CLEVELAND CLINIC QUARTERLY
Volume 38, July 1971
Copyright © 1971 by The Cleveland Clinic Foundation
Printed in U.S.A.

Carcinomas of the thyroid

GEORGE CRILE, JR., M.D.
Department of General Surgery

WILLIAM A. HAWK, M.D.
Division of Laboratory Medicine

IT is difficult to reconcile the various points of view about the treatment of cancer of the thyroid unless surgeons stop talking about cancer of the thyroid as an entity and start to break it down into its component parts. The problem is that cancer of the thyroid is not like cancer of the stomach or cancer of the colon, in which most of the tumors follow the same patterns of metastases and are of approximately the same degree of malignancy. Cancer of the thyroid is more like cancer of the skin, in which there is a spectrum of tumors that includes such different entities as the highly malignant melanoma, the moderately malignant squamous-cell carcinoma, and the relatively benign basal-cell carcinoma.

No one would make a general statement as to how all types of cancer of the skin should be treated, or advise prophylactic dissection of lymph nodes in the treatment of a basal-cell cancer of the skin. Yet in the treatment of certain cancers of the thyroid, such as the encapsulated angioinvasive carcinoma, although metastasis to regional nodes is nearly as rare as it is in basal-cell cancer, some surgeons advocate prophylactic dissection of lymph nodes. The trouble is that they are thinking of thyroid cancer as an entity.

One of the chief difficulties lies in the nomenclature of thyroid carcinomas and in the lack of understanding between surgeons and pathologists. It is unfortunate that thyroid cancers are classified as papillary, follicular, or undifferentiated, in accordance with their morphologic characteristics rather than in accordance with their biological behavior. Pathologists who classify tumors morphologically may, in their final diagnoses, fail to discriminate between a well-differentiated nonencapsulated tumor (that is predominantly follicular with only a few papillary areas), and a well-differentiated, encapsulated follicular carcinoma; they tend to call both types follicular carcinoma. To be meaningful, a classification must take into account not only the morphologic characteristics but also the biological behavior of the neoplasm. The classification of carcinomas listed below includes such considerations.[1]

I. Papillary carcinoma
   a. Usual papillary carcinoma, whether predominantly papillary or predominantly follicular or mixed.
   b. Microcarcinoma

II. Follicular carcinoma
    a. Encapsulated angioinvasive carcinoma
    b. Invasive carcinoma
III. Medullary (solid) carcinoma
IV. Anaplastic carcinoma
V. Lymphomas

Carcinomas of low malignancy

Papillary carcinomas. The commonest cancers of low malignancy are the papillary carcinomas, constituting 60 to 70 percent of all thyroid cancers. These tumors occur chiefly in young persons, often a few years after radiation therapy to the head, chest, or neck, given in childhood for some benign condition. Papillary carcinoma may be multicentric in the thyroid and tends to metastasize early to regional nodes. Distant metastasis is rare. Growth of the tumor tends to be readily suppressed by feeding of desiccated thyroid. In a patient between puberty and 45 years of age, papillary carcinoma, if treated by a proper operation and not cut into, implanted in the wound and thus disseminated, is associated with almost as good a 10- to 15-year life expectancy as the patient would have had if he had never had the cancer.[2]

In women the survival curves in regard to papillary carcinoma are superimposable, up to 15 years, on those of cancer-free women of the same age and race. In males or in patients of either sex who are very young (prepubertal) or beyond middle age, papillary carcinoma tends to be more invasive and to metastasize to lungs or bone. In females, between puberty and menopause, the disease tends to be almost benign in regard to distant metastasis. Fortunately, in both sexes the growth of tumors that occur in youth is generally suppressible by the feeding of desiccated thyroid.

The operations that one of us (G. C., Jr.) has recommended for the treatment of cervical metastases of papillary carcinoma of the thyroid are much more extensive than standard radical neck dissections, and entail removal (when involved) of the midline (Delphian) nodes, the superior mediastinal nodes, the paratracheal nodes, and the carotid and scalene nodes, as well as the nodes of the jugular chain that are routinely removed in conventional neck dissections. After making a high, wide, thyroidectomy incision, or in males, an incision parallel to the anterior border of the sternocleidomastoid muscle, the belly of the sternocleidomastoid muscle is freed from its attachments, and a band put around it. The muscle may then be elevated so that the nodes beneath it and posterior to it can be resected. In similar fashion the carotid artery and vagus nerve are mobilized and the jugular vein too, unless it is more convenient, on one side, to resect the vein. Often bilateral dissections are done through the same high transverse incision that is used for the thyroidectomy. The involved nodes are not removed individually but, insofar as possible, in groups within their envelopes of fatty and areolar tissue.

