MALIGNANT DISEASES OF THE THYROID GLAND *

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Within recent years better understanding of malignant disease has brought the realization that the histologic morphology of the tissue is not always a criterion by which such growths may be differentiated or classified, and does not always indicate what may be their clinical course. This is particularly true of the malignant tumors of the thyroid gland, there being certain points in their origin, development, structure and growth characteristics which are just as important as their microscopic morphology and must be taken into consideration in order to distinguish the different types of growth and to understand the reasons for their peculiar variations. Therapeutic procedures should be planned on the basis of the growth characteristics of each different type of neoplasm.

DEVELOPMENT AND STRUCTURE

The main body of the thyroid gland originates from an anlage in the primitive pharynx as an outgrowth of epithelial cells on its dorsal surface. Two lateral anlages also appear but are unimportant except as they may become aberrant thyroids. The anlage of the thyroid enlarges by progressive hyperplasia of the epithelial cells into a glandular arrangement to form the individually peculiar terminal compartments, or acini, which constitute the functioning part of the gland. No excretory ducts are formed. From the mesothelial bed of the primitive thyroid a fibro-elastic capsule and stroma develop to form septa which divide and subdivide the organ into lobes, lobules and a large number of terminal acinar vesicles. The glandular epithelium of the acini lies directly upon the connective tissue stroma, there being no true basement membrane.

The concentric hyperplastic development of the glandular structures of the thyroid causes the oldest cells to lie in the center of the lobules and therefore not infrequently a superfluity of closely packed cells may be amassed within certain lobules, thus forming a nodule or tumor composed of modified glandular structures, and this is an adenoma. Because of their embryonic character the adenomas of the thyroid, as is true of similar tumors in glandular organs, may undergo many changes of function, growth or degeneration.

The thyroid gland is abundantly supplied with blood vessels. The large bilateral superior thyroid arteries to the lateral lobes

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are branches of the external carotids, and the paired inferior arteries come from the subclavians. These vessels terminate as a rich plexus of arterioles and capillaries within the connective tissue which surrounds the acini so that the epithelial cells are separated from the circulating blood only by the thin endothelial lining of the vessels. Veins and venous sinuses also are very numerous in the gland, and empty into a large plexus beneath the thyroid capsule from which the blood escapes into the thyroid veins. The bilateral superior and middle veins empty directly into the internal jugulars and the inferior veins which drain the deeper parts of the gland empty into the left innominate vein. Thus the venous communication is directly to the superior vena cava and thence to the heart.

The lymphatic vessels follow the course of the blood vessels, most of the main stems passing to the superior deep cervical lymph nodes. The lymph vessels of the isthmus and adjacent parts of the lateral lobes also drain to the anterior surface of the trachea and there is a direct communication from the capsular lymphatic plexus to the neighboring structures.

Clinical Aspects of Development and Structures

This review of the development and anatomic structure of the thyroid is important from the clinical standpoint for the following reasons, which will be discussed later in connection with the different types of malignant tumors.

(1) Thyroid tissue consists largely of glandular epithelial cells. Hence, on the basis of the laws of probability, epithelial neoplasms or carcinomas should occur with proportionately greater frequency than the mesothelial neoplasms or sarcomas.

(2) The character of the concentric and hyperplastic development of the thyroid glandular structure predisposes to the production of localized adenomatous tumors which may undergo many kinds of degenerative changes, including malignancy, because of their inherent embryonic stimulus to hyperplastic growth.

(3) The acini of the thyroid have no basement membrane, and because their cells lie in such close proximity to the vessels, they may readily penetrate into the circulating blood and may be quickly distributed to different parts of the body as metastases.

(4) The lymphatic distribution and drainage of the thyroid cause the deeper cervical lymph nodes to be involved by certain types of malignant processes fairly early, frequently before they

can be determined clinically, and the abundant infracapsular plexus permits direct extension to adjacent structures, particularly to the trachea.

Malignant Adenomas

The term malignant adenoma was suggested by Dr. Allen Graham to designate those carcinomas of the thyroid which originate in pre-existing adenomas, exclusive of the papillary cyst adenomas. This group constitutes about 90 per cent of all malignant lesions of the gland, and at least 90 per cent of the epithelial thyroid malignancies can be proved to have originated in pre-existing adenomas.

