DIAGNOSTIC NUCLEAR MEDICINE

Survival Time and "Cure" in Papillary and Follicular Thyroid Carcinoma with Distant Metastases: Statistics Following University of Michigan Therapy

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Between 1947 and 1980, 103 patients with well-differentiated thyroid carcinoma with metastases outside the neck were treated with sodium iodide (I-131) after surgical treatment. Forty-one patients had distant metastases first detected an average of 7.44 yr after the initial operation establishing the diagnosis of thyroid carcinoma. Follicular and papillary carcinomas gave the same survival time in patients, matched for age and sex, who had metastases outside the neck. Those considered to be free of their metastatic disease after I-131 therapy survived three times as long as those with persistent disease. Patients freed of their metastases had a higher conformity rate with half of our ten procedures of "ideal" treatment, compared with patients not freed of their metastases.

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Several excellent studies have been published comparing the efficacy of surgery, I-131, and the administration of thyroid hormone on the rates of recurrence and death in the treatment of well-differentiated thyroid carcinoma (*1–7*). The incidence of metastases outside the neck, in most studies, is 10–50% (*8,9*).

The effectiveness of radioiodine in the treatment of thyroid cancer remains to be determined, despite 33 yr of experience (1947–1980).

In 1974, a review of the literature indicated that more than 75% of patients with thyroid cancer and distant metastases died within 5 yr after the diagnosis was established (*10*). We therefore decided to evaluate the success or failure of the basic ten steps used in our treatment of well-differentiated thyroid cancer in this group of patients with metastases outside the neck, followed for up to 33 yr, whose lifespan would be expected to be considerably shortened.

Our report, in 1974, of the results of treatment of patients with well-differentiated thyroid cancers and distant metastases presented some evidence that total thyroidectomy followed by treatment with I-131 was effective. However, the report was limited to 36 patients.

We now report on all 103 such patients including those referred to us after treatment that we considered inadequate by our criteria. An attempt was made to evaluate the relationship between conformity to our procedures of treatment and survival time or "cure."

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METHODS

Patient population. Most papillary carcinomas contained follicular elements. No "pure papillary" carcinomas are included. "Follicular" carcinomas contained no appreciable papillary elements. All histopathologic slides were reviewed by one of us (RHN).

The methods for selecting patients for treatment by surgery and I-131 have been described (*1,5*). Routinely, the lobe of the thyroid gland containing a suspicious nodule is totally removed with the isthmus. A frozen section is done, and if the carcinoma is larger than 1.0 cm, a total extracapsular thyroidectomy is completed. If the frozen section is equivocal and the permanent histologic sections show a cancer, a total thyroidectomy

is done within a few days or 6 wk later. Thyroid hormone is withheld for 6 wk after the operation.

Iodine-131 images of the *neck* and *chest* (and other areas when indicated) were done 24 hr after 2 mCi of $Na^{131}I$, using a rectilinear scanner beginning in 1954, a photoscanner in 1962, and a wide-field gamma camera with a high-energy collimator in 1979. If significant uptake is found in the region of the thyroidal bed, cervical lymph nodes, lungs, or bones, a therapeutic dose of $Na^{131}I$ is administered. The patient is discharged from the hospital when the total-body content of I-131 has decreased to <30 mCi. The patient is given a maintenance dose of 0.15–0.2 mg of sodium L-thyroxine. After a year, replacement thyroid hormone is discontinued for 6 wk and the following tests are repeated: serum TSH (beginning 1974), T_4 (1971–), T_3 RIA (1976–), CBC, chest radiograph and scintigrams of the neck and chest (and other areas as indicated). If the scan shows no significant uptake, the patient resumes taking thyroid hormone and is asked to return in 2 yr. When the I-131 images are normal 3 yr after treatment, the patient is asked to return at intervals of 5 yr for life. In nine patients we have observed uptake of I-131 before recurrent neoplasm becomes palpable or is detected by radiographs of the chest. This has occurred as late as 15 yr after the patient is considered to be free of metastatic neoplasm.

