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CONTROVERSIES IN THE TREATMENT OF THYROID CANCER: THE UNIVERSITY OF MICHIGAN APPROACH



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Rising Incidence of Well-Differentiated Thyroid Cancer

Between 1973 and 1977 in the United States, there was a 50% increase in the incidence of papillary and follicular carcinoma of the thyroid (Figure 1).¹ In women, it was the third most common cancer in 15- to 19-year-olds, second in 20- to 24-year-olds, and third in 30- to 34-year-olds.² In the United States, papillary carcinomas outnumber follicular carcinomas by approximately 3:1. E.D. Williams and associates have shown a rising incidence of papillary carcinoma of the thyroid in patients on a high iodine diet.³ In iodine-deficient areas of the world, follicular carcinoma is more prevalent than papillary carcinoma.⁴

Death rate. With modern surgery and sodium I 131 therapy, rarely should a patient die of well-differentiated thyroid cancer.⁵ The major cause of death from well-differentiated thyroid carcinoma seen in patients referred to the University of Michigan (U-M) Hospital is a reluctance of the physician to treat the patient aggressively while the patient is curable; we also see a reluctance to stop treating the patient when he or she has progressed to an incurable state.⁵ These attitudes appear to exist because of a lack of understanding that generally well-differentiated thyroid cancer grows slowly in the young (ages 16 to 40 years), and faster in the very young (0 to 16 years) and in persons older than 40 years of age.

Children under 15 years of age. Winship and Rosvoll found the death rate from thyroid carcinoma to be 18% in 562 children under 16 years of age.⁶ Most patients died during the first post-operative year, but 24 died after having had the disease for

more than ten years. When mortality was correlated with the patient's age at the time of diagnosis, 61.5% of 57 children diagnosed before age 7 years were dead at follow-up.⁷ Of 430 children diagnosed between 7 and 15 years of age, 12.8% were

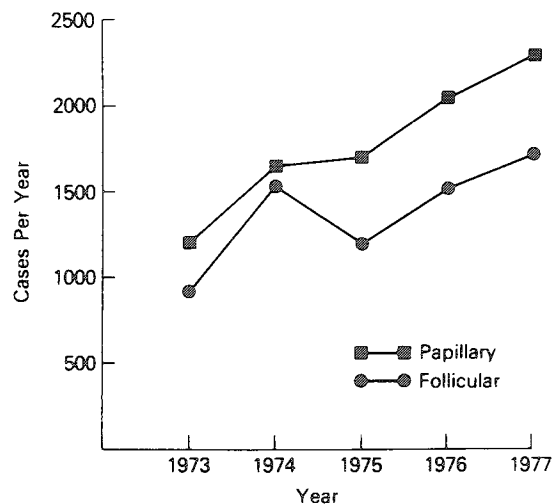


Figure 1

Graph from 1973-1977 Surveillance Epidemiology and End Results Program (SEER) of the National Cancer Institute showing a 50% increase in the incidence of papillary and follicular carcinoma of the thyroid between 1973 and 1977 in the United States. These data are based on 11 population-based registries, including five states and six metropolitan areas that make up approximately 10% of the US population. (From Brennan MF, Bloomer WD: Cancer of the endocrine system, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology*. Philadelphia, JB Lippincott Co, 1982, Fig 28-3, p 973.)

This is the second of two articles dealing with the general topic of "Controversies in the Treatment of Thyroid Cancer." The first article, by Robert Leeper, MD, of the Memorial Sloan-Kettering Cancer Center, New York, NY, appeared in THYROID TODAY, Volume V, Number 4, July/August 1982.

dead at follow-up. In spite of these figures, there seems to be a reluctance to do a total thyroidectomy in a child with proven thyroid cancer, while it is accepted surgical practice to treat Graves' disease in children with a 95% to 100% "total" thyroidectomy!^{18,9}

There also is a reluctance to use ¹³¹I after surgery in children under 15 years of age who have thyroid cancer, perhaps because of the lack of knowledge of the above death rate.

