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Postoperative Treatment of Thyroid Cancer with Radioactive Iodine[1]

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Despite numerous reports which have appeared in the medical literature during the past decade, the therapeutic efficacy of radioactive iodine (I^{131}) in the management of thyroid cancer remains controversial. A major factor in this controversy is the relatively small number of thyroid cancer patients who have been treated with I^{131}. Furthermore, because of the remarkable longevity of most thyroid cancer patients only a few of these treated patients have been followed for periods sufficient to be considered of therapeutic significance. The evaluation of this form of therapy is further confounded by the multiple and combined modalities of therapy employed. These have included the use of antithyroid agents, thyrotropic hormone, desiccated thyroid, x-ray therapy and a host of surgical procedures. In the present series an attempt has been made to follow a relatively consistent therapeutic regimen involving four basic modalities of therapy: surgical thyroidectomy, thyrotropic hormone stimulation, cancerocidal doses of I^{131}, and thyroid extract administration.

METHODS

Since 1949, 45 patients have received therapeutic amounts of I^{131} and have been followed for more than one year in the Radioisotope Service, Veterans Administration Center, Los Angeles. Cancer metastases and postsurgical remnants were localized by means of the mechanical scintiscanner after patients had received large tracer doses of I^{131} preceded by injections of thyrotropic hormone. Individual therapeutic doses of I^{131} ranging from 100 to 150 mc also preceded by thyrotropic hormone injections were administered to patients with functioning metastases. Smaller doses were used to ablate postsurgical thyroid remnants. Total I^{131} dosage ranged from 85 to 660 mc. All patients received thyroid extract in tolerance doses upon the completion of I^{131} therapy. A detailed description of this therapeutic regimen has been described previously (1).

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The patients were predominantly male which may be attributed to the prevailing male population of the Veterans Administration hospitals. The patients ranged in age from 21 to 73 years.

All patients had thyroid surgery prior to I^{131} therapy. Forty-two had total thyroid removal and 23 had associated radical neck dissections. In 3 patients, surgery was limited to unilateral lobectomy.

Tumors were differentiated cell types with the exception of 3 undifferentiated and two Hűrthle cell carcinomas.

RESULTS

Twenty-nine patients in this series had proved metastatic lesions; 18 are living and 12 (41%) have lived 5 or more years (Table I). Twenty-two of the 29 patients had demonstrable I^{131} uptake in their metastases.

All of the 16 patients who were free of metastases at the time of initial thyroid surgery were living although 4 have been lost to follow up after postsurgical intervals of 3 to 7 years.

At the time of this report, 11 patients were dead. Eight of the 11 deceased patients died as a direct result of thyroid cancer (see Table II). Four patients had undifferentiated or Hűrthle cell tumors, 7 had differentiated tumor cell types. In 5 cases there was demonstrable I^{131} uptake by metastatic lesions. The average survival of these patients was 3.7 years.

No complications from I^{131} therapy were observed in the present series.

DISCUSSION

In the present study four basic principles of management have been employed. Of these the primary procedure is thyroid ablation. It is our belief that all patients with thyroid cancer should have total thyroid removal. The rationale supporting this viewpoint is two-fold: (1) The presence of multifocal intraglandular neoplasia either as multicentric foci of origin or as contralateral metastases is well documented (2-4), (2) most metastatic lesions do not concentrate I^{131} in the presence of functioning thyroid tissue. However, once the thyroid has been removed tumor metastases may begin to concentrate I^{131} to a variable de-

TABLE I

Auth. & Yr.	*I^{131} Treat. Pt.*	*Thyroid-ectomy*	*Anti-thy. Drug*	*TSH*	*Pts. with Metastatic Disease*		
					Alive	*Dead*	*% Survival 5 yrs. or more*
Blahd—1963	45	42	1	44	18	11	41
Benua[18]—1962	59	28	19	7	—	—	57
Catz[19]—1959	44	33	0	44	10	8	17
Halnan[20]—1957	76	37(?)	14	0	56	20	9
Haynie[21]—1963	200	(?)	0	0	81	40	27(?)
Maloof[22]—1956	21	15	14	0	13	8	38

gree. Increased I^{131} uptake in thyroid cancer metastases after thyroidectomy was first recognized by Rawson in 1948 (5). The importance of thyroid ablation has been widely confirmed and it has now become an established prerequisite to the I^{131} therapy of thyroid cancer metastases. In addition as much as possible of the primary carcinoma should be removed to preserve the airway and to prevent or relieve compression of the esophagus.

Although the importance of total thyroidectomy in thyroid cancer is more or less generally accepted, the question of cervical dissection of lymph nodes is unsettled. Most thyroid surgeons are agreed that prophylactic lymph node dissection is not indicated. On the other hand, the proper surgical approach when cancerous lymph nodes are present is the subject of considerable controversy. The most widely accepted practice seems to be radical dissection of the cervical region on the involved side when there is positive evidence of lymph node involvement.

The second principle of management is the use of pituitary thyrotropic hormone stimulation to enhance I^{131} uptake in thyroid cancer metastases. The use of this agent to augment the I^{131} uptake of metastases was described by Trunnell and collaborators in 1948 (6). It is currently used in many clinics throughout the

TABLE II

SUMMARY OF DEATHS
METASTASES

Case	*Age*	*Histol.*	*Locat.*	*Uptake*	*Ablat.*	*Survival (yrs.) after I^{131}*	*Cause of Death*
T. T.	73	Adenoca.	Spine	No	No	2	Ca. pancreas
I. K.	45	Follicular	Cerv. Pulmo. Brain	Yes	No	2½	Thy. ca.
T. W.	62	Papillary	Cerv. Pulmo.	Yes	Yes	1½	Myocardial Infarct.
J. M.	62	Hürthle cell	Pulmo. Sternal	No	No	8	Thy. ca.
J. M.	54	Mixed Pap. & foll.	Cerv. Mediast.	Yes	No	3	Hemoperit. after liver biopsy
J. B.	58	Undiff.	Bone	No	No	2½	Thy. ca.
W. M.	58	Follicular	Cerv. Bone	No	No	3	Thy. ca.
F. G.	58	Hürthle cell	Bone Liver	No	No	6	Thy. ca.
C. D.	50	Undiff.	Generalized	No	No	1½	Thy. ca.
M. A.	38	Papillary	Cerv. Brain	Yes	No	1¼	Thy. ca.
E. P.	31	Follicular	Cerv. Brain	Yes	No	5	Thy. ca.

country and appears to be an effective adjunct in the I^{131} treatment of thyroid cancer metastases. This agent is not however without its complications. Nearly 25 per cent of the patients in the present series had some form of sensitivity reaction.

The prolonged administration of antithyroid drugs may also increase the concentration of I^{131} in thyroid cancer metastases (7,8). The use of these agents however is associated with serious disadvantages which include long periods of myxedema and drug reactions. For these reasons, with one exception, antithyroid drugs were not employed in this series.

The third principle of management is the administration of I^{131} in undivided cancerocidal doses of 100 to 150 mc. Smaller or divided doses have been shown to be less effective and to increase tumor radioresistance (7, 9, 10). On the other hand, larger therapeutic doses exceeding 200 mc have been associated with hematological complications and pulmonary fibrosis (10-13).

The use of desiccated thyroid extract in tolerance doses following I^{131} therapy is the fourth principle of management. Although thyroid extract has been employed as replacement therapy for many years, its possible therapeutic value in thyroid cancer was first described by Frantz in 1950 (14). Frantz and coworkers noted that tumor growth in a patient with thyroid cancer metastases was arrested following thyroid extract therapy. The rationale for the use of this agent in the treatment of thyroid cancer is based on experiental studies suggesting the promotion and dependency of thyroid cancer on endogenous pituitary thyrotropic hormone secretion and the ultimate suppression of thyrotropic hormone production by exogenous thyroid administration (15-17). Long term control of patients with thyroid cancer metastases, however, has been less rewarding than anticipated. Nevertheless the use of thyroid hormone in the management of thyroid cancer as an adjunctive agent would seem to be indicated.

An attempt has been made to appraise the results of I^{131} therapy in the postoperative treatment of thyroid cancer metastases in a number of the larger reported series, including our own. The results of this evaluation are tabulated in Table I. It is immediately apparent that a random and variable use of therapeutic modalities was employed. Furthermore, despite the therapeutic management employed, approximately one-third to one-half of the I^{131} treated patients who had metastases had died at the time these reports were written. Less than one-third of the patients had survived or had been followed for more than 5 years. All patients who were reported to be free of metastases and who received only supplementary I^{131} therapy after initial thyroid surgery were living and had been followed for varying intervals up to 9 years.

Because of the inconsistencies of management in the above reported series and the relatively benign biological course of this disease, a realistic appraisal of the efficacy of I^{131} treatment of thyroid cancer is extremely difficult. Despite the uncertainty of the benefits to be derived from treatment, therapeutic procrastination is not warranted. It is important to recognize that thyroid cancer may have a fatal outcome even though the majority of tumors are slow growing, highly differentiated cell types. In Hirabayashi and Lindsay's excellent study of 390 thyroid

cancer patients, 11 per cent of the patients with papillary carcinomas and 33 per cent of the patients with follicular carcinomas did succumb to their disease (2). It is essential therefore that once the diagnosis of thyroid cancer is established, vigorous and definitive patient management should be promptly instituted. Since differentiated thyroid cancer metastases are often successfully ablated with I^{131}, all patients who have such tumors should be considered candidates for I^{131} therapy. Demonstrable benefit has been derived from this therapy in as many as two-thirds of thyroid cancer patients.

SUMMARY

1. This report reviews the experience of the Radioisotope Service, Veterans Administration Center, Los Angeles, California, in the postoperative treatment of thyroid cancer with radioactive iodine since 1949. Forty-five patients have received therapeutic amounts of I^{131} and have been followed for more than one year.

2. Cancer metastases were localized by means of the mechanical scintiscanner after patients had received large tracer doses of I^{131} preceded by injections of thyrotropic hormone.

3. A consistent therapeutic regimen was followed involving four basic modalities of therapy: surgical thyroidectomy, thyrotropic hormone stimulation, cancerocidal doses of I^{131} and thyroid extract administration.

4. Twenty-nine patients in this series had proved metastatic lesions; 11 are dead, 18 are living, and 41 per cent have lived 5 or more years. All patients who were free of metastases after initial thyroid surgery are alive.

5. No complications from I^{131} therapy were observed. This is attributed to the conservative dosage regimen employed.

6. The results of the use of I^{131} in the postoperative treatment of thyroid cancer in other reported series have been reviewed.

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