Radioiodide is never given for ablation of remnants in the thyroidal bed unless significant uptake of I-131 (generally >2% of the dose at 24 hr) is demonstrated by the scan. All possible thyroid tissue, normal or neoplastic, is excised from the neck without mutilation before treatment with I-131. It is frequently impossible to determine whether a patient has distant metastases before the removal of all normal thyroid tissue (*1*,*5*), which effectively competes with the metastases for uptake of I-131.

Our treatment of well-differentiated thyroid carcinoma has been divided into ten procedures to determine the rate of "conformity" to these procedures and to determine the effect of "conformity" on survival time and "cure" rate. Lack of "conformity" means that the procedure was not carried out because the patient had never been asked to have the procedure, or refused the procedure, or died before the procedure was carried out, etc.

In summary, these 10 procedures are:

1. Thyroidectomy done within 1 yr after a suspicious nodule has been detected.
2. Lobectomy with frozen section, and completion of total thyroidectomy within 6 mo.
3. Withholding of thyroid hormones for 6 wk before an I-131 scan of the neck is done.
4. Scintiscan done within 3 mo after the thyroidectomy.
5. Treatment with I-131 for residual I-131 uptake.
   (a) Not less than 100 mCi for uptake in the thyroidal bed.
   (b) Not less than 150 mCi for uptake in the cervical nodes.
   (c) Not less than 175 mCi for distant metastases.
6. T_4 given between follow-up examinations.
7. Reexamination of the patient within 1 yr after treatment with I-131.
8. Reexamination of patient at 3 yr if the one-year scan is negative.
9. Reexamination of patient once every five years if patient considered to be "disease-free" after three years.
10. Treatment again, with more than 150 mCi of I-131, if recurrence of uptake occurs.

Biostatistics. The charts of 532 patients with thyroid cancers who were treated with radioactive iodine between January, 1947 and June 30, 1980 were reviewed.

All statements containing the term "survival" refer to the years of follow-up from the time the patient first had a histologic diagnosis of papillary or follicular carcinoma to time of last contact before June 30, 1980. The terms "alive" or "dead" are derived from the examination of the written records in our clinic and/or from the University of Michigan Medical Center Cancer Registry. The term "free of disease by all criteria" is designated by "without" disease and "not free of disease" at time of last follow-up (designated by "with") are based upon physical examinations, radiographs, and I-131 scans. If the patient has died, death certificates, autopsy reports, or the most recent examinations by referring physicians also form the basis for the designation "with." All but two of the living patients were followed since January, 1977. These two had follow-up examinations from 1969 to 1973 and from 1968 to 1974, respectively.

One hundred three patients (of the 532 treated with radioiodine for thyroid carcinoma) were found to have metastases outside the neck. These patients form the basis for this study.

Chi-square tests were performed, and those groups having less than five patients were subjected to a Yates correction factor (*11*). Tests were not done where there were no patients in a subgroup.

In each of the ten "conformity" and "nonconformity" groups, an analysis was made for a statistical bias of age difference in each of the two pathology groups. Using a t-test for comparison of two means, we found no significant difference in age in any of the "conformity versus nonconformity" groups under comparison except under Procedure 5 in the follicular carcinoma group. Here the age of the "conformity to" group was 15 yr older (56.2 yr compared with 40.56 yr in the nonconforming group). This difference, however, reinforces the value of con-

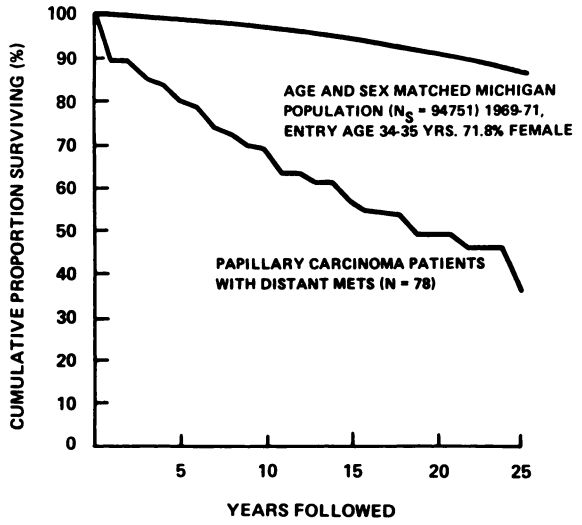

FIG. 1. Cumulative proportion survival of 78 patients having papillary thyroid carcinoma with distant metastases, treated with $Na^{131}I$, compared with age- and sex-matched Michigan Life Table population for 1969–1971 with entry age of 34–35 yr.

formity to this step because the older group survived just as long (10.13 yr) as the younger nonconforming group (10.22 yr).

We had insufficient data on the size of the primary in patients having their primary surgery elsewhere to evaluate any possible difference in size of primary

RESULTS

Survival related to age, sex, histopathologic type, geographical area, and time period. Figure 1 presents the cumulative proportion survival of 78 patients with papillary carcinoma of the thyroid with distant metastases treated with $Na^{131}I$, compared with an age- and sex-matched Michigan Life Table population (N = 94,751) for 1969–1971, with an entry age of 34–35 yr, 71.8% female.

Figure 2 is similarly prepared for patients with follicular carcinoma with distant metastases (N = 25) compared with an age- and sex-matched Michigan Life Table population (N = 89,185) as of 1969–1971, entry age 50–51 yr, 52% male.

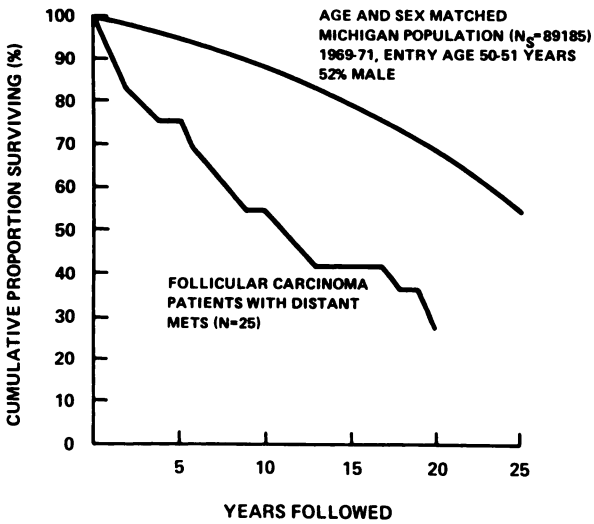

FIG. 2. Similarly prepared graph for patients with follicular carcinoma with distant metastases, as of 1969–1971, entry age 50–51 yr.

It is evident that patients with well-differentiated thyroid carcinoma with metastases outside the neck have a survival rate lower than that of the normal population.

When patients with papillary carcinomas were compared, weighted by age and sex, with those having follicular carcinomas (40 yr of age or older versus less than 40 yr of age), there is no significant difference in cumulative survival rate between the two groups ($p > 0.25$).

As of June 30, 1980, 48 patients with papillary thyroid carcinoma were alive and 30 were dead (Table 1).

Of the 30 patients who were dead, 21 died with residual thyroid carcinomas (hereafter abbreviated "with"): 15 from thyroid carcinoma, one from another cancer, two from "strokes," one from pneumonia, and two from heart disease. The remaining nine died free of their thyroid carcinomas by all criteria (hereafter abbreviated "without"). Four died from other cancers. One of these four developed a hepatocellular carcinoma 10 yr after the diagnosis of thyroid cancer. Two died from carcinomas of the lung, 26 and 25 yr, respectively, after the diagnosis of thyroid carcinomas. One patient died of a malignant melanoma diagnosed concurrent with the discovery of her thyroid carcinoma. Three patients died of heart disease, one from a "stroke," and one from obstruction of the bowel.

Nine patients with follicular carcinomas of the thyroid gland are alive and 16 are dead (Table 1). Fifteen died "with" their disease: 11 died of thyroid carcinoma, two of pneumonia, one of heart failure, and one of bronchogenic carcinoma. The one with a follicular carcinoma who died "without" disease died of a "stroke." No patient died from or with leukemia.

Our data will be based on 34 patients with papillary thyroid carcinomas "with" their disease and 44 "without"; and 17 with follicular carcinomas "with" their disease and 8 "without," for a total of 51 patients "with"

TABLE 1. WELL-DIFFERENTIATED THYROID CANCER WITH METASTASES OUTSIDE THE NECK (103 PATIENTS)

	Alive (N)	Dead (N)
Papillary	48	30
Follicular	9	16
	57	46

TABLE 2. AGE AT DIAGNOSIS AND AVERAGE SURVIVAL TIME BY PATHOLOGY TYPE AND DISEASE STATUS AT LAST FOLLOW-UP

Papillary	Avg. age (yr)	Avg. surv. time (yr)	(N)
W/Disease	45	7.6	34
Alive	38.9	10.7	13
Dead	49.3	5.8	21
W/O Disease	26	16.3	44
Alive	21.6	16.74	35
Dead	42.2	14.78	9
Total alive	26	15.0	48
Total dead	47	8.4	30

and 52 "without," all with metastases outside the neck (mediastinum and/or lung, bone, and liver).

Table 2 compares age and average survival time (ST) by pathology type and disease status at last follow-up in the group with papillary carcinomas. Patients alive and without disease (16.7 yr ST) survived half again longer than those alive and with disease (10.7 yr). Those who died without thyroid carcinoma (14.8 yr ST) survived three times as long ($p < 0.0005$) as those who died with thyroid carcinoma (5.8 yr). Those alive and free of disease (21.6 yr of age) were half the age of those alive with disease (38.9 yr) ($p < 0.0005$).

All of our patients took thyroid hormone between follow-up examinations except for two patients (12%) in the group that died with their disease.

Table 3 presents the same data for patients with follicular carcinoma. Patients with follicular carcinomas without disease (alive and dead) had a survival time (17.5 yr) that is over twice the survival time (7.2 yr) of those with disease (alive and dead) ($p < 0.0005$).

The patients with follicular carcinomas without disease (36 yr of age) were younger than those with persistence of their disease (57 yr of age) after treatment ($p < 0.0005$).

TABLE 3. AGE AT DIAGNOSIS AND AVERAGE SURVIVAL TIME BY PATHOLOGY TYPE AND DISEASE STATUS AT LAST FOLLOW-UP

Follicular	Avg. age (yr)	Avg. surv. time (yr)	(N)
W/Disease	57	7.2	17
Alive	53	11.5	2
Dead	57	6.7	15
W/O Disease	36	17.5	8
Alive	31.4	19.0	7
Dead	71	7	1
Total alive	36	17.3	9
Total dead	58	6.7	16

TABLE 4. LOCATION OF METASTASES—PAPILLARY

		Mediastinal (N)	Lung (N)	Bone (N)	Other (N)
Alive—	with	4	8	1	
	without	19	14	2	
Dead—	with	1	11	8	1 (liver)
	without	2	6	1	
	Total	26	39	12	

LOCATION OF METASTASES—FOLLICULAR

Alive—	with	0	1	1	0
	without	5	1	1	0
Dead—	with	1	4	10	0
	without	0	0	0	1
	Total	6	6	12	1

All the groups with follicular carcinoma were significantly older than comparable groups with papillary carcinoma.

Table 4 relates the category of dead or alive with or without disease to the location of the metastases outside the neck for papillary carcinomas and for follicular carcinomas.

It is evident that the most common location of metastases outside the neck in papillary carcinoma is in the lung, secondly in the mediastinum, and thirdly in bone. The data suggest that I-131 finds it easiest to clean out metastases in the mediastinum, less so in the lungs, and most difficult in the bones.