The lobe of the thyroid on the affected side is always removed completely together with the isthmus and part of the contralateral lobe. Only if there is gross bilateral involvement of thyroid or nodes is a true total thyroidectomy performed. It is often impossible to distinguish a parathyroid from an involved capsular node, and if all the thyroid is removed without regard for the parathyroids the incidence of tetany is prohibitively high.

In a personal series of 307 consecutive patients with papillary cancer of the thyroid, all but three of whom have been followed for from 5 to 27 years after operation, there has been no death from local recurrence or from cervical metastases of papillary carcinoma. Two patients, each of whom had undergone four operations before consultation at the Cleveland Clinic, had had cancer implanted in their necks and there was advancing local recurrence at the time they died from systemic metastasis, but neither in these patients, nor in any patients in this series was local recurrence the cause of death.

Prophylactic neck dissection was not performed unless cervical nodes were grossly involved at the time of exploration. Tumor has appeared in the nodes of only 4 percent of the patients who did not at the time of operation have gross evidence of nodal involvement. In each case the cancer was permanently controlled and the patient has remained well for from 8 to 19 years after a small second operation for removal of the affected group of nodes.

Unless the recurrent laryngeal nerve was already paralyzed by invasion of cancer it was usually possible to preserve the nerve. Even when it was densely adherent to the primary tumor or to metastases in paratracheal nodes it was possible to tease the tumor off the nerve. There have been no local recurrences after this procedure. Although the trachea was never sacrificed there were no recurrences in the thyroid area.

Total thyroidectomy was performed in 9 percent of the patients, yet there was only one instance of recurrence of cancer in the residual thyroid (0.3 percent). It is now more than 20 years since the second operation and the patient appears to be free of cancer. Unilateral vocal cord paralysis (including that in patients who had incurred it preoperatively) occurred in 11 percent of the patients, and permanent tetany in 2 percent. In only 4 percent of the patients were the sternocleidomastoid muscles sacrificed, and in only 2 percent were the eleventh nerves resected. In only one operation was it necessary to perform a thoracotomy to gain access to mediastinal nodes. Thus, in the majority of patients the only morbidity of disfiguration was a thyroidectomy scar.

Life-table analysis of 140 consecutive patients operated on from 5 to 25 years before showed that in the 75 female patients upon whom the first definitive operation was performed by one of us (G. C., Jr.) the rate of survival up to 15 years was as high as would have been expected in a group of the same sex, race, and age who had not had papillary carcinoma. Beyond 15 years the number of patients is too small to be of statistical significance,

but clinically only one patient (and she had been operated on several times elsewhere before being treated at Cleveland Clinic) died of thyroid cancer.

In the entire series of 307 patients with papillary cancer of the thyroid the 5-year survival rate was 94 percent. Seventy-six of the patients, however, had been admitted with recurrences after a thyroid operation elsewhere. Fourteen percent of these ultimately died of cancer as compared to only 5 of 231 (2 percent) of those upon whom one of us (G. C., Jr.) performed the first definitive operation on the thyroid. An additional 1 percent of the patients in this group are living with uncontrolled cancer.

Since 70 percent of the 307 patients had involvement of nodes, and 4 percent had preoperative pulmonary metastases, it is apparent that the patients in this series were not selected.

In recent years the results of treatment have been better than in the earlier period. Ninety patients with previously untreated papillary carcinoma were treated in the 5-year period 1960 through 1964. Operations were even less radical than in the earlier period, yet no patient has died of cancer and only one has progressing disease. Since in our entire experience we have never seen a patient who went for 5 years without recurrence and then had a fatal recurrence of the disease, it is safe to say that, short as the follow-up is, it indicates that the ultimate mortality rate from cancer will be less than the postoperative mortality that would be incurred by routinely performing total thyroidectomies and radical neck dissections.

Since the growth of many papillary carcinomas can be suppressed by feeding desiccated thyroid, it is important to prescribe full suppressive doses for the duration of the patients' lives. The incidence of recurrence after operations has been reduced by more than 50 percent since 3 gr of Armour's brand of desiccated thyroid or its equivalent has been given daily. In many patients with extensive metastasis the tumor has either regressed or stopped growing. After the growth of a tumor has been suppressed there has been little or no tendency for it to escape from control. Thirty-two patients, with distant metastases mainly to the lungs, have been treated by desiccated thyroid and have been followed for from 5 to 27 years. In 18 of them the metastases either have shrunk or remained unchanged. In 14 patients similarly treated the metastases did not respond. The best responses occurred in patients who gave a history of having had radiation in infancy or childhood for benign disease of the head and neck, and in the younger patients, especially if they were female.

