Poorly Differentiated Neoplasms of the Thyroid Gland

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CANCER OF THE THYROID is an uncommon disease with an incidence of approximately 25 in 1,000,000 people causing about 1100 deaths yearly. It is a multi-variate lesion in which the prognosis is determined by the morphologic features of the tumor, age and sex of the patient, and stage of the disease. Of these factors, by far the most important is morphology. The early mortality of thyroid cancer is due principally to the poorly differentiated neoplasms which comprise from 15–20% of all malignant thyroid neoplasms. Well-differentiated cancers, five times as common as poorly differentiated lesions, have a much better prognosis (Fig. 1). The grim prognosis of poorly differentiated thyroid neoplasms is well illustrated by a recent report from the Mayo Clinic based on an experience with 160 patients.[2] The average duration of life of these patients was approximately 6 months. There was one long-term survival of a patient who had small cell carcinoma, 22 years after thyroidectomy and irradiation. A slightly better prognosis has been cited by Staunton and Martin with a 15% 5-year survival for anaplastic cancer.[22]

Poorly differentiated neoplasms of the thyroid include those which have a predominantly small, giant, spindle cell or anaplastic histopathologic pattern. Despite the overall poor prognosis of poorly differentiated thyroid neoplasms, careful examination of the clinical course of these patients indicates that there are important differences in the origin, biologic characteristics and natural history of these neoplasms which affect survival and should influence therapy. This report reviews the experience of the University of Iowa and the North Carolina Memorial Hospitals with poorly differentiated thyroid neoplasms in order to identify such differences and thereby increase the effectiveness of treatment.

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Materials and Methods

One hundred and seven patients with poorly differentiated thyroid neoplasms seen at the University of Iowa and North Carