continues unchanged.

Disease is currently diagnosed at a more favorable stage. Major capsular invasion was present in 70% of patients treated from 1931 to 1950, in 51% of patients seen from 1951 to 1960, and in only 25% of patients treated from 1961 to 1980. Similarly, incidence of blood vessel invasion has gradually dropped from 54% to 38% and from 38% to 25% during the same time periods. Extraglandular invasion was present at operation in 20% of patients treated from 1951 to 1960 and in only 11% of patients treated from 1961 to 1980. The percentage of patients with intraglandular disease has progressively increased from 33% from 1931 to 1940 to 89% from 1961 to 1980. Currently, 67% of tumors are less than 2 cm and only 4% are more than 4 cm in diameter. The trend toward earlier discovery of thyroid tumors has probably been due in part to increased awareness by the public and health professionals of an association between these tumors and childhood exposure to radiation.

Changing trends in therapy are also apparent. Thyroid nodules were excised in one-third of our patients from 1931 to 1940 but in only 4% of patients from 1961 to 1980. Bilateral subtotal thyroidectomy was the procedure used in 77% of patients in the present series. Nodal dissection was performed in 47% of patients from 1951 to 1970 but in only 31% of patients from 1961 to 1980. In the earlier period, 92% of nodal dissections were radical, but these were progressively replaced by modified and limited neck dissections.

None of our 57 patients treated with unilateral thyroidectomy had recurrence or died of disease, and therefore more extensive surgery was clearly not indicated. Of patients treated with bilateral subtotal thyroidectomy, 12% had recurrence, and 8% died of disease. Comparison of these 2 groups showed a similar distribution of follicular and papillary tumors. The tumors in the group of patients who had unilateral thyroidectomy appear to have been found at a more favorable stage as suggested by a lower percentage of larger lesions and a higher percentage of smaller lesions with differences being statistically significant. A lower incidence of major capsular invasion and of extraglandular involvement and a higher percentage of patients with surgically occult lesions were also found in patients who had unilateral thyroidectomy, but differences were small and not statistically significant.

Patients with all macroscopic tumor removed had significantly better recurrence and death rates than those with residual disease. In the latter group one-third of patients had recurrence, and one-quarter of patients died of disease. Therefore, removal of all macroscopic tumor appears to be indicated when feasible. Recurrence and death rates were similar in patients who underwent nodal dissection and patients in whom nodal dissection was not performed.

According to our data, the best prognoses appear to be associated with occult tumors, small tumors, absence of blood vessel invasion (especially with follicular tumors), minimal or no capsular invasion, younger age of patients, and intraglandular disease. Risk groups according to age and sex at the time of original tumor presentation and initial treatment can closely predict the biologic behavior of these tumors and are better indicators than pathologic features, extent of disease, and modalities of therapy used [6, 8]. Low-risk patients died of disease less frequently than high-risk patients, and their recurrences were treated successfully more often. This relationship between age at initial presentation and outcome has been reported by others [9, 10].

Pathologically positive nodes did not appear to affect survival. Of patients with positive nodes, 8% died of disease as compared with 6% of patients with negative nodes. We did not demonstrate a

survival advantage in patients with positive nodes as we had reported previously [4], but neither was a deleterious effect noted. The lack of adverse effect of positive nodes on mortality rates has been observed by others [11, 12]. The 28% incidence of positive nodes found in this series probably is less than the actual incidence because lymph nodes were not sampled routinely. Noguchi et al. [13] have reported an 80% incidence of microscopic nodal metastases in specimens from prophylactic neck dissections in patients with papillary thyroid carcinoma. Therefore, patients presenting with papillary thyroid carcinoma will most often have nodal metastases [14]. Nevertheless, no evidence has yet shown that prophylactic neck dissection improves survival [14]. Thus, our practice continues to be to perform limited or modified nodal dissection in patients with clinically positive nodes but to defer nodal dissection in patients with negative nodes at the initial operation and to consider such dissection only when nodes become clinically apparent.

Multifocal disease was documented in only 11% of our patients. Since our study was retrospective, this figure may be biased, and the true incidence may be somewhat higher. Nonetheless, outcome in this group of patients was similar to that in the remainder of our series. Although multicentricity has been reported to be a common occurrence [15], its prognostic importance remains undetermined.

Thirty-three patients (11%) had recurrence. This group included patients with residual carcinoma at the time of their initial operation and 2 patients who originally presented with a thyroid mass and pulmonary metastasis. Recurrence rates were higher for patients who at the time of their original presentation and operation had tumors more than 3 cm in diameter (56% recurrence rate), extraglandular involvement (52%), macroscopic residual cancer (34%), blood vessel invasion (24%), major capsular invasion (22%), pathologically positive nodes (18%), and follicular carcinoma (14%).