Microcarcinomas. A group of the microcarcinomas of the thyroid have been called "nonencapsulated sclerosing tumors." [3, 4] These tumors are from 1 to 10 mm in diameter and are present in about 3 percent of all thyroids examined at routine autopsy.[5] The tumors appear to be similar to the microcarcinomas of the prostate that are present so frequently in men more than 50 years of age. When a microcarcinoma is removed in the course of a thyroidectomy done for another reason, it should be considered as an inci-

dental finding that requires no additional surgical treatment. We have not seen metastases from such tumors. On the other hand, an occult microfocus of true papillary carcinoma may give rise to extensive metastases in cervical nodes.[6] In the latter case the malignant potential is expressed in metastases long before the tumor is clinically evident; whereas in the former case, if no metastases are seen at the time of operation it is unlikely that they subsequently will develop.

Encapsulated angioinvasive carcinomas. Encapsulated angioinvasive carcinomas are almost never multicentric and seldom metastasize to regional nodes.[7] All that is required to give the patient with an encapsulated follicular carcinoma the best possible prospect of cure is to remove completely the affected lobe. Attempts to perform total thyroidectomy or node dissection are useless and merely increase morbidity. It is important, however, to remove the tumor with the capsule intact, preferably by lobectomy, so that tumor tissue does not become implanted in the wound and recur. When removal is complete the prognosis in these patients is almost as good as that in those of similar age and sex with papillary cancer.

The growth of encapsulated follicular cancers is rarely controlled by desiccated-thyroid feeding as is that of the papillary variety, but ^{131}I may be effective. The prognosis becomes more grave when the patients are elderly men. The average age of patients who were well 5 or more years after operations for encapsulated angioinvasive cancers was 44 years, whereas the average age of those who died of the cancers was 62 years. No patients less than 54 years of age died of this type of cancer. The prognosis was worse in men than in women: 33 percent of the men died of cancer, and 8 percent of the women.

Carcinomas of intermediate malignancy

Invasive follicular carcinoma. Although the invasive follicular carcinoma is so uniformly fatal that it hardly can be called a tumor of moderate malignancy, it grows so slowly that more than half of our patients who died of it had survived for more than 5 years after operation. Whether the encapsulated angioinvasive carcinoma is a chronologically early phase of the invasive follicular adenocarcinoma is difficult to say, but we doubt that it is. Analysis of age, sex, and duration of history suggests that each of the follicular types of thyroid tumors is an entity, and does not originate in another type. Invasive follicular carcinomas are tumors of high malignancy invading blood vessels and surrounding tissues, but their rate of growth may be relatively slow.

Between the years 1946 and 1958 at the Cleveland Clinic, diagnosis of atypical adenoma was made 15 times, that of encapsulated follicular carcinoma 38 times, and that of invasive follicular carcinoma 15 times. The characteristics of the tumor of each group are summarized in *Table 1.*

There is little about the duration of the goiters before operation, the age and sex of the patients, the relative size of the tumors in the different groups

Table 1.—Comparison of histories and physical findings in various types of thyroid tumors

		Type of follicular carcinoma	
	Atypical adenoma (15 patients)	Encapsulated (38 patients)	Invasive (15 patients)
Duration, preoperative (median)	1.5 yr	3 yr	3 yr
Sex, male	44%	32%	20%
Age, average	45 yr	47 yr	59 yr
Size of neoplasm (large)	22%	68%	57%
Follow-up data			
Postoperative metastasis	0%	11%	73%
To nodes	0%	3%	13%
Systemic	0%	8%	60%
Follow-up, 5 to 25 yr			
Living free of cancer	67%	70%	0%
Dead of cancer	0%	16%	86%
Living with recurrence	0%	3%	0%
Dead of other causes	5%	8%	7%
Untraced after 4 yr	28%	3%	7%

or their tendencies to metastasize to nodes or systemically to suggest that with the passing of time the tumors progress from one type to another. Although the invasive follicular carcinoma may grow slowly and patients may live with metastases for many years, our experience has shown it to be ultimately fatal, usually as a result of systemic metastasis. Angioinvasion is a prominent histologic feature of these tumors, and they seem to metastasize through the bloodstream before the diagnosis is made. Operations are mainly palliative. If lymph nodes are involved they should be removed along with the primary tumor as simply as possible so as not to add the morbidity of a radical operation to the burdens of a patient already having distant metastases.