Adults aged 20 to 30 years. Metastases of well-differentiated thyroid cancer outside the neck have been seen in 19.4% of patients we have treated with ¹³¹I after surgery.⁵ In these 78 patients with papillary thyroid carcinoma and 25 patients with follicular carcinoma, 39.4% did not have their metastases detected at the time of the original surgery. The metastases were first detected outside the neck 7.44 years after the original surgery, with a range of 1 to 25 years. In the majority of patients, the metastatic cancer could not be detected at the time of the original surgery because a "nodulectomy" or subtotal thyroidectomy left sufficient thyroid gland to compete with metastases for uptake of ¹³¹I. In many instances, ¹³¹I was not used after surgery to look for metastases.

Figure 2 shows the cumulative survival rate of the 78 papillary carcinoma patients under our care in comparison with 94,751 control subjects in Michigan during 1969 to 1971. The mean matched entry age was 34 to 35 years. Of the 30 patients with papillary carcinoma, 21 died with residual thyroid carcinoma; six died for reasons not directly attributable to this malignancy. As indicated in Figure 2, there is a marked divergence between the cumulative survival rates of the patients with papillary carcinoma who were harboring distant metastases and their age-matched and sex-matched controls. Since our experience has shown that it may be impossible to detect distant metastases without near-total thyroidectomy, aggressive therapy appears indicated to make certain that any distant metas-

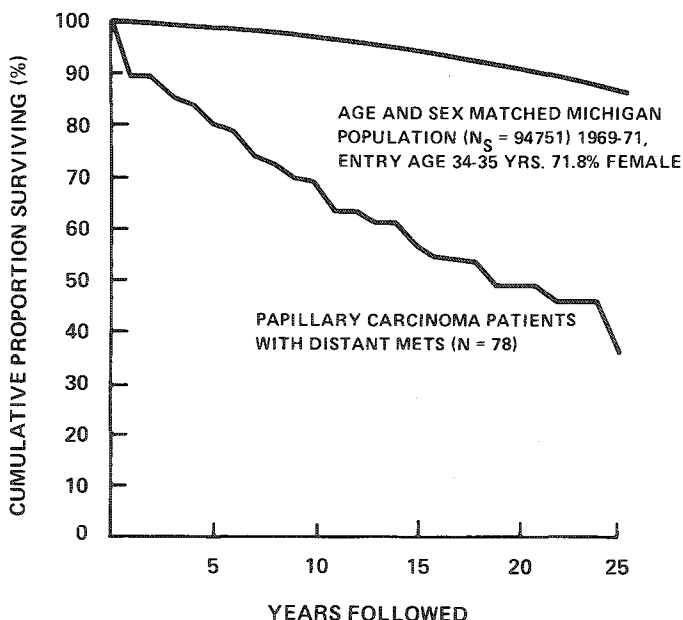


Figure 2
Cumulative survival rate of 78 papillary thyroid cancer patients with metastases outside the neck. See text for matching of sex, age, and geographical location.

tases are vigorously treated at the earliest possible time, and in the hope that thyroid ablation will forestall both local growth and the development of metastases. Figure 3 presents the cumulative survival rate for follicular carcinoma. Of the 16 patients with follicular carcinoma, 11 (75%) died as a direct consequence of the malignancy.

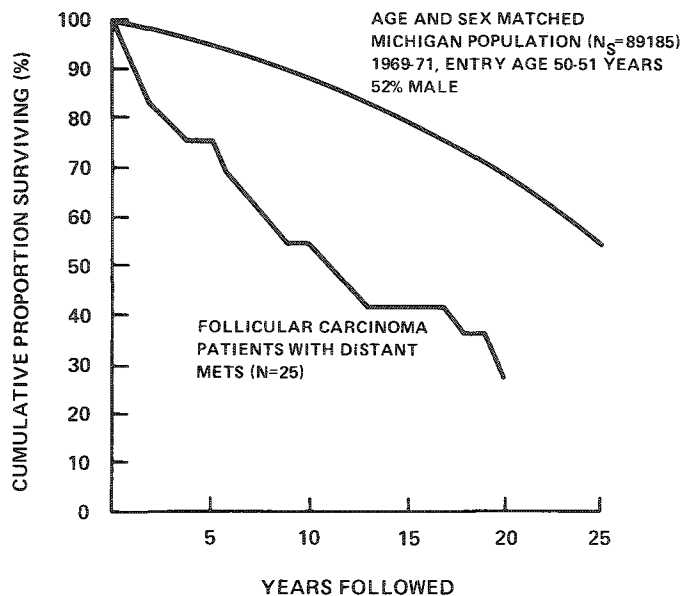


Figure 3
Cumulative survival rate of 25 patients with follicular carcinoma with metastases outside the neck.