The best survival among patients who had recurrence was found with papillary lesions, with recurrence in nodes, and in the low-risk group as defined by age and sex. Cures were achieved in 53% of patients with local recurrences and in 25% of patients with recurrent distant metastatic disease.

Patients with involved nodes at the initial operation had recurrence more often than did those with negative nodes. Nodal recurrences frequently were treated successfully, and they were anticipated in patients in whom both positive and negative nodes were found initially. Patients in low-risk groups presented with positive nodes more often than patients in high-risk groups (34% versus 19%).

Total thyroidectomy has been advocated [1–3] as the procedure of choice for differentiated thyroid carcinoma because of the multicentricity of the disease and the increased incidence of local recurrence after lesser operations. Although foci of carcinoma in the opposite lobe have been reported in as many as 30% of patients in whom the lobe was routinely evaluated and in 82% of those studied by subserial section [15], analysis of the 16 patients in our series who presented with a local recurrence failed to demonstrate that a more extensive procedure would have prevented such recurrences. In 15 of the 16 patients the initial treatment was bilateral near-total or subtotal thyroidectomy; in 1 patient, because the disease was inoperable, biopsy only was performed. Extraglandular extension to soft tissues of the neck at the time of initial operation was common in these patients. The 2 patients (0.6% of the series) in whom we believe more extensive resection perhaps could have prevented a local recurrence are alive with no evidence of disease after treatment of the recurrence. It appears unlikely that the ultimate survival of these 16 patients would have been different with a more extensive operation. In the 8 patients with local recurrence who died, extensive initial extraglandular disease and macroscopic residual tumor or distant metastatic disease were present at the time of initial treatment. Although studies [1–3] have shown that total thyroidectomy can be accomplished safely by experienced surgeons, a 21% incidence of hypoparathyroidism and a 3% incidence of recurrent nerve paralysis have also been reported [16] using this technique. In our series, hypoparathyroidism or recurrent nerve paralysis occurred in 0.3% of all patients corresponding with 0.4% of patients who underwent bilateral subtotal thyroidectomy. In performance of thyroid surgery, lesser operations than total thyroidectomy are much safer. The only potential role of total thyroidectomy is to facilitate radioactive iodine therapy in patients who have metastatic disease or in whom local recurrence of metastatic disease is likely to develop. We believe that bilateral subtotal thyroidectomy or ipsilateral total lobectomy with contralateral subtotal lobectomy accomplishes the same goal. Total thyroidectomy has no effect on rates of local recurrence and survival. It does not address the fact that most patients with differentiated thyroid carcinoma will have microscopic nodal metastasis at the time of initial operation despite clinically negative nodes. In other words, even if multifocal primary thyroid disease is removed by total thyroidectomy, microscopic disease will remain in nodes, thus defeating the rationale for the procedure.

External therapeutic radiation was associated with a 58% survival rate in our series. Therapy with radioactive iodine was associated with a survival rate of 73%. However, the value of anticipatory prophylactic use of radioactive iodine cannot be determined by our study. Patients who received

radioactive iodine for this purpose had a higher recurrence rate (16% versus 5%) and a higher death rate (8% versus 2%) than patients in whom this was not used. However, patients who received this therapy had more aggressive forms of this disease initially.

Comparison of patients who did and did not receive thyroid hormone suppression therapy revealed similar outcomes except that fewer patients with occult lesions received this therapy. The percentages of unilateral thyroidectomies performed in the 2 groups were comparable. In a previous retrospective report [17] we found no clear evidence favoring prophylactic use of thyroid hormone suppressive therapy. However, in addition to the retrospective nature of this study, it was not designed to identify a possible benefit. Regression of metastatic disease can be achieved with thyroid hormone suppression, and we continue to advocate this therapy sufficient to suppress serum levels of thyroid-stimulating hormone in all patients who have had hemilateral or bilateral subtotal thyroidectomy for thyroid cancer. Crile et al. [18] have reported recently on the benefits of bilateral subtotal thyroidectomy and thyroid-stimulating hormone suppression therapy for patients under 45 years of age who present with distant metastatic disease.

On the basis of the Lahey Clinic experience we conclude the following:

The incidence of well-differentiated thyroid carcinoma is increasing in men, and the extent of disease being seen and treated is progressively improving.

The factors that affect patient outcome are risk group as defined by age and sex of the patient; presence of extraglandular extension, major capsular invasion, and blood vessel invasion; the possibility of surgical removal of all tumor; and to a lesser extent the pathologic type of tumor.

The presence of nodal metastases does not appear to affect survival rate adversely.