Medullary (solid) carcinoma. The term medullary carcinoma is a misnomer because the tumor is not soft but stony hard.[8] *Solid carcinoma* would be a better name, or *amyloid-forming cancer,* because amyloid is almost always present. This tumor is undifferentiated in structure but its cells are regular and not anaplastic. It produces an amyloid stroma that can be shown by special stains. Medullary carcinoma metastasizes to lymph nodes and through the bloodstream, is locally invasive, and should be treated by radical removal of the affected part of the thyroid and the involved nodal groups Fewer than half of the patients treated are permanently cured, but the tumor grows slowly and many patients live for 5 or more years after treatment. Sometimes the metastases penetrate the capsules of the nodes and

invade the surrounding tissues, making it necessary to do a formal, block-dissection type of lymphadenectomy. The 5-year survival rate in 21 patients having medullary carcinoma was 54 percent (11 patients); but when followed longer, still more ultimately died of the disease or are living with incurable recurrences. Of those who died of medullary carcinoma, four lived for from 7 to 27 years after operation.

Lymphomas. Lymphomas of the thyroid respond well to radiation therapy. In recent years, because struma lymphomatosa responds well to thyroid feeding and because many lymphosarcomas arise in glands that show changes of struma lymphomatosa, we have treated all patients with lymphomas of the thyroids by a combination of radiation and suppressive doses of desiccated thyroid (3 gr daily). Whether or not the desiccated thyroid contributes to the improved results, about half of the patients treated in this way have remained well.[9] Operation is not necessary, because the lymphomas are so radiosensitive that persistence or local recurrence has been no problem.

Highly malignant tumors

Anaplastic carcinoma. Anaplastic carcinomas of the thyroid are among the most malignant of all tumors. Their course, from onset to death, is usually less than 1 year and often as short as 4 months. Anaplastic carcinomas invade locally and metastasize to regional nodes and to lungs. Most of them are inoperable when first diagnosed. If attempts are made to remove them, fungating recurrences into the wound are common. Needle biopsy to establish the diagnosis, followed by radiation therapy is the most effective way of controlling the local lesion until the patient dies of metastases.

Only one of 24 patients with anaplastic carcinomas has remained well after operation. The tumor was considered inoperable, but part of it was removed and the rest treated by what is now thought to have been inadequate roentgenotherapy. For unexplained reasons the patient has remained well for more than 10 years.

Summary

Those who know the natural histories of the various types of cancer of the thyroid recognize that their variability makes it impossible to define any single method of treatment applicable to all types. If biological predeterminism exists, it is most apparent in these types of cancer. The highly malignant tumors are rarely cured no matter how early or extensive the operations, and the ones of low malignancy may be cured by simple operations even after long delay. This does not condone either delay or inadequate surgery, but it does mean that in case of doubt there is time for a few months' trial of medical treatment of benign-appearing nodules. Classic radical operations rarely are required in the treatment of tumors of low malignancy, and rarely are of value in malignancies of the highest grade.

References

1. Crile, G., Jr.; Hazard, J. B., and Dinsmore, R. S.: Carcinoma of thyroid gland, with special reference to clinico-pathologic classification. J. Clin. Endocrinol. **8:** 762–765, 1948.

2. Crile, G., Jr.: Survival of patients with papillary carcinoma of the thyroid after conservative operations. Amer. J. Surg. **108:** 862–866, 1964.

3. Hazard, J. B.: Small papillary carcinoma of the thyroid; a study with special reference to so-called nonencapsulated sclerosing tumor. Lab. Invest. **9:** 86–97, 1960.

4. Hazard, J. B.; Crile, G., Jr., and Dempsey, W. S.: Nonencapsulated sclerosing tumors of thyroid. J. Clin. Endocrinol. **9:** 1216–1231, 1949.

5. Mortenson, J. D.; Bennett, W. A., and Woolner, L. B.: Incidence of carcinoma in thyroid glands removed at 1000 consecutive routine necropsies. Surg. Forum (1954), **5:** 659–663, 1955.

6. Hazard, J. B., and Kenyon, R.: Encapsulated angioinvasive carcinoma (angioinvasive adenoma) of thyroid gland. Amer. J. Clin. Path. **24:** 755–766, 1954.

7. Hazard, J. B., and Kenyon, R.: Atypical adenoma of thyroid. A.M.A. Arch. Path. **58:** 554–563, 1954.

8. Hazard, J. B.; Hawk, W. A., and Crile, G., Jr.: Medullary (solid) carcinoma of thyroid—a clinicopathologic entity. J. Clin. Endocrinol. **19:** 152–161, 1959.

9. Crile, G., Jr.: Lymphosarcoma and reticulum cell sarcoma of the thyroid. Surg. Gynec. Obstet. **116:** 449–450, 1963.