The data for follicular carcinomas indicate that most patients with osseous metastases die with their metastases in spite of treatment with I-131.

Relationship of freedom from disease and survival to conformity to the University of Michigan Medical Center surgical and $Na^{131}I$ therapeutic procedures. When the data base is analyzed by histopathologic diagnosis and "alive" or "dead," "with" or "without" disease, the numbers are too small to indicate more than a trend.

Papillary carcinomas—"Conformity" with those procedures in treatment in which a trend is evident. (See Table 5).

Procedure

2. Lobectomy with frozen section and completion of total thyroidectomy within 6 mo:
   Those who died with their disease had the lowest rate of conformity (55%), significantly different ($p < 0.05$) from those alive without their disease (83%).
3. Withholding of thyroid hormones for 6 wk before an I-131 scan of the neck is done:

TABLE 5. PAPILLARY

#2 Lobectomy with frozen section and second lobectomy within six months			
Alive W	Alive W/O	Dead W	Dead W/O
10/12 = 83%	29/35 = 83%	11/20 = 55%	7/9 = 78%
#3 Off T_4 and T_3 six weeks before scan			
Alive W	Alive W/O	Dead W	Dead W/O
8/12 = 67%	33/35 = 94%	10/16 = 63%	4/7 = 57%
#4 Scan within three months of surgery			
Alive W	Alive W/O	Dead W	Dead W/O
7/11 = 64%	33/35 = 94%	7/16 = 44%	7/9 = 78%
#5 Treat with I-131 for residual uptake (>100 >150 >175 mCi)			
Alive W	Alive W/O	Dead W	Dead W/O
7/12 = 58%	19/35 = 54%	8/21 = 38%	4/9 = 44%
#10 If recurrence of uptake, treat again with >150 mCi			
Alive W	Alive W/O	Dead W	Dead W/O
5/9 = 56%	12/14 = 86%	3/12 = 25%	4/5 = 80%

TABLE 6. FOLLICULAR

#1 Have TX within one year of goiter		
Alive W	Alive W/O	Dead W
1/2 = 50%	5/7 = 71.4%	7/14 = 50%
#3 Off T_4 and T_3 six weeks before scan		
Alive W	Alive W/O	Dead W
1/2 = 50%	6/6 = 100%	7/14 = 50%
#4 Scan within three months of surgery		
Alive W	Alive W/O	Dead W
0/2 = 0%	7/7 = 100%	7/14 = 50%
#5 Treat with I-131 for residual cancer with adequate doses (>100, >150, >175 mCi)		
Alive W	Alive W/O	Dead W
1/2 = 50%	5/7 = 71.4%	8/14 = 57%

Those alive without disease had the highest conformity rate (94%), significantly different ($p < 0.05$) from the other groups (57-67%).

4. Scintiscan done within 3 mo after the thyroidectomy:
   Those alive and without disease had the highest conformity rate (94%), significantly different ($p < 0.001$) from those who died with their disease (44%).
5. Treatment with I-131 for residual I-131 uptake:
   Those patients dead with their disease had the lowest conformity rate (38%). This rate, however, is not significantly different ($p > 0.9$) from the group dead without their disease (44%).
10. If recurrence of uptake occurs, treatment must be with more than 150 mCi of I-131:
    The patients dead with their disease had the lowest conformity rate (25%), significantly differ ($p < 0.01$) from those alive without their disease (86%).

Follicular carcinoma. (See Table 6.) The data are too limited to do chi-square tests in two instances and not significant in the two instances where they were done.

Procedure

1. A thyroidectomy done within 1 yr after a suspicious nodule has been detected:
   The highest mean conformity rate (71.4%) was in the category of those alive and without disease. This, however, is not significantly different ($p > 0.60$) from those alive or dead with their disease (50%).
3. Withholding of thyroid hormones for 6 wk before an I-131 scan of the neck is done:
   The highest conformity rate was in patients alive and free of their disease (100% vs. 50% for the other two categories).
4. Scintiscan done within 3 mo after the thyroidectomy:
   The highest conformity rate was in the category of those alive and without disease (100%), compared with conformity rates of 0% and 50% in the other two categories.
5. Treatment with I-131 for residual I-131 uptake:
   The highest conformity rate (71.4%) was in the category of patients alive and without their disease, compared with a conformity rate of 50-57% in the other two categories.

Time from the first operation (histopathologic diagnosis) to the first detection of distant metastases. In about two thirds of the patients (60.6%), the metastases outside the neck were detected at the time of the first operation (Table 7). Distant metastases were first detected in the remaining third (39.4%) after an average period of 7.44 yr (1-25 yr).

We have made a statistical analysis of the percentage of patients who had their first surgery at our hospital and those who had their first surgery elsewhere, and have added these percentages to Table 7. Note that in six subgroups, patients having their first surgery at our hospital had a higher fraction of metastases detected initially, and in two subgroups ("Pap alive w/o" and "Pap dead w/o") the same percentage with metastases detected initially. These data might suggest that patients having their primary surgery at our hospital had a more threatening cancer than those with their first surgery performed elsewhere. We think this is not so, for two

TABLE 7. TIME TO DETECTION OF DISTANT METASTASES FROM TIME OF FIRST SURGERY, AND PERCENTAGE OF PATIENTS HAVING INITIAL SURGERY ELSEWHERE

	Total (N)	Present at time of surgery (N)	% *	Later (N)	% *	Range (yr)	Average (yr)
Pap. alive with	13	6	(50)	7	(71.4)	2–25	10.4
Pap. alive W/O	35	24	(25)	11	(27)	1–16	5.72
Pap. dead with	21	10	(10)	11	(63.6)	1–18	6.36
Pap. dead W/O	9	6	(33)	3	(33)	2–6	4.33
Foll. alive with	2	0		2	(100)	5–10	7.50
Foll. alive W/O	7	4	(0)	3	(07)	6–13	9.0
Foll. dead with	15	11	(18)	4	(100)	3–13	8.75
Foll. dead W/O	1	1	(100)	—		—	—
	103	62		41			7.44

* Percent of patients having first surgery elsewhere.

reasons: (1) Our initial surgery was more extensive than in patients who had their initial surgery elsewhere. (2) We routinely keep the patient off all thyroid hormone for 6 wk after the initial surgery and perform a scintigraphic search for metastases (as described above). We therefore expect to detect metastases in a higher fraction of patients after their initial surgery than when only partial thyroidectomy was done and there was no prompt tracer search for metastases with the patient off thyroid medication for 6 wk.

DISCUSSION

Several original observations have resulted from this study.

With the exception of our own preliminary study (*10*), we have found none limited to well-differentiated thyroid carcinomas with metastases outside the neck.

It is the first study covering 33 yr of the use of $Na^{131}I$ for the treatment of well-differentiated thyroid carcinomas. Cumulative survival curves in patients with papillary and follicular carcinoma with metastases outside the neck have not been published previously. There have been no comparisons of cumulative survival curves with a regional normal population matched for age, sex, duration of follow-up, and covering roughly the same time of study. The previous publication by Woolner et al. (*12*) was not limited to metastases outside the neck, and compared one control curve matched in age and sex to three populations for papillary carcinomas (occult, intrathyroidal, and extrathyroidal) and to two populations for follicular carcinomas (noninvasive and invasive), but not matched to time or the population considered for study.

Most authors have reported that the prognosis is worse with follicular than with papillary carcinomas, and that an age greater than 40 yr (*1,6*) is an important risk factor. We are not aware that our observation has previously been made that when groups of patients with papillary carcinomas and follicular carcinomas are matched as to age and sex, the prognosis is as poor with one as with the other. This observation supports our policy of treating young patients with papillary carcinoma as aggressively as older patients with follicular carcinomas, since the prognosis will be the same if they live past 40–50 yr of age.

