CANCER OF THE THYROID GLAND

HOWARD M. CLUTE, M.D., AND SHIELDS WARREN, M.D.

(From the Lahey Clinic and the Pathology Laboratories of the New England Deaconess and the New England Baptist Hospitals, and the Department of Pathology, Harvard Medical School)

Cancer of the thyroid gland occurs in many different clinical and histologic forms, and its variations have resulted in the use of a widely varying nomenclature. In 1928 Clute and Smith (1) attempted to correlate the histologic findings in thyroid malignancy with the clinical course of the disease. At that time Dr. Lawrence Smith, working with material then available, suggested the following histologic grouping: (1) malignant adenomas, including papillary adenoma and the fetal adenoma; (2) squamous-cell carcinoma; (3) giant-cell carcinoma; (4) small-cell carcinoma. He found that, although there were minor variations in the histologic picture in any one group, there was a marked uniformity in the ultimate clinical course of the cases in the group.

It is the purpose of the present writers to carry this study further, to attempt a still simpler clinical classification of thyroid malignancy based on the histologic findings, and to apply these findings to the prognosis and treatment of the individual case. Furthermore, we wish to bring to date all information on the cases previously studied and to add to them the further cases of thyroid malignancy which have occurred in the Clinic in the three years—1927, 1928, and 1929—which have elapsed since the earlier study was completed.

MATERIAL

The present paper includes all cases of thyroid malignancy which have been operated upon or which have come to autopsy in the Lahey Clinic from 1916 to January 1, 1930. It covers, therefore, all the cases previously studied and reported by Clute and Smith with the exception of 12 inoperable cases from which we have no microscopic specimens.

To the cases which were included in the previous study of thyroid malignancy and the new cases of thyroid cancer which have occurred since January 1927, we have added 34 other cases.

1 Read before the New York Pathological Society at the Academy of Medicine, March 26, 1931.
obtained by a review of the slides from all the adenomata which were operated on during the years 1923 to 1927 inclusive. In this group were 1,114 cases, 34 of which were found to show evidence of invasion of the blood vessels by masses of epithelial tissue. Prior to 1927 blood vessel invasion was only occasionally utilized as a criterion of probable malignancy. These 34 cases, as is true of the 61 similar cases seen since 1927, showed no other evidence grossly or microscopically of malignancy. We feel, nevertheless, that they must be regarded as at least potentially malignant since 6 of the 95 cases have run a course characteristic of thyroid malignancy.

**Incidence of Thyroid Malignancy**

In the Lahey Clinic, during the years 1916 to January 1, 1930, 6,535 patients have been operated upon for disease of the thyroid gland. Of this number of cases, 187 we class as malignant, which gives an incidence of malignancy in this material of 2.86 per cent. We recognize that a large portion of the 187 cases is made up of the adenomata with blood vessel invasion and of papillary cystadeno-mata, namely 133 cases. Nevertheless, since these are to be considered as potentially malignant because of their invasion of blood vessels and because of their relatively undifferentiated histologic appearance, and because some, impossible to differentiate from others in the group, produce metastases and cause death, we feel they should be classed as cancers of the thyroid. Of this group of 187, all save 7 have been followed to January 1, 1931; of the 7 who are “lost,” 6 are in the relatively benign group of adenoma with blood vessel invasion.

**Grouping of the Cases**

In order to obtain a useful clinical interpretation of the histologic picture of thyroid malignancy, it seems to us that the best analysis can very possibly be made on the basis of the clinical degree of malignancy. For this purpose, therefore, we have established three clinical groups of thyroid malignancy: Group I, cases of low or potential malignancy; Group II, cases of moderate malignancy, in which there is a hope of cure; Group III, markedly malignant cases, in which there is practically no hope of cure.

We have further attempted to correlate this clinical classification with the histologic appearance presented by the tumor. In Group I we have placed (1) the adenoma with blood vessel in-
vasion and (2) the papillary cystadenoma. In Group II we have adenoecarcinoma (1) of the papillary type and (2) of the alveolar type. In Group III are the patients with (1) squamous-cell carcinoma, (2) small-cell carcinoma both of (a) the compact and (b) the diffuse type, (3) giant-cell carcinoma, and (4) a subgroup in which we place one patient with probable fibrosarcoma (see Chart I).

