THYROID TODAY®
Editor: J. H. Oppenheimer, MD
Volume V, Number 4
July/August 1982

ISSN 0190-0625

CONTROVERSIES IN THE TREATMENT OF THYROID CANCER: THE NEW YORK MEMORIAL HOSPITAL APPROACH

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Thyroid cancer is a unique neoplasm in many respects, not the least of which is the number of publications and controversies generated by this relatively rare group of cancers. The American Cancer Society estimated that 9,900 cases would be diagnosed in the United States in 1981 and that only 1,050 deaths would occur during that year.[1] The biologic behavior of these cancers is also unique in several respects, and it is perhaps these unusual features that give rise to much of the controversy surrounding this area.

Prolonged benign course. Patients with papillary cancer have been reported to live 25 years with pulmonary metastases that cause little or no disability to the patient.[2] The autopsy protocols of Memorial Sloan-Kettering Cancer Center (13,188 autopsies between 1948 and 1977) contain two reports of patients who died from papillary cancer, and no other cause, 33 and 34 years after diagnosis. The only treatment of the two patients had been external beam radiation, performed in the mid 1930s, after biopsy confirmation of the disease at the ages of 12 and 22 years.

Anaplastic transformation. In the Memorial series, only 22 patients died of papillary cancer and no other cause. Of the 12 patients aged 50 years or less at the time of initial diagnosis, five died of anaplastic conversion to a giant or spindle cell carcinoma. Three of these conversions occurred five years after the patients had received external beam radiation as part of the primary therapy for papillary cancer; one 23-year-old patient converted 13 years after receiving ^{131}I as part of the primary therapy. One patient had no radiation therapy. Four anaplastic conversions were the cause of death in ten patients in whom the diagnosis was made after the age of 50 years. None of these four had received external beam radiation therapy, but one died of anaplastic conversion three years after receiving ^{131}I therapy for lung metastases. Whether radiation plays a role in this conversion, especially in the younger patients, remains a moot point.

Relation of age to prognosis. The death rate for papillary cancer, which represents approximately two thirds of all thyroid cancer seen at the Memorial Hospital, is quite low and age-dependent. Cady et al in a series from the Leahy Clinic reported that the gross 20-year death rate from papillary thyroid cancer or its surgical treatment was 10.9%.[2] The series consisted of 441 patients seen from 1931 to 1960 with a minimum 15-year follow-up. The death rate for patients aged 50 years or less at diagnosis was 3.8%, whereas that for patients older than 50 years was 29%. The 15-year death rate for patients of all ages with operable papillary cancer treated during the years 1951 to 1960 was 8%. The 20-year gross death rate for all patients with follicular cancer diagnosed prior to the age of 41 years was 6.8%; the combined death rate for operable differentiated cancer found in men below the age of 41 years and women below the age of 51 years was only 1% during the years 1951 to 1960.[3]

Apparent protective effect of lymph node metastases. Cady reported that death rates were inversely proportional to the number of lymph nodes involved.[2] Mazzaferri et al reported an inverse relationship between recurrence rates in papillary cancer and age at diagnosis, but a direct relationship between deaths and increasing age.[4] (See THYROID TODAY, Volume I, Number 10, 1978.) The death rate for papillary cancer in that study was 0.2% within ten years for patients under the age of 40 years at the time of diagnosis. Such biologic behavior, ie, a better prognosis for patients with increasing numbers of involved lymph nodes, is unique in the field of cancer.

In the following discussion, I shall attempt to analyze three major controversies in the treatment of differentiated thyroid cancer and discuss the merits of each side as well as describe the approach taken at the New York Memorial Hospital.

Total vs Less Than Total Thyroidectomy

The extent of thyroid surgery, particularly in papillary cancer, has aroused arguments for decades. Proponents of total (or near total) thyroidectomy cite the well-known multifocality of papillary carcinoma as the reason for advocating a total thyroidectomy.[4,5] Tollefson and DeCosse found that 30% (11/37) of patients who underwent a total thyroidectomy for disease that was grossly confined to one lobe or isthmus had papillary cancer in the contralateral lobe.[6] All contralateral disease was less than 1 cm in diameter. Clark et al reported a multifocality incidence of 58% when entire specimens from total thyroidectomies were examined histologically.[7] Of 164 patients in the Tollefson and DeCosse series who had only a lobectomy or lobectomy plus removal of the isthmus, only six (3.7%) developed recurrences in the contralateral lobe. The recurrence rate in the thyroid for all patients (218) with a less than total thyroidectomy, 13 of whom had gross bilateral disease, was 5% (11/222) during an average follow-up period of 11 years.