Our results show that well-differentiated thyroid cancers with metastases outside the neck have a significantly decreased survival rate compared with that of patients with no metastases, or with a control population. We have previously recorded that the death rate in patients with lung metastases was four times that in patients without lung metastases (*1*).

As a tertiary center for thyroid carcinoma, our clinic has been privileged to care for patients with well-differentiated thyroid carcinoma not treated by our ten main steps of surgical and $Na^{131}I$ treatment. As a result we have accumulated patients freed of lung metastases by all criteria for periods of 27 yr, 25 yr, 23, 21, etc., as well as patients who never had adequate surgery or a thyroid scan with I-131 for as long as their first 21 years of management, and in many instances had hopelessly widespread metastases outside the neck when we first saw them.

One might speculate that patients treated elsewhere had biologically worse disease that inherently defeated therapy different from, but as good as, that advocated at the University of Michigan. A statistical analysis, however, revealed no such difference in biological behavior in that a comparison by age at diagnosis and

survival time revealed no difference between the groups having their first surgery at our hospital and those having theirs elsewhere.

Distant metastases were first detected in 41 patients (39.4%), an average of 7.44 yr (range 1–25 yr) after their first operations, the disease in some cases being far advanced and incurable carcinoma when first discovered. We (*5*) and others (*13,14*) have previously observed that cervical lymph-nodal, pulmonary, and osseous metastases can be detected by I-131 scans when the metastases had not yet become palpable or visible by radiography (*5*). This is an argument for reexaminations by scintiscans throughout the patient's life.

It would be of interest to know what fraction of the patients in this series had metastases outside their necks detectable by scan before the metastases could be visualized by radiograph. Unfortunately, we do not have this information because of several factors. It is well established (*5*) that the majority of distant metastases cannot be visualized by scan until adequate surgery has been done to remove the thyroidal competition with the metastases for uptake of I-131. Only about half of the patients in each pathology group who died with metastases had had adequate thyroid surgery. About 1/3 of those who died with disease had had a scan within 3 mo of surgery and off T_4 and T_3 for 6 wk before scan. In our experience, it is a rare occurrence for a patient with well-differentiated thyroid carcinoma, who has prompt and adequate surgery with a scan off T_4 and T_3 within 3 mo of surgery, and ablation of a remnant, ever to develop distant metastases detectable either by scan or by radiograph. By definition, therefore, this collection of 103 patients—with distant metastases either detected at the time of the original surgery or who developed detectable metastases 1–25 yr after the primary surgery—either had biologically aggressive disease or experienced a delay in obtaining adequate treatment.

There is little doubt that patients with distant metastases that concentrate I-131 should receive I-131 therapy. There is, however, argument about the use of I-131 therapy in patients who do not initially have distant metastases. An effort was made to break the data down into these subgroups for statistical treatment but there were too few patients in each subgroup to permit meaningful comparison.

Similarly, when an attempt was made to compare subgroups of patients who died with their thyroid carcinoma compared with patients who died from their carcinoma, the subgroups were too small to produce meaningful results.

We might also comment that patients with persistent disease do worse than those with disease that can be eradicated, and older patients are more likely to have persistent disease. Our data support this comment. Indeed, we believe that for this reason, the ideal time for an aggressive attempt to eradicate the disease is before age 40 in men and age 50 in women.

Most important in this regard is our observation that patients freed of their well-differentiated thyroid carcinoma metastases outside the neck have a survival three times that of patients not freed of their metastases with $Na^{131}I$.

CONCLUSION

Based on a 25-yr follow-up of patients with distant metastases from well-differentiated carcinoma of the thyroid—those expected to have the worst prognosis—we have found that if they can be freed of their metastases with radioiodine, they are likely to survive three times as long as patients not thus freed.

Patients freed of their metastases had a statistically demonstrable higher conformity rate with half of our ten procedures of treatment as compared with patients not freed of their metastases.

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