**Consideration of Individual Groups**

*Group I:* In Group I we have placed those patients having adenomata with blood vessel invasion and papillary cystadenomata, since our experience has shown that all these tumors either are of an extremely low degree of malignancy or their malignancy is open to question from the histologic point of view. Ninety-five patients have had adenomata with blood vessel invasion and all but six of these have been followed to date, all for more than a year since operation.

The histology of these 95 cases is varied, the picture ranging from that of the highly undifferentiated embryonal adenoma to the relatively well differentiated fetal adenoma. As would be expected, the tendency to blood vessel invasion is somewhat more marked in the less differentiated growths. The tendency was not observed in the most highly differentiated adenomata, the so-called simple adenomata, or the colloid adenomata. Unfortunately no histologic or clinical criterion has been found to differentiate those adenomata with blood vessel invasion that may cause further difficulty from those that have no effect so far as the patient is concerned. Some of the extraordinarily cellular and highly undifferentiated adenomata have not shown blood vessel invasion, whereas some of the more highly differentiated, even with foci of well formed follicles containing a slight amount of colloid, have invaded the blood vessels and given rise to metastases. Of the 95 patients 8 were males and 87 were females, an unusual preponderance of females in the occurrence of adenomata of the thyroid with blood vessel invasion. The youngest patient was twenty-one and the oldest sixty-seven.

In the group of adenoma with blood vessel invasion there have been four deaths to date from a recurrence of the tumor, a mortality rate of four per cent. The first of these four patients, "C," was operated upon in 1924, when an adenoma was removed from the thyroid but was not at the time recognized as malignant either
clinically or histologically. In 1925 there was a recurrence of the tumor, which was excised. In 1926 the patient returned to the hospital with a second tremendous recurrence in the neck and numerous metastases in the lungs. She died some two years after the original operation. Re-examination of the original adenoma showed blood vessel invasion. The second patient, "L," also had a recurrence, ten months after operation, with metastases in the chest, and died shortly afterward. In the third patient, "P," in less than a year following removal of an adenoma a local recurrence with laryngeal pressure, requiring a tracheotomy, had occurred. The last patient, "T.H.," was operated upon in 1922. Six years later she returned with a growth in the neck and this was removed. The operation was not successful, however, because of serious technical difficulties, and the patient died soon after it. The possibility of malignancy was not recognized at the time of the first operation, but recent examination of the slide showed blood vessel invasion in an adenoma. Microscopic examination of the tissue removed at the second operation showed small-cell carcinoma, distinctly different from the adenoma which had been present at the first operation. Whether this case should be termed a six-year recovery for adenoma with blood vessel invasion is, of course, a questionable point.

It seems to us significant that, of the 95 patients having blood vessel invasion in an adenoma, all who went for a year or more with no evidence of recurrence have been well for the entire follow-up period, with the possible exception of the patient just described, who, six years after the removal of the adenoma, succumbed to an operation for small-cell carcinoma. In all practical probability, if a patient goes one year after the removal of an adenoma showing blood vessel invasion without evidence of recurrence or metastases, the prognosis for the future is excellent.

It is our belief, based on this group of cases, that the complete removal of an adenoma with blood vessel invasion is the treatment of choice. The value of x-ray treatment is difficult to analyze. It is significant, however, that in the 34 cases which were discovered by searching old slides, and in which there had never been any occasion for x-ray treatment, since malignancy was not previously suspected, there have been no deaths and no recurrence of malignancy, with but two exceptions. In these two cases recurrences appeared within a very short time of the original operation; they were then recognized as cases of malignancy and were treated
with x-rays. In the other group of 61 cases which were recognized as malignant because of blood vessel invasion, x-ray therapy has been given in almost every instance. One patient is still well eleven years after operation but has at present a large, hard, firm mass in her neck. She is still having x-ray treatment at intervals. X-ray treatment was given in each of the four fatal cases in this group but applied vigorously only when it was recognized that a recurrence of malignancy had taken place. In each of these cases x-ray failed to stop the progress of the disease.

![Fig. 1. Fetal Adenoma of the Thyroid with Blood Vessel Invasion. × 300](image)

The possibility of the occurrence of myxedema after x-ray treatment is not great, since it occurred in only one of this group of patients and in this instance was not troublesome, yielding readily to therapy.

We may, then, summarize the clinical situation as we see it in patients with adenoma of the thyroid showing blood vessel invasion, as follows. The ideal treatment is early surgery which removes the adenoma completely. This operation we would follow with x-ray treatment at proper intervals, for one year. If, at the end of one year, there is no evidence of any recurrence in the neck
and if x-ray pictures of the chest are free from any evidence of trouble, we would dismiss the patient from further x-ray treatment, having him return only once a year for examination.

The second division of the first group of low or potentially malignant thyroid tumors is made up of the papillary cystadenomata. Of these we have 38 cases, 5 in males and 33 in females. Thirty-seven of these patients have been followed for a year or more, up to five years, only one patient in the group being "lost." The tumors of this division, the papillary cystadenomata, have an extraordinary tendency to arise from aberrant thyroid tissue. Their histologic picture is very distinctive, a dense fibrous tissue capsule surrounding one or more large cystic cavities, into which project long, delicate, branching stalks of connective tissue ordinarily covered over with a single layer of well differentiated, tall, columnar epithelium. As a rule, only a single layer of cells is present, although occasionally a pseudo-stratified appearance is observed and at times the cells may be two or three layers deep. Occasionally mitoses can be seen in the epithelial cells, though these are rare. Rarely the cyst may be blood filled, due to hemorrhage.
In some instances extension of an epithelial covered bud into a dilated vein may be seen. Penetration of the capsule by the tumor occasionally occurs.

Results in this group of thyroid tumors have been most satisfactory from the clinical point of view. Only 2 patients of the 38 have died. The first was inoperable when first seen, and a biopsy only was performed. With x-ray treatment, however, the patient lived comfortably for nearly two years after the biopsy and then died with malignancy in the neck. The other patient died six months after operation, from metastases to the brain.

In this group it has been our experience that x-ray treatment is of very distinct value. Thus, in one case which was inoperable when first seen, permitting only a biopsy, complete removal of the tumor was possible after a long series of x-ray treatments. In two other cases which were inoperable and in which only biopsies were done, the tumors have now completely disappeared under x-ray treatment alone. In one of these cases a year and seven months has elapsed with no evidence of trouble, and in the other three and a half years.

Papillary cystadenoma in the majority of cases, in our experience, is almost a benign tumor. The fact, however, that occasional cases do occur which resist x-ray treatment and which are inoperable, makes it necessary to class these tumors as of low or potential malignancy. In both of the patients who died, blood vessel invasion was apparent in the microscopic section, but the blood vessels were invaded also in ten other cases of this group in which there has as yet been no recurrence.

*Group II:* There are certain patients with thyroid malignancy for whom there is some hope of cure. These we call the second group. Histologically this group consists of cases of adenocarcinoma (1) of the papillary type and (2) of the alveolar type. Most of the tumors in this group originate in pre-existing adenomata. Of the papillary type of adenocarcinoma we have 7 cases, all except one in females. These tumors may resemble very closely the papillary cystadenomata just described, with the exception that there is practically always a piling up of the epithelium with numerous mitoses and rarely the appearance of struma giant cells. They may show greater degrees of anaplasia, some of the tumors being made up of large epithelial masses in which the struma is barely apparent although the papillary arrangement is still maintained. In these the epithelium shows frequent mitoses and there
is marked variation in the size of the cells. All of the members of this group show blood vessel invasion.

It is our experience that papillary adenocarcinoma in the thyroid gland is somewhat susceptible to x-rays. In this group, for example, are two patients in whom the first operation was either very limited or was only a biopsy, but who received a year or more of intensive x-ray treatment. In each case the tumor was so reduced in size and became so freely movable that it could be excised. In the first of these patients a biopsy was done in 1927 and after a year of x-ray treatment a large group of nodules was removed from his neck. He is now dead from multiple metastases in the neck and chest, two years after the second operation and three years after he first came for treatment. The second patient in the group had an adenoma removed and thirteen months later, after much x-ray treatment, secondary excision of a recurrent nodule. Two years after the first operation this patient is still apparently well. In another patient of this group biopsy was done and the tumor has been held in check by x-ray for one year and six months. Two patients have gone over a year and a half and
are well. The remaining two patients were dead within a few months of the operation. Of the seven patients having papillary adenocarcinoma, then, three are dead; one presents recurrent masses in the neck, and three are well one and a half years to three years after operation.

The alveolar type of adenocarcinoma is represented in our series by 14 patients, all but one of whom are females. Seven of the 14 have been followed more than a year since operation and are still alive and well. One patient of the fourteen was well six months after operation but has since been lost. Four of the patients are alive for one and a half years to four years since operation, but now have glands palpable in the neck, or metastases in the chest, or both. The other two patients in the group are dead of the tumor.

These alveolar adenocarcinomas attempt, with greater or less success, to form thyroid follicles. The epithelium ranges from low cuboidal to columnar and is frequently only a single layer thick, although often four or five or more layers may occur. Rarely colloid may be formed. At times entirely undifferentiated
cellular masses are seen. Mitoses vary in number but tend to be fairly frequent. Occasional very large, single, nucleated tumor giant cells are seen. The cells are moderate in size and fairly uniform, and the nuclei are relatively large, oval, and hyperchromatic. Blood vessel invasion is invariably present and, if the tumors have reached any size, the invasion of normal thyroid tissue and of adjacent structures is strongly marked.

As in the papillary type of adenocarcinoma, it was possible in one of the patients to do a secondary removal of a large piece of thyroid tissue after four years of x-ray treatment. This patient still has many palpable glands in her neck and is receiving active x-ray treatment. The original specimen and the specimen which was taken four years later both showed the alveolar type of adenocarcinoma.

Although we would use x-ray treatment in all postoperative cases of alveolar type adenocarcinoma, we do not feel, from this experience with it, that it will necessarily control the extension of the growth to any marked degree.

Fig. 5. EPIDERMOID CARCINOMA ORIGINATING FROM THE THYROGLOSSAL DUCT. × 225
Group III: In Group III we have placed all those patients having marked malignancy, for whom our experience has shown practically no hope for cure. The first division of this group—the squamous-cell carcinoma—is represented by only one case, previously reported (1). This patient died in spite of x-ray treatment, three months after the operation. The tumor failed to show any change with x-ray therapy. It is difficult to say from what tissue in the thyroid this tumor originated, but it may be derived from remnants of the thyroglossal duct, from which epidermoid carcinoma is known occasionally to arise.

The second type of growth in the group with marked malignancy is the compact, small-cell carcinoma, of which there are 17 representatives in our series. Of these 17 patients, only 3 were male. The compact type of small-cell carcinoma is closely similar to some of the less differentiated medullary carcinomata seen elsewhere in glandular organs, as, for example, the breast. The cells are small, close packed, with prominent hyperchromatic nuclei. Mitotic figures are numerous. The stroma varies in amount but divides the tumor cells into small clusters.
extensive invasion and destruction of the normal thyroid tissue. Lymphatic and vascular channels contain masses of tumor tissue. There is no attempt at the formation of alveoli.

All the members of this group were followed. Fourteen of the 17 patients are dead, one has definite metastases in the chest one and two-thirds years after operation, one has gone two and two-thirds years and one over one year with no evidence of trouble.

Small-cell carcinoma of the compact type, then, is a most deadly type of thyroid malignancy. The longest that any patient in the group has remained well, to our knowledge, is two and two-thirds years, while 15 of the 17 in the group are either dead or have metastases and evidences of recurrence of the tumor. X-ray treatment has been given to every one of these patients who was sufficiently well to receive it, but in no case has it seemed to us to control the extension of the growth. The prognosis in this group of cases is completely bad.

The diffuse type of small-cell carcinoma is also a very serious type of thyroid tumor. From the histologic standpoint it is one of the most interesting groups. This is the tumor considered by Graham (2) as possibly related to the lymphoid group. The cells

---

**Fig. 7. Small-cell Carcinoma of the Thyroid, Diffuse Type. \( \times 150 \)**
Fig. 8. Small-cell Carcinoma of the Thyroid, Diffuse Type. \( \times 150 \)

Fig. 9. Small-cell Carcinoma of the Thyroid, Diffuse Type. \( \times 300 \)
are small but relatively scanty in cytoplasm. The nuclei are large, at times vesicular, with a considerable amount of chromatin. Mitotic figures are very frequent. As a rule, tumor giant cells are not seen. The outstanding feature of this type of tumor is the diffuse character of the growth and the way in which single cells or small clusters of cells insinuate themselves among the strands of the stroma. This group may be difficult at times to differentiate from Riedel's struma.

In this group we now have 8 cases, all but one in females. One patient in the group has gone one year and nine months with no difficulty. The other 7 patients are dead. The longest time that any member of this group has lived is three and a half years. This patient was operated upon in 1926, at which time the tumor was inoperable and only a biopsy was done. He was given a great deal of x-ray treatment, and all evidence of thyroid tumor disappeared. A few months ago, however, he was admitted to another hospital, where he died from a retroperitoneal tumor, undoubtedly malignant. This is the only case in the group in which x-ray
treatment has been of proved value in our experience. Nevertheless, from this case alone we would urge its use. The prognosis in this group of small-cell carcinoma of the diffuse type is utterly bad in spite of any form of treatment and the usual course of the disease is rapid in spite of surgery and x-ray therapy.

The third type of cancer in Group III is the so called giant-cell carcinoma, of which we have six examples. The thyroid tumors by far the most bizarre in histological appearance are those in this group. They have frequently been classified as fibrosarcoma and in certain cases there is still some question as to whether carcinoma or sarcoma is the proper term to be applied. On the whole the most characteristic picture is that of a tremendous number of tumor giant cells, extremely variable in size and shape and often containing multiple mitoses. In among the tumor giant cells may be numerous fat spindle cells, some of which very closely resemble fibroblasts. The tumors are generally extremely vascular and there may be much necrosis. When first seen, they are generally already extensive and their rapidity of growth is extremely striking. Their invasive powers are unusually marked, and practically all of the thyroid is rapidly destroyed and the adjoining structures are
invaded. A striking feature of this type of growth is its marked tendency to invade the blood vessels. At times the difficulty of differentiating in this type of tumor between fibroblasts and elongated epithelial cells is marked. However, the transition can frequently be traced from the fat spindle cell to epithelial cells in definite alveolar arrangement. With the phosphotungstic acid hematoxylin stain it has been extremely difficult to bring out the presence of fibrils in this tissue.

All of our 6 patients with giant-cell carcinoma were females. Of these, one could not be followed; one has lived for two and a half years with no evidence of any difficulty, and the remaining 4 are dead; all of these died within a relatively short time of the operation. In this group x-ray has been used but little because of the rapid extension of the tumor, and thus far both surgery and x-ray have been of no avail to hold in check the rapid growth of the neoplasm once it was begun.

The last division in Group III is probable fibro-sarcoma (3). This type of growth is quite similar in histologic appearance to the
Fig. 13. Fibrosarcoma of the Thyroid. × 225

Fig. 14. Papillary Adenocystoma of the Thyroid (Left); Metastatic Involvement of Lymph Nodes (Right)
giant-cell carcinoma described above, but fibroglia fibrils were demonstrated in relation to most of the spindle cells which made up the bulk of the tumor, and the histologic picture in general very closely resembled that of the usual rapidly growing fibrosarcoma. There was but one patient in our series who could be classed in this group. She was a female, forty-six years of age, who lived some two years after operation, with much x-ray treatment, and is now dead.

### Table I

*Cancer of the Thyroid, Lahey Clinic, 1916–1929.*

<table>
<thead>
<tr>
<th>GROUP I: LOW OR POTENTIAL MALIGNANCY</th>
<th>Total cases</th>
<th>Fatal cases</th>
<th>Percentage mortality</th>
<th>Living cases with recurrence or metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adenoma with blood vessel invasion</td>
<td>95</td>
<td>4</td>
<td>4.2%</td>
<td>3</td>
</tr>
<tr>
<td>2. Papillary cyst adenoma</td>
<td>38</td>
<td>2</td>
<td>5.2%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total Group I</strong></td>
<td><strong>133</strong></td>
<td><strong>6</strong></td>
<td><strong>4.5%</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP II: MODERATE MALIGNANCY WITH HOPE OF CURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adenocarcinoma</td>
</tr>
<tr>
<td>(a) Papillary type</td>
</tr>
<tr>
<td>(b) Alveolar type</td>
</tr>
<tr>
<td><strong>Total Group II</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP III: MARKED MALIGNANCY WITH PRACTICALLY NO HOPE OF CURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Squamous-cell carcinoma</td>
</tr>
<tr>
<td>2. Small-cell carcinoma</td>
</tr>
<tr>
<td>(a) Compact type</td>
</tr>
<tr>
<td>(b) Diffuse type</td>
</tr>
<tr>
<td>3. Giant-cell carcinoma</td>
</tr>
<tr>
<td>4. Fibrosarcoma (probable)</td>
</tr>
<tr>
<td><strong>Total Group III</strong></td>
</tr>
<tr>
<td><strong>Total for all Groups</strong></td>
</tr>
</tbody>
</table>

7 cases were "lost" for follow-up.

From our study of these patients with thyroid malignancy it appears that there is a very helpful relationship between the clinical course of the different types of tumor and their histologic structure. We believe that the groups of low malignancy, moderate malignancy, and marked malignancy are clear cut histologically and tend to follow certain fairly regular clinical channels.
Into Group I of tumors having low or only potential malignancy fall the largest number of clinical cases—133—with a mortality of only 4.5 per cent. Furthermore, our experience tends to show that if a Group I tumor fails to recur or metastasize within a year after operation, later trouble need not be expected. We also believe that Group I tumors are especially susceptible to x-ray radiation.

In Group II we have 21 cases with 5 deaths—a mortality rate of 23.9 per cent. Four of the 17 living are known to have recurrences or metastases, which appeared from a year and a half to four years and a half after treatment was undertaken. Clinically, the tumors of this group are much more dangerous than those in Group I, because of their higher immediate mortality, and because of their ability to recur and metastasize after nearly five years of apparent cure. X-ray treatment, however, is seemingly of value in retarding their growth and in certain instances in rendering inoperable tumors operable. Although the outlook is not nearly as good in Group II tumors, we may nevertheless look upon these cases as definitely having a hope of cure.

The tumors which we have grouped from their clinical characteristics in Group III all show histologic evidence of active malignancy and rapid growth. There are 33 patients in this group, of whom 27 (82 per cent) are dead, one is lost, and one has metastases in the neck and chest. Only 4 are living from one to three years after operation. In this group we feel the prognosis is utterly bad. The tumors recur soon after operation, their growth is rapid, and a fatal ending soon occurs. Thus, of the 27 patients who died, only one lived over three years after operation (three and a half years), 4 lived as long as two years, and 16 died in less than six months after treatment was established. Furthermore, these tumors tend to be sudden in onset and to have very rapid growth. Apparently they often arise in the absence of a previously noted adenoma. X-ray radiation has failed in our experience to alter their course to any marked degree.

**SUMMARY**

1. All cases of thyroid malignancy with histologic specimens treated in the Lahey Clinic up to January 1st, 1930, are reviewed. There have been 187 cases of malignancy in 6,535 goiter cases operated upon. One hundred and eighty of these 187 cases of thyroid malignancy have been followed for at least a year after operation. Seven have been "lost."
2. A clinical and histologic correlation of these patients has been made for the purpose of foretelling the probable clinical course of the different types of tumors and their probable responses to treatment.

3. Follow-up studies of these patients demonstrate the practical value of the grouping adopted.

References