Two deaths attributable to papillary thyroid cancer occurred in patients who had less than total thyroidectomies and recurrences in the contralateral lobe. Both patients had total lobectomies and subtotal or near total contralateral lobectomies. Operations were performed in 1942 and 1943; the report does not state whether the patients received thyroid suppression treatment. One patient with obvious bilateral cervical adenopathy died after uncontrolled local recurrence. The other patient died of pulmonary metastases, the local recurrence having been successfully treated by surgical means. Thus, the death rate due to local recurrence in patients who had less than total thyroidectomy was 0.45% (1/222) or 9% of the recurrences. Only one patient died of disease of the ten patients who had total thyroidectomies as the only surgical procedure in the absence of clinically positive evidence of cervical lymph node involvement at the time of surgery. The death rate due to thyroid cancer for all 282 patients in the Tollefson and DeCosse series treated by a variety of surgical procedures was 7%. Those investigators came to the conclusion that total thyroidectomy, in the absence of gross contralateral disease, was not justified.[6] Cady et al decided the extent of surgery did not correlate well with survival.[2] If total thyroidectomy were without morbidity, its use could be justified; but Mazzaferri et al, proponents of total thyroidectomy, reported this procedure caused a 24% incidence of permanent hypoparathyroidism, recurrent laryngeal nerve paralysis, or other nerve damage, if done in conjunction with a radical or modified neck dissection for papillary cancer.[4] The complication rate was 12% if a neck dissection was not performed. Less than total thyroidectomy was associated with a 10% permanent morbidity rate (4/39) if a neck dissection was performed and a 1% rate if a neck dissection was not performed. Hypoparathyroidism requires life-long care, calcium level monitoring, the ingestion of daily medication, and, sometimes, adjustment of vitamin D2 intake from winter to summer.

On a national level, this can be a considerable expense. Bilateral vocal cord paralysis fortunately is rare but can be a life-threatening problem. Clearly, the risks of total vs less than total thyroidectomy is dependent on the skill of the surgeon, and the decision for or against "total" thyroidectomy will be contingent, at least in some measure, on this factor.

In the report by Mazzaferri et al, the only death among patients who had been treated with thyroid hormone suppression occurred in a patient who had a "total thyroidectomy."[4] Of the four other deaths due to papillary cancer, all had less than total thyroidectomies but none had received thyroid hormone suppression. One patient who died had manifested obvious lung metastases at the time of diagnosis and a biopsy was done; thus the lack of definitive surgery for this patient could not explain the outcome. Another patient treated with radiation after less than total thyroidectomy, but without thyroid hormone replacement, developed anaplastic cancer. As described above and in a previous paper,[8] anaplastic conversion may be a sequela of the irradiation of papillary cancer, especially in patients who are 50 years of age or less at the time of treatment. Further analysis of the Mazzaferri et al report shows that among patients who received thyroid hormone replacement, but no additional ^{131}I treatment or external beam radiation treatment, total thyroidectomy exerted no significant effect on recurrence rates as compared to less than total thyroidectomy by χ^2 analysis.[4] Similarly, when those patients who had less than total thyroidectomy, thyroid hormone suppression, and ^{131}I therapy were compared to patients managed with a similar regimen but after total thyroidectomy, no significant difference in recurrence rates could be demonstrated. Failure to demonstrate a beneficial effect of total thyroidectomy achieves additional importance since one might anticipate that treatment compliance by those patients with less than total thyroidectomies would not be as satisfactory as by patients with total thyroidectomies. In addition, those having total thyroidectomies also had more modified or radical neck dissections, procedures that could have been responsible for a decrease in recurrence rates.[9]