When a pre-existing benign adenoma of the thyroid undergoes malignant change, the growth may present many combinations of morphologic transitions such as fetal, intermediate or mixed colloid adenomas, and any one, two or all of these transitions may be found in a single tumor; in fact, it is seldom that only one type is found. Therefore, adenocarcinoma, medullary carcinoma, scirrhous carcinoma, papillary carcinoma or carcinoma resembbling sarcoma or any combination of these forms may occur in a malignant adenoma, or may be found in thrombi within the vessels. Because of this variability of structure, it is difficult to make a diagnosis of the type of growth on the basis of morphology alone; therefore, before the true character of the neoplasm can be established it is necessary to study the type of structure of the pre-existing adenoma, its duration and rate of growth, the character and reaction of the stroma, and especially the evidence of invasion of the blood vessels.

The difficulty which attends the diagnosis of these neoplasms and the chance of making an error, if only the histologic morphology of the tissue is taken into consideration to the exclusion of the other characteristics, is illustrated by the following reviews. Over a period of about twenty years, up to 1932, there were 330 cases at the Cleveland Clinic which were thought to be malignant thyroid neoplasms. Of these, 186 were diagnosed as malignant adenomas because of their histologic morphology by four or five different pathologists. When they were reviewed a few years ago by Dr. Allen Graham it was necessary to discard 108 cases as not malignant, leaving only 78 cases of true malignant adenoma. As shown by Table 1, this elimination of so many cases was probably correct because of the 108 cases eliminated, only 4 patients are dead and all from some intercurrent disease, while of the 78 patients finally proved to have malignant adenoma, 46 are dead of malignant disease. Treatment evidently was not a factor in the low mortality in the group of cases dis-

TABLE I
MALIGNANT THYROIDS
Series of Cleveland Clinic Foundation to 1931

	Total	Traced	Living	Dead	Dead Per cent
No operation	48	36	5	31	86
Operation—no pathology	15	10	1	9	90
Parastruma	1	1	0	1	100
Epidermoid	1	1	0	1	100
Myxosarcoma	1	1	0	1	100
Lymphosarcoma	11	10	2	8	80
Spindle cell	5	4	1	3	75
Sarcoma-carcinoma	5	5	1	4	80
Carcinoma—unclassified	16	15	2	13	87
Scirrhous	6	6	0	6	100
Papillary	15	15	9	6	40
Malignant adenoma	78	71	25	46	65
Adenocarcinoma not in adenoma	17	16	16	0	0
Multiple types	3	3	3	0	0
	222	194	65	129	
Adenomas discarded by Dr. Graham	108	86	82	4	

carded, because but few of these patients were irradiated, while the 78 patients with true malignant adenoma had both operation and irradiation in most instances.

This discussion illustrates the error which may be made in considering a thyroid tumor to be malignant when it is not malignant if only morphology of the tissue is the criterion on which the diagnosis is made.

An error in the opposite direction is illustrated by the statement of Wilson* who said:

"In the Mayo Clinic, of ninety-seven patients operated on who have died of the disease or who when last heard from were known to have undoubted recurrences, usually metastatic, there were fifty whose clinical histories before the first operation contained no suggestion of malignancy. The glands removed at operation from all of the ninety-seven were examined pathologically, yet at the first operation twenty-three of these were passed by the pathologist without suspicion of malignancy."

This quotation suggests that a considerable number of malignant thyroid growths may escape the observation of the pathologist if only the morphology of tissue is the basis for the diagnosis.

* Wilson, L. B. Malignant tumors of thyroid. *Ann. Surg., 1921, 74, 129.*

Of course, these errors were made in a period years past and since that time the accuracy of diagnosis has improved considerably, but there still exists the possibility of error in either direction.

Malignant adenomas are primarily encapsulated by the connective tissue which surrounds the pre-existing adenoma, but since the neoplastic epithelial cells lie in direct contact with numerous blood vessels in and around the tumor, these will be filled with neoplastic cells in almost every instance by the gradual expansion and invasion of the growth. They metastasize by way of the blood stream even though the growth may not have broken through its own capsule. This manifestation in the blood vessels is characteristic and distinguishes malignant adenomas no matter what the histologic structure may be.