In some cases, the decision of whether to treat or not treat with ¹³¹I at various ages has been based upon patient age and cell pathology.^{10,11} We found, however, that when female and male subjects under and over age 40 years were matched, there was no difference in the survival rate between follicular thyroid carcinoma and papillary carcinoma.⁵ Thus, it appears that previous statements on the apparent worse prognosis of follicular carcinomas were statistically biased because of the lack of careful age and sex matching of various study groups.

The U-M Surgical and ¹³¹I Therapeutic Approach

Our methods for selecting patients for treatment by surgery and ¹³¹I have been described.^{5,12} 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 biopsy results are equivocal, and the permanent histologic sections show a cancer, a total thyroidectomy is done within a few days or six weeks later. Thyroid hormone is withheld for six weeks after the operation.

Iodine 131 images of the neck and chest (and other areas, when indicated) are done 24 hours after 2 mCi of Na ¹³¹I. The following equipment has been used by U-M hospitals for this procedure: a rectilinear scanner beginning in 1954, a photo-scanner 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 ¹³¹I is administered. The patient

is discharged from the hospital when the total body content of ^{131}I has decreased to <30 mCi. The patient is given a maintenance dose of 0.15 to 0.2 mg of sodium L-thyroxine (T_4) daily. After one year, replacement thyroid hormone is discontinued for six weeks and the following tests are repeated, with dates of introduction to U-M hospitals given parenthetically: serum thyroid-stimulating hormone (TSH) (1974), T_4 (1971), triiodothyronine radioimmunoassay (T_3 RIA) (1976), complete blood cell count (CBC), chest radiograph, and scintiscans of the neck and chest and other areas as indicated. If the scintiscan shows no significant uptake, the patient resumes taking thyroid hormone and is asked to return in two years. When the ^{131}I images are normal three years after treatment, the patient is asked to return at intervals of five years for life. In nine patients, we observed uptake of ^{131}I before recurrent neoplasm became palpable or was detected by radiographs of the chest. This occurred as late as 15 years after the patient was considered to be free of metastatic neoplasm.

Radioiodide is never given for ablation of remnants in the thyroidal bed unless significant uptake of ^{131}I (generally $>2\%$ of the dose at 24 hours) is demonstrated by the scintiscan. All possible thyroid tissue, normal or neoplastic, is excised from the neck without mutilation before treatment with ^{131}I . It is frequently impossible to determine whether a patient has distant metastases before the removal of all normal thyroid tissue, which effectively competes with the metastases for uptake of ^{131}I .^{12,13}

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.⁵ *Lack of conformity* means that the procedure was not carried out because the patient had never been asked to have the procedure, refused the procedure, or died before the procedure was carried out.

In summary, these ten procedures are:

1. Thyroidectomy done within one year after a suspicious nodule has been detected.
2. Lobectomy with frozen section, and completion of total thyroidectomy within six months.
3. Withholding of thyroid hormones for six weeks before a ^{131}I scan of the neck is done.
4. Scintiscan done within three months after the thyroidectomy.
5. Treatment with ^{131}I for residual ^{131}I 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. Sodium L-thyroxine given between follow-up examinations.
7. Reexamination of patient within one year after treatment with ^{131}I .
8. Reexamination of patient at three years if the one-year scintiscan is negative.
9. Reexamination of patient once every five years if patient is considered to be disease-free after three years.
10. Retreatment with more than 150 mCi of ^{131}I , if recurrence of uptake occurs.