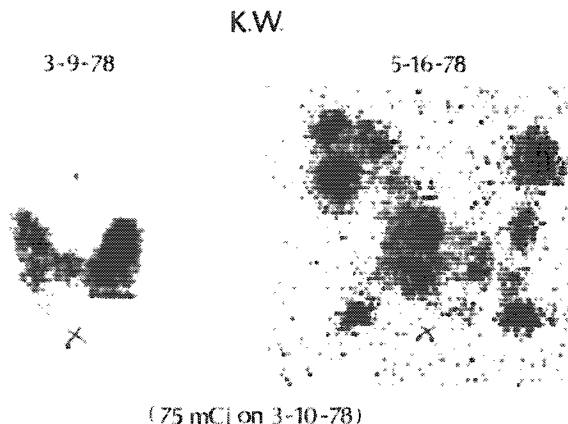
Total thyroidectomy has also been advocated in order to prepare the patient for ^{131}I therapy. However, a true total thyroidectomy frequently is not actually performed. At least 15 (16%) of the 94 patients who underwent total thyroidectomy, as reported above,[4] who were subsequently treated with ^{131}I, must have had residual uptake in the thyroid bed, since only 18 less than total thyroidectomies could have been represented in the 33 treatments for residual thyroid bed uptake. Varma cites a previous report that indicated 60% of patients had some thyroid bed uptake of ^{131}I after "total thyroidectomy."[10]

Thyroid Ablation

In discussing this procedure, it is necessary first to define terms. We reserve the term "ablation" for the use of a fixed dose of ^{131}I to eliminate any ^{131}I-concentrating tissue that remains in the thyroid bed after definitive surgery. Others consider this procedure to be definitive therapy since they assume that the high radiation levels provided by ^{131}I concentrated in normal thyroid tissue surrounding any multifocal disease that may be present are sufficient to eradicate the disease. In at least one instance, this has been shown not to be the case.[11]

There is no question about the necessity for postsurgical ablation of ^{131}I-concentrating tissue in the presence of known or suspected metastatic disease outside the bed of the thyroid. Most differentiated thyroid cancer will not concentrate ^{131}I in the presence of significant amounts of normal thyroid tissue. At our institution, we routinely administer an

ablative dose of 75 mCi ^{131}I to patients with suspected or known metastatic disease who, after 24-hour neck scans and 48-hour whole body scans, demonstrate residual uptake in the bed of the thyroid but no uptake in metastatic sites. Should we find uptake in the metastases, we proceed to dosimetry as described below. However, only a few patients will demonstrate ^{131}I uptake in metastatic deposits in the presence of significant amounts of residual normal thyroid tissue. When known distant metastases are present, and biopsy proof of papillary or follicular cancer has been obtained, we will perform a total thyroidectomy with ^{131}I (Figure), since we do not feel that a noncurative surgical procedure is justified under these circumstances. The radiation thyroiditis that can occur after ^{131}I thyroid ablation probably causes less morbidity than does an attempt at total surgical thyroidectomy.



The patient was a 12-year-old girl with no history of head or neck irradiation who had been followed for two years with a diagnosis of Hashimoto's thyroiditis. She came to Memorial Hospital after a cervical lymph node biopsy revealed papillary thyroid carcinoma. Physical examination showed bilateral cervical adenopathy and a small nodule in the right lower pole of the thyroid. Chest tomograms revealed multiple small nodules throughout both lung fields. A rectilinear thyroid scan (upper left) showed a normal thyroid configuration and patchy distribution of the ^{131}I in the right lower lobe. She received 75 mCi ^{131}I; approximately two months later, repeat scans (upper right) showed bilateral uptake in cervical lymph nodes. Whole body scanning showed bilateral diffuse uptake of ^{131}I in lungs that had not been present on the previous scan. There is no evidence of disease at this time after three ^{131}I therapies (214 mCi, 201 mCi, and 250 mCi) given at yearly intervals.

The main controversy concerning ablation is its use as a routine procedure in all patients with differentiated thyroid cancer.[4,5] One reason given for using routine ablation after presumably successful primary surgery is to prevent recurrence in the contralateral lobe. However, as pointed out above, in the absence of known contralateral disease, contralateral recurrence rates are quite low. Recurrences outside the thyroid are undoubtedly decreased to some extent since follow-up scans after successful ablation usually reveal uptake in cervical or mediastinal nodal metastases in a significant percentage of cases, more commonly in younger patients than in older patients. In a very few instances, previously unrecognized distant metastatic disease may be uncovered. Therapeutic doses of ^{131}I used to treat such metastatic disease should cause some decrease in recurrence rates. However, the data of Mazzaferri et al barely support this thesis.[4] If patients who had a total thyroidectomy and thyroid hormone suppression treatment are compared to the same type of patients who also were given ^{131}I, the difference in recurrence rates is significant only at the 3% to 5% level by χ^2 analysis. On the other hand, ^{131}I treatment had no significant influence on recurrence rates among patients with a less than total thyroidectomy, treated with thyroid hormone suppression. Hutter et al who were pioneers in the area of radical neck dissections, came to the conclusion that prophylactic neck dissections in the absence of clinically palpable cervical lymphadenopathy decreased the recurrence rate but did not significantly affect the death rate.[9] Our feeling is similar with respect to the routine use of ^{131}I for ablation.