Malignant adenomas are found in patients past middle age who have had a goiter for a long time which has begun to enlarge suddenly. The progress of the enlargement may be relatively slow, even with occasional regressions unrelated to any physiologic process. A hard tumor is found in the thyroid, usually unilaterally, but a smooth, firm, general enlargement sometimes occurs depending somewhat upon the duration and the rate of growth.

About half of the cases can be diagnosed clinically, the others being discovered by the pathologist after removal of thyroid tissue for goiters, supposedly benign.

Adenocarcinoma Not In Adenoma

Occasionally a peculiar lesion is encountered in the thyroid which may be called "adenocarcinoma not originating in adenoma." This lesion has some characteristics of carcinoma but is of very low grade malignancy. It originates in acinar epithelium, remains quite localized, is not encapsulated and no mitotic figures are demonstrable. It might be called "carcinomatoid" and is only of interest to pathologists, as it gives no clinical signs or symptoms and is not fatal.

Scirrhous Carcinoma

The sort of stimulus to neoplastic growth which causes a scirrhous carcinoma to develop in the thyroid gland produces the same histologic changes in this organ as are found in scirrhous carcinomas in other structures. Fibrous tissue predominates and the neoplastic epithelial cells occur in masses of strands as if the malignant reaction were held in restraint so that glandular arrangement cannot take place. The growths are not encapsulated and, therefore, progressively invade the surrounding tissues

which they destroy by infiltration through the lymphatics and compress the blood vessels in fibrous tissue. It cannot be determined that scirrhous carcinomas of the thyroid begin in adenomas, though there is no reason why they should not do so. As previously mentioned, a malignant adenoma may present localized areas of scirrhous formation along with other types of malignant changes.

These neoplasms seldom are discovered early by clinical examination but in the late stages and after recurrence, they are extremely hard and fixed and the invaded lymph nodes are sometimes palpably enlarged. They grow very slowly but progressively and are of low grade malignancy from the standpoint of rapidity of growth but destroy life by local constriction even before metastases develop.

Papillary Carcinomas

Adenomas of the thyroid, like adenomas in other organs, may also undergo cystic degeneration and in turn these cystic adenomas may become malignant. When this occurs, multiple finger-like processes are formed in the walls of the acini in the arrangement which is characteristic of papillary carcinoma. The growth is at first confined within its capsule, but gradually the neoplastic columnar cells of the papillæ invade and break through the thin stroma at the base of the acini in which they develop, and thus extend to adjacent acini and the lymphatics. They do not invade blood vessels, because of the avascularity of the cysts in which they originate, and because they are confined and primarily encapsulated. As would be expected from the nature of their origin and the character of their growth, these neoplasms are of a comparatively low grade of malignancy. As indicated previously, some malignant adenomas may contain areas with papilliferous formation.

Clinically, the papillary carcinomas are usually unilateral, rather firm, nodular tumors which grow slowly but sometimes become very large. As the tumor progresses the structures about it are infiltrated and compressed and the skin may become red and edematous with eventual breakdown and ulceration.

Carcinoma-Sarcoma

A rare tumor of mixed carcinoma and sarcoma occurs in the thyroid. The epithelial structures show changes characteristic of carcinoma and the abundant stroma presents the appearance of fibrosarcoma. There are numerous mitotic cells arranged atypically in both epithelial and mesothelial elements. Theoretically, this type of tumor may begin as carcinoma which, because of some

peculiarity of growth or physiologic reaction, causes neoplastic stimulus to the stroma so that it also becomes malignant. However, there is little proof of the theory. Usually this tumor is erroneously considered to be carcinoma, or is occasionally classified as fibrosarcoma, depending upon the type of cells which are found. There is no possibility of differentiating this growth clinically; it must be distinguished by microscopic examination. It appears as a hard, rapidly extending mass in a lobe of the thyroid.

Sarcoma

True sarcomas of the thyroid are rare in spite of the fact that the literature contains many reports of such cases. If the relative proportion of mesothelial elements to the epithelial structures is taken into consideration, it must be realized that sarcomas should be comparatively uncommon. The usual mistake is to call a very cellular, malignant adenoma a sarcoma. However, sarcomas originate in the mesoblastic elements of the stroma and a study of different regions will usually distinguish them from malignant adenomas by the absence of epithelial cells in the tumor.

The most common type of sarcoma of the thyroid is lymphosarcoma and it has the same characteristics as similar neoplasms in any other organ. The growth is highly malignant and quickly infiltrates the thyroid and adjacent structures. Clinically, patients with lymphosarcoma give a short history of very rapid growth and usually the entire organ is firm and fixed and the patient complains bitterly of choking. The rapid infiltration of the gland and adjacent structures, particularly extension into the upper mediastinum, usually destroys the host before distant metastases become evident.

Fibrosarcomas, or spindle cell sarcomas, originating in the stroma also are seen occasionally, but they are very rare. They grow more slowly than lymphosarcomas and clinically are indistinguishable from other tumors.

Metastases

Every patient for whom an operation on the thyroid is contemplated should first have a roentgenographic examination of the chest. Such an examination may reveal unsuspected benign intrathoracic or substernal thyroids or metastases from a malignant goiter that may or may not be discovered by clinical examination. Pulmonary metastases usually are seen as multiple tumors or as a shower of small nodules of various sizes, particu-

larly in the bases and they gradually enlarge and coalesce as the disease progresses.

Metastases may also occur in bones, especially in long bones, but also to some extent throughout the rest of the skeletal system. When an otherwise unexplainable, but obviously malignant, lesion is discovered in a bone by roentgen examination, the thyroid should be suspected as the primary source of a neoplasm, even though there may be no other evidence of disease of this organ.

Occasionally metastases occur in soft tissues as slowly growing tumors without any definite clinical characteristics and only microscopic examination will disclose their thyroid origin.

Distant metastases are almost always from malignant adenomas. They develop from neoplastic cells which have invaded blood vessels, become detached and are distributed through the circulation and form neoplastic emboli in various locations. The other types do not often produce distant metastases because these growths extend through the lymphatics. Because metastases have the histologic morphology and probable function of the parent neoplasm which may closely resemble normal thyroid tissue, they have been mistaken for aberrant thyroid rests.

When metastases are present, operations upon the thyroid usually are not indicated. However, even when metastases are present or when the growth has invaded the structure contiguous to the thyroid, it may be necessary to do a decompression operation to remove some of the growth, or to perform a tracheotomy in order to relieve respiratory difficulty. Roentgen irradiation should be administered following such palliative operations to inoperable neoplasms and to metastases, some of which may thus be held in check for some time.

Treatment of Malignant Goitre and its Results

The procedure for the treatment of malignant tumor of the thyroid should be based upon its known growth characteristics. Only about 50 per cent of cases can be diagnosed clinically before operation; therefore, half of them have had some sort of operation and are only discovered by the pathologist.

When a definite diagnosis of malignant goiter can be made by clinical examination the condition usually is inoperable from the standpoint of curability because of the probability of invasion of the vessels in the tissues which cannot be removed. Sometimes, however, palliative operations are advisable and at least a biopsy should be done to determine the type of neoplasm in order to

carry out a logical therapeutic procedure. In any case, in operating on a patient with malignancy of the thyroid, the surgeon should always have in mind the possibility of causing embolic metastases by harsh manipulation.

In our series of 48 cases of different types of malignant disease of the thyroid which were considered to be inoperable, 36 patients have been traced and 5 are still alive; the longest survival in a proved case has been ten years. This patient received roentgen irradiation following a postoperative recurrence of a malignant adenoma. The average length of life of the patients living has been forty-one months and of the dead was twenty-seven months.

When a malignant adenoma is discovered, treatment is begun with roentgen irradiation regardless of whether or not the surgeon believes he has removed all of the growth, because there is always the possibility of invasion of the blood vessels outside the field of operation. Since about 90 per cent of the malignant neoplasms of the thyroid are malignant adenomas, the blood vessels are probably invaded and so interstitial irradiation is seldom employed at the time of operation. This treatment may be used with less hazard after the neoplasm has been rendered dormant by roentgen irradiation, or later, if it is obvious that the roentgen treatment has not been entirely efficacious. Most of the malignant adenomas are quite sensitive to irradiation not only because the neoplastic cells in the tumor and those in the vessels are radiosensitive, but also, no doubt, because of the secondary fibrosing and obliterating effect upon the capillaries which prohibits further extension. Roentgen irradiation alone has been quite efficacious in our experience.

Of 78 cases of proved malignant adenoma in our series, 32 per cent of the patients are alive, the longest for seventeen years and the average for six and one-fourth years.