Using these procedures in 103 patients with well-differentiated thyroid carcinoma with metastases outside the neck, those considered to be free of their metastatic disease after ^{131}I therapy survived three times as long as those with persistent disease.⁵ Patients free of their metastases had a higher

conformity rate with the procedures compared with patients not free of their metastases.⁵

Total Thyroidectomy v Subtotal Thyroidectomy

There is general agreement that the risks of total versus subtotal thyroidectomy is dependent upon the skill and experience of the surgeon. We agree that the risks of a true total thyroidectomy for proven thyroid cancer by an *inexperienced* surgeon are unnecessary. We also believe that the risks are unnecessary for a total thyroidectomy in a child for the treatment of Graves' disease by an inexperienced surgeon. However, we also believe the solution to the problem is *not* inadequate surgery followed by ^{131}I ablation of uptake in the remnant for several reasons:

1. Adequate surgery is more effective than ^{131}I in removing the primary cancer. The most common cause of death from thyroid carcinoma is invasion of the structures of the superior thoracic inlet.¹⁴ We have reviewed the literature showing that the death rates are lower after adequate surgery at the primary operation.¹³
2. Total surgical thyroidectomy may remove thyroid cancer that does not concentrate ^{131}I . Leeper has reported an alarming death rate from anaplastic transformation of well-differentiated thyroid cancer in patients not having a total surgical thyroidectomy.¹¹
3. There is a lower recurrence rate after total surgical thyroidectomy than after subtotal. Recurrence of well-differentiated thyroid cancer after subtotal thyroidectomy has been found to be twice as common as after bilateral total thyroidectomy.¹⁵
4. Recurrences after inadequate surgery result in a higher surgical morbidity from further surgeries and a 19% to 25% incidence of metastases that do not concentrate ^{131}I therapeutically.^{16,17}

Mazzaferri and Young reported that in 576 patients during a ten-year follow-up, there were 84 recurrences.¹⁶ All six deaths from carcinoma occurred in this group. Nineteen percent of the patients with recurrences could not have their disease eradicated by any technique. Deaths in these patients occurred after they reached 30 years of age. Cervical lymph node metastases were associated with an increased recurrence rate.

In a study of 352 patients, the M.D. Anderson group found 97 patients with recurrent disease.¹⁷ One fourth of these patients failed to concentrate radioiodine. Forty-four patients died of progressive thyroid carcinoma. Their deaths began after age 40 years. It also should be remembered that recurrences that occurred because the surgeon initially wished to be "conservative" led to a logarithmically increasing incidence of surgical morbidity for each repeated surgery because of distorted anatomy.

In a group of patients with papillary thyroid carcinoma, Sawyer et al found that recurrences occurred in eight of nine patients (89%) after nodulectomy and/or subtotal thyroidectomy.¹⁸ Furthermore, five patients (56%) in this group died from the disease. In the group of ten patients with follicular carcinoma who were similarly treated, four (40%) developed recurrences and one patient died from the cancer.

Block has also reviewed the literature showing that it is not possible to predict which lesions will respond to limited surgery.¹⁹ The malignancy has already spread to involve regional cervical nodes in approximately 50% of patients with papil-

lary adenocarcinoma even though metastases are not clinically evident. Summarizing their experience, Sawyer et al have indicated that "a significant number of patients with papillary and follicular adenocarcinoma of the thyroid will die of their disease. Most of the patients with these types of thyroid malignancies are young and have a long life expectancy. Thus, some radical surgery appears reasonable and justified. The more radical surgery for this disease need not be more mutilating than repeated, limited procedures."¹⁸

Ablation of Uptake of ¹³¹I in Surgical Remnant

There appears to be no disagreement on the necessity for ¹³¹I ablation of uptake in the thyroidal remnant in the presence of known metastatic disease. In our patients with known metastases outside the neck, however, the metastases were not detected for a mean of 7.44 years (1 to 25 years). The only way we can be certain of the presence of metastases that will concentrate ¹³¹I is to ablate the competing uptake in the thyroidal remnant down to 2% or less of the tracer dose at 24 hours after administration of the tracer.

Advocates of the use of 29.9 mCi of ¹³¹I to ablate uptake in "normal" remnants believe this dose will ablate the uptake in a normal remnant.²⁰ Presumably, therefore, the 39% of their patients whose remnants were not ablated with 29.9 mCi, and who required an additional 100-mCi dose, later had thyroid cancer in a previously judged normal remnant. Other authors who followed their patients for longer periods to check on the ablative effects of 29.9 mCi of ¹³¹I in normal remnants found that a second dose was required in 12 of 13 patients and in 16 of 17 patients.^{21,22} Thus, we must conclude either that 29.9 mCi will not ablate uptake in normal thyroid remnants, or that the majority of normal thyroid remnants actually contain well-differentiated thyroid cancer that concentrates ¹³¹I.

The reluctance to use a 150-mCi ablating dose in such patients is difficult to understand since none of our 103 patients with distant metastases treated with ¹³¹I, and followed up to 33 years from their first treatment doses, died with or from leukemia, nor did they have an increased incidence of second cancers.⁵ Similarly, Leeper reports that the administration of far larger doses of ¹³¹I than 150 mCi has not been associated with a case of leukemia at Memorial Hospital in 22 years.¹¹

Yet some patients who consult us for a second opinion have been started on radiation therapy and/or cancer chemotherapy before a trial of ¹³¹I therapy for well-differentiated thyroid carcinoma. Chabner at the National Cancer Institute has reported that, in ovarian cancer patients living two years after initiation of chemotherapy, the risk of developing acute leukemia is increased by a factor of 67 to 171.²³ Similarly, in patients with Hodgkin's disease, the risk of developing a second cancer four years after lymph node irradiation and chemotherapy is increased by a factor of 21!

Intensity of ¹³¹I Doses

We use a standard dose of 150 mCi of ¹³¹I for adults with a thyroidal remnant because it is successful in 95% of patients who have had adequate surgery.²⁴ The same dose commonly fails in patients who have had inadequate surgery. Freedberg et al studied 51 postmortem examinations, seven days to 11 years after administration of ¹³¹I to euthyroid cardiac patients.²⁵ They concluded that about 50,000 rads to the normal thyroid gland

was required for its total destruction, most of this delivered by the first dose.

We administer 175 mCi when there is demonstrated residual uptake of ¹³¹I in lymph nodes after extensive surgical plucking of such lymph nodes. We administer a standard adult dose of 200 mCi for metastases outside the neck.

The reasons we use this "standard" dose of 200 mCi for adults with metastases outside the neck are:

1. In 1956, the Atomic Energy Commission (AEC) Subcommittee on Human Use began to include in the ¹³¹I license a limit of 200 mCi on single doses for cancer.²⁶ The AEC Subcommittee on Human Use based this action on a study that failed to find data to prove that single doses greater than 200 mCi were more effective than doses of 200 mCi. They also found that doses greater than 200 mCi were associated with an increased incidence of complications.²⁶
2. Patients who have died from their thyroid carcinoma have received larger total doses than patients free of their metastases.^{11,12}
3. Since it has been demonstrated that blood doses greater than 200 rads carry an increased risk of complications (primarily bone marrow depression), it is reasonable to do studies that allow a calculation of the dose required to deliver a blood dose of 200 rads.

The reasons we do not use this procedure, however, are that:

1. A minimum of four days of patient study are required after administering the tracer dose.¹¹
2. The treatment dose usually exhibits different kinetics than the tracer dose.²⁶
3. The proponents of this procedure have demonstrated that treatment doses in excess of 200 mCi carry an increased risk of complications.²⁶

In spite of this fact, the Sloan-Kettering group has stated that dosimetry calculation allowing a 200-rad blood dose "has allowed us to give an average, single therapeutic dose of 309 mCi" (range, 70 to 654 mCi).¹¹ They have suggested that when the disease is rapidly progressive, the limits are increased to 300 rads to blood or 150 mCi body retention at 48 hours. It is our experience, however, that aggressive treatment of far advanced, rapidly progressive, well-differentiated thyroid cancer seldom, if ever, is successful. It has been reported that a series of doses estimated to deliver up to 500,000 rads failed to decrease the size of the tumor.²⁷ Rarely, if ever, are bone marrow metastases cured, even when total doses reach as high as 2.5 Ci.

It is for this reason that we urge more adequate surgery and ¹³¹I ablative therapy in younger, curable patients with well-differentiated thyroid cancer, and cessation of ¹³¹I therapy when the patient has developed rapidly progressive, hopelessly advanced disease. We believe this approach is more conservative than inadequate surgery and inadequate ¹³¹I therapy when the disease is curable, and aggressive therapy only when the disease is incurable.

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