In a disease in which the death rate from differentiated thyroid cancer in younger patients may currently be 1% or even less, it does not seem reasonable to expose all patients to whole body doses of radiation, which may be leukemogenic in a small percentage of cases.[12] If recurrences do appear, they are usually treatable by surgery or ^{131}I therapy. We prefer to maintain most patients on carefully monitored thyroid hormone replacement, which may be the most effective single modality in decreasing recurrence rates. Our own indications for thyroid ablation are listed in Table I.

Table I. Indications for ^{131}I Ablation and Therapy

	Histology		
Patient Age, yr	Papillary	Follicular	Comments
0-20	All	All	1
21-41	Selected	Selected	2
41+	Uncertain	All	3

Comments:

1. **At least 20% of patients in this age group will have lung metastases, some of which can be identified only by ^{131}I scans.[16,17] The disease is very treatable in this age group.[8]**
2. **Selected patients include those with distant metastases, recurrent disease, inoperable disease, or known residual disease.**
3. **All follicular cancer is ablated in this age group because of the marked increase in death rates and in order to find distant metastases as soon as possible. The indications for ablation in older patients with papillary cancer are indefinite. Previously published results have shown that ^{131}I therapy for metastatic disease has no effect on survival, that the probability of the metastases taking up ^{131}I is less than 50%, and that conversion to anaplastic cancer may occur after ^{131}I therapy.[8]**

Size of Therapy Doses

There has been some controversy as to whether patients with functioning thyroid carcinoma should be treated with a series of "standard" doses of ^{131}I, generally 150 mCi, or whether the doses should be individualized by careful dosimetry after appropriate tracer studies. In most cases, the treatment of a few cervical lymph node metastases can be readily accomplished by one or two 150-mCi doses of ^{131}I. However, when it is necessary to treat distant metastases, and especially when a large bulk of tumor tissue is present, we believe dosimetry is essential in allowing us to provide a maximal dose with safety. We thus avoid the risk of permanent bone marrow suppression or pulmonary fibrosis when large tumor deposits are present in bone or when extensive pulmonary metastases exist. Moreover, dosimetry allows us to give much larger doses of ^{131}I safely when treating distant metastases. An example of the effectiveness of dosimetry on dose size is shown in Table II. An analysis of 70 patients treated at this hospital since 1973 is shown in Table III. The dosimetry procedure has been described elsewhere[13,14,15]

and has been recently shortened to a four-day procedure when it was found that a four-day study gave essentially the same results as an eight-day study. Dosimetry has allowed us to give an average, single therapeutic dose of 309 mCi ^{131}I (range, 70 mCi to 654 mCi) without observing permanent bone marrow suppression or pulmonary fibrosis. Total doses exceeded 1 Ci in six patients; a maximum dose of 2.1 Ci was given to one patient. Leukemia resulting from ^{131}I therapy has not been seen in this hospital in 22 years, due probably to our practice of treating only at yearly intervals.

Table II. Effect of Dosimetry on ^{131}I Dose Size

Date	Calculated Therapy Dose (mCi)	Neck Uptake (% at 24 Hours)
2/8/75	75 (ablation)	—
5/1/75	70	43
7/1/75	88	35
4/16/76	169	—
4/14/77	213	26
4/25/78	271	—
4/18/79	640 (320 given)	0.6

The patient had documented papillary carcinoma proven by cervical lymph node biopsy at age 5 years. Pulmonary metastases were demonstrated by chest roentgenogram at age 6 years. No therapy of any type was given until 17 years later when she returned with massive bilateral lymphadenopathy, marked tracheal compression, stridor, and pulmonary metastases. Complete thyroidectomy was accomplished with 75 mCi ^{131}I. The initial calculated dose was quite small but as body retention (as shown by uptake) decreased, dose sizes became larger. The patient now has no evidence of disease after a total dose of 1.2 Ci.