The *adenocarcinomas not originating in adenomas* are so localized and of such low grade malignancy that none of them require irradiation. Of 17 patients with this carcinomatoid growth, 16 of whom have been traced, all are well.

Scirrhous carcinomas may be recognized at operation as a very hard growth. It is almost a certainty that such a growth has invaded the lymphatics and other structures contiguous to the thyroid and has extended widely through the lymphatics, and for this reason cannot be entirely excised. Scirrhous carcinomata are highly resistant to irradiation, and since they destroy life before distant metastases develop, they should have interstitial irradiation followed by roentgen irradiation, although even with

this procedure the prognosis is very bad. Of the 6 patients we have seen, all of them are dead; the patient who survived for the longest period after operation lived for only six months.

Occasionally a papillary carcinoma may be so localized and encapsulated that it may be excised completely, but when there is clinical, gross or microscopic evidence or a suspicion that the growth has extended through the lymphatics into the surrounding thyroid gland structure or adjacent tissues outside the field of operation, irradiation should be administered. These growths do not invade blood vessels early as do malignant adenomas, and therefore the application of interstitial irradiation is not so hazardous. If and when this type of growth is recognized at operation, interstitial irradiation may be applied at once to be followed later by roentgen treatment. If the neoplasm is discovered subsequent to operation, it is advisable to depend upon roentgen irradiation unless growth continues, and then a second more extensive operation and implantation of radium in one form or another may be necessary. Some of these growths yield to irradiation. Papillary carcinoma has been found in 15 of our cases. Nine patients are alive, one ten and three-fourths years and the average for six years.

The carcinoma-sarcomas and the spindle cell sarcomas are also highly malignant and radioresistant, and usually only recognizable by the pathologist. Of 5 cases of carcinoma-sarcoma at the Cleveland Clinic, the longest survival period was eleven months and all 5 patients with spindle cell sarcoma died within five months.

The lymphosarcomas of the thyroid are more undifferentiated and therefore more radiosensitive. Operation alone seldom can effect a cure and it is advisable to employ both interstitial and roentgen irradiation. Eleven lymphosarcomas have been encountered in our series; 9 of the patients were traced, 1 died immediately postoperatively and of the 7 known dead, the longest survival period was seven months. One patient is still alive after ten years and another has been well for almost two years; these patients had röentgen therapy following operation.

Technique of Irradiation

The technique of applying radium irradiation to malignant goiters should be planned according to the type and size of growth. The more resistant neoplasms should be given as great an intensity as is possible. Either gold radon seeds or needles may be employed as indicated, the former preferably for the infiltrating growths and the latter for those larger tumors. The

container should be placed to irradiate the trachea without damaging it. As has been pointed out, it is better not to thrust needles into malignant adenomatous tissue, and so roentgen irradiation should be employed primarily to be followed by interstitial irradiation, if necessary.

In administering roentgen irradiation we have been using 200 kv. and heavy filtration (0.5 to 0.75 mm. Cu) giving an effective wave length of about 0.15Å.

The skin tolerance dose is considered to be 800 roentgens when back-scattering is included.

The fields are planned to crossfire anteriorly and posteriorly the thyroid area, the supraclavicular region and the upper mediastinum regardless of whether or not the growth is considered to be bilateral. The roentgen beam is directed to the midline from each portal and includes the trachea and thyroid isthmus which should receive a therapeutic dose on account of the probability of neoplastic invasion. Inflammation within the trachea may ensue at the height of the irradiation reaction, but usually can be relieved by intratracheal injections of oil, although in some patients who have had extensive invasion necessitating large doses of radiation, a tracheotomy may be necessary. Ulceration in the trachea has been produced in a few instances but this has not been a serious complication and the temporary discomfort is better than death from the disease.

The cases of malignant thyroid neoplasms which have been discussed are from the surgical services of Dr. George W. Crile, Dr. William E. Lower, Dr. Thomas E. Jones, and Dr. Robert S. Dinsmore of the Cleveland Clinic Foundation. All of the cases have been studied pathologically by Dr. Allen Graham. Of the total of 257 proved cases of malignant disease of the thyroid seen before 1932, 222 are included in this report; the others are too recent to be of interest. One hundred and eight additional cases, at first considered to be malignant on the basis of their histologic morphology, have been discarded after more detailed study by Dr. Graham because of insufficient evidence of malignancy. Unfortunately, some of these discarded cases have been included in previous reports.