Nodal recurrences can be cured in most patients and local recurrences can be treated successfully in about one-half of patients, but recurrent distant metastases are lethal in 75% of patients. Nevertheless, success of treatment and survival rate in patients with recurrent disease are greatly influenced by risk group.

Our analysis of the patients in the series who presented with a local recurrence indicates that total thyroidectomy would not have prevented recurrence or improved survival rate.

Therapy should be employed selectively based on analysis of risk group and prognostic clinical and pathologic factors. We believe that for small or occult intraglandular papillary carcinoma in low-risk patients, unilateral thyroidectomy is probably sufficient treatment. For patients with follicular tumors and larger papillary carcinomas, a bilateral subtotal thyroidectomy is advisable. In patients who are at high risk, who have larger tumors, in whom capsular invasion is found, who have distant metastatic disease, or in whom distant metastatic disease or local recurrence is likely to develop, total or near-total lobectomy on the side of the tumor and a subtotal lobectomy on the contralateral lobe are indicated, to be followed by anticipatory prophylactic radioactive iodine therapy for ablation of remaining thyroid tissue. We do not advocate prophylactic node dissection and would select modified or limited node dissection in patients with clinically positive nodes.

Résumé

De 1961 à 1980, 309 malades ont été opérés pour cancer différencié de la thyroïde à la Lahey Clinic. L'étude de cette expérience comparée à celle des précédentes décennies a démontré une augmentation progressive de la fréquence de la maladie chez l'homme, des formes moins étendues de la maladie et de la thyroïdectomie bilatérale subtotale (77% des malades); elle a démontré aussi l'abandon de la dissection ganglionnaire prophylactique et le remplacement de la dissection radicale du cou par une dissection cervicale modifiée et limitée. Dans cette série comportant en moyenne une évolution postopératoire de 13 ans, le taux des récidives a été de 11% et le taux de la mortalité a été de 7%. Les facteurs déterminants de l'évolution sont multiples. Ils concernent l'âge et le sexe, l'étendue du cancer (taille de la tumeur et étendue de l'atteinte ganglionnaire), l'invasion de la capsule, l'invasion vasculaire, la possibilité de pratiquer l'exérèse complète du processus tumoral et à un moindre degré le type anatomo-pathologique, ceci contrairement aux conceptions classiques. L'atteinte des ganglions va de pair avec le taux de la récidive mais n'affecte pas la survie. L'existence de foyers multiples ne paraît pas jouer un rôle pronostic défavorable. L'étendue multifocal ne paraît pas être un facteur pronostic adverse. Le traitement fut suivi de succès chez 73% des malades qui présentaient une récidive ganglionnaire, 53% de ceux qui étaient victimes d'une récidive locale et 27% de ceux qui accusaient des métastases. Les résultats furent meilleurs chez les patients à faible risque. Aucun des décès attribuables à la récidive locale n'aurait pu être évité par la thyroïdectomie totale. Un cas de paralysie du nerf récurrent et un cas d'hypoparathyroïdie furent constatés après thyroïdectomie bilatérale subtotale ou thyroïdectomie presque totale. On peut conclure de ces observations que des interventions moins importantes que la thyroïdectomie totale sont suffisantes pour traiter efficacement les malades qui présentent un cancer thyroïdien bien différencié.

Resumen

Trescientos nueve pacientes recibieron tratamiento quirúrgico inicial por carcinoma diferenciado de tiroides en la Clínica Lahey entre 1961 y 1980. La revisión de esta experiencia y su comparación con lo ocurrido en las décadas previas reveló un incremento progresivo en la incidencia de esta enfermedad en hombres, un incremento en las formas menos avanzadas de la enfermedad y un incremento en la utilización de la tiroidectomía bilateral subtotal (77% de los pacientes), la eliminación de la disección ganglionar profiláctica, y el reemplazo progresivo de la disección radical de cuello por disecciones ganglionares modificadas y limitadas. En esta serie, con un promedio de seguimiento de 13 años, 11% de los pacientes presentaron recurrencia y 7% murieron por la enfermedad. Se demostró que los factores determinantes del resultado final fueron los grupos de riesgo definidos según edad y sexo, extensión de la enfermedad (tamaño del tumor y extensión de la enfermedad extraglandular), invasión capsular, invasión de los vasos sanguíneos, posibilidad de resecar la totalidad del tumor durante la operación y, en un grado menor de lo que ha sido previamente informado, tipo histopatológico. La presencia de ganglios afectados tuvo influencia sobre la tasa de recurrencia pero no parece ser un factor adverso de pronóstico. El envolvimiento multifocal no se manifestó ser un factor pronóstico adverso. El tratamiento resultó exitoso en el 73% de los pacientes con recurrencias glandulares, en el 53% de los pacientes con recurrencias locales y en el 27% con recurrencias distantes. Las recurrencias fueron tratadas exitosamente con mayor frecuencia en los pacientes de bajo riesgo que en los de alto riesgo. Ninguna de las muertes por recurrencia local pudo ser prevenida mediante la tiroidectomía total inicial. La parálisis del nervio recurrente laríngeo y el hipoparatiroidismo se presentaron sólo en un paciente (0.4%) que fue sometido a tiroidectomía subtotal, o casi total, bilateral. Hemos llegado a la conclusión de que el aproche selectivo utilizando procedimientos quirúrgicos menos radicales que la tiroidectomía total es suficiente en el manejo de todos los pacientes con carcinoma tiroideo bien diferenciado y que no es necesario realizar tiroidectomía total.

Acknowledgment

The authors wish to acknowledge statistical analysis of the data by Elton Watkins, Jr., M.D., Sias Surgical Research Unit.

References

1. Clark, O.H.: Total thyroidectomy: The treatment of choice for patients with differentiated thyroid cancer. Ann. Surg. *196*:361, 1982
2. Katz, A.D., Bronson, D.: Total thyroidectomy: The indications and results of 630 cases. Am. J. Surg. *136*:450, 1978
3. Attie, J.N., Moskowitz, G.W., Margouleff, D., Levy, L.M.: Feasibility of total thyroidectomy in the treatment of thyroid carcinoma: Postoperative radioactive iodine evaluation of 140 cases. Am. J. Surg. *138*:555, 1979
4. Cady, B., Sedgwick, C.E., Meissner, W.A., Bookwalter, J.R., Romagosa, V., Werber, J.: Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann. Surg. *184*:541, 1976
5. Rossi, R.L., Nieroda, C., Cady, B., Wool, M.S.: Malignancies of the thyroid gland: The Lahey Clinic experience. Surg. Clin. North Am. *65*:211, 1985
6. Cady, B., Sedgwick, C.E., Meissner, W.A., Wool, M.S., Salzman, F.A., Werber, J.: Risk factor analysis in differentiated thyroid cancer. Cancer *43*:810, 1979
7. Rothman, K.J., Boice, J.D., Jr.: Epidemiologic Analysis with a Programmable Calculator, new edition. Boston, Epidemiology Resources, Inc., 1982
8. Cady, B., Rossi, R.L., Silverman, M., Wool, M.: Further evidence of the validity of risk group definition in differentiated thyroid carcinoma. Surgery *98*:1171, 1985
9. Halnan, K.E.: Influence of age and sex on incidence and prognosis of thyroid cancer: Three hundred forty-four cases followed for ten years. Cancer *19*:1534, 1966
10. Russell, M.A., Gilbert, E.F., Jaeschke, W.F.: Prognostic features of thyroid cancer: A long-term follow-up of 68 cases. Cancer *36*:553, 1975
11. Clark, R.L., Cole, V.W., Fuller, L.M., Healey, J.E., Jr., Hill, C.S., Jr., Ibanez, M.L., Macdonald, E.J., White, E.C.: Thyroid. In Cancer of the Head and Neck, W.S. MacComb, G.H. Fletcher, editors. Baltimore, Williams and Wilkins, 1967, pp. 293–328
12. Hirabayashi, R.N., Lindsay, S.: Carcinoma of the thyroid gland: A statistical study of 390 patients. J. Clin. Endocrinol. Metab. *21*:1596, 1961
13. Noguchi, S., Noguchi, A., Murakami, N.: Papillary carcinoma of the thyroid. I. Developing pattern of metastasis. Cancer *26*:1053, 1970
14. Rossi, R.L.: Lymph node metastasis in thyroid carcinoma: Incidence, patterns of progression, and significance. In Le Ganglion non envahi. Paris, France, Institut Gustave-Roussy, 1982, pp. 91–100
15. Clark, R.L., Jr., White, E.C., Russell, W.O.: Total thyroidectomy for cancer of the thyroid: Significance of intraglandular dissemination. Ann. Surg. *149*:858, 1959
16. Farrar, W.B., Cooperman, M., James, A.G.: Surgical management of papillary and follicular carcinoma of the thyroid. Ann. Surg. *192*:701, 1980
17. Cady, B., Cohn, K., Rossi, R.L., Sedgwick, C.E., Meissner, W.A., Werber, J., Gelman, R.S.: The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. Surgery *94*:978, 1983
18. Crile, G., Jr., Antunez, A.R., Esselstyn, C.B., Jr., Hawk, W.A., Skillern, P.G.: The advantages of subtotal thyroidectomy and suppression of TSH in the primary treatment of papillary carcinoma of the thyroid. Cancer *55*:2691, 1985