Table III. Status and Treatment of 70 Patients Treated at Memorial Hospital for Metastatic Differentiated Thyroid Cancer, 1974-1981

Status	No. of Patients	No. of ^{131}I Treatments						Average Total Dose
		1	2	3	4	5	6	mCi ^{131}I
Cured	21	13	6	1	0	0	1	463
Dead of disease	17	9	3	3	0	1	1	630
Dead, other causes	4	2	2	0	0	0	0	568
Under treatment	19	10	6	1	2	0	0	514
Living with disease No further Rx	6	5	1	0	0	0	0	466
Lost to follow-up	3	2	1	0	0	0	0	379
Total	70	41	19	5	2	1	2	520

Each treatment delivered a calculated 200 rads to blood in most cases; treatments were given at yearly intervals. "Cures" were determined by roentgenogram, clinical examination, and scans. Recently, thyroglobulin assays have been used as additional evidence for presence or absence of disease.

We can calculate that on the average 1 mCi of ^{131}I gives approximately 0.67 rads to blood. Our usual dose-limiting criteria is 200 rads to blood. Three 150-mCi doses of ^{131}I given in a single year would give 300 rads to blood, a very considerable dose. Frequently, the bone marrow has insufficient time to recover and this may be a cause of leukemia after ^{131}I therapy. Moreover, 19% of the initial doses given to the 70 patients whose treatment is summarized in Table III were below 200 mCi. Dosimetry showed that in these patients 1 mCi of ^{131}I delivered more than 0.67 rads to the blood. Had these patients received a 200-mCi standard dose of ^{131}I, their bone marrow exposure would have been more than 200 rads. The maximum exposure from a single dose would have been 560 rads, a dose that would have had severe effects on the bone marrow and probably would have produced permanent bone marrow suppression. The author believes that dosimetry should be used more frequently, at least in the presence of extensive metastatic disease.

Conclusion

I have attempted to present both sides in the argument in three controversial areas that surround the treatment of thyroid cancer. Due to failure to accurately stage disease, failure in ascertaining compliance rates in taking thyroid hormone replacement, and failure to describe indications, dose size, and results of ^{131}I therapy, most of the data used on both sides of these arguments are of poor quality. It appears that a large prospective study is urgently needed to answer many of these questions in a definitive manner. Our own philosophy of treatment at this time is to recommend a less than total thyroidectomy if there is no contralateral disease. We recommend that thyroid hormone suppression be used in all cases, since there is good agreement on its efficacy at least in papillary cancer,[2,4] and that patients be regularly monitored with a thyrotropin-releasing hormone test for compliance and adequacy of pituitary suppression. We advocate ^{131}I ablation and therapy, if indicated, only in selected cases. Therapy should be given under dosimetric control, especially in the presence of extensive metastatic disease, if only to avoid occasional therapeutic mishaps.

References:

1. Silverberg E: *CA* 1981; 31:13.
2. Cady B, Sedgwich CE, Meissner WA, et al: *Ann Surg* 1976; 183:541.
3. Cady B, Sedgwich CE, Meissner WA, et al: *Cancer* 1979; 43:810.
4. Mazzaferri EL, Young RL, Oertel JE, et al: *Medicine* 1977; 56:171.
5. DeGroot LJ (ed): *Endocrinology*. New York, Grune and Stratton Inc, 1977, p 509.
6. Tollefson HR, DeCosse JJ: *Am J Surg* 1963; 106:728.
7. Clark RL, White EC, Russell WO: *Ann Surg* 1959; 149:858.
8. Leeper RD: *J Clin Endocrinol Metab* 1973; 36:1143.
9. Hutter RVP, Frazell EW, Foote FW: *CA* 1970; 20:87.
10. Varma VM, Beirwaltes WH, Nofal MM, et al: *JAMA* 1970; 214:1437.
11. DeGroot LJ, Reilly M: *Ann Intern Med* 1982; 96:51.
12. Pochin EE, Werner SC, Ingbar SH (eds): *The Thyroid*. New York, Harper and Row Publishers Inc, 1971, p 467.
13. Benua RS, Cicale NR, Sonenberg M, et al: *Am J Roent Rad Ther Nuc Med* 1962; 87:171.
14. Rawson RW, Leeper RD: in Blahd WH (ed): *Nuclear Medicine*. New York, McGraw-Hill Book Co, 1965, p 735.
15. Leeper RD, Shimaoka K: *Clin Endocrinol Metab* 1980; 9:383.
16. Exelby PE, Frazell EL: *Surg Clin North Am* 1969; 49:249.
17. Harness JK, Thompson NW, Nishiyama RH: *Arch Surg* 1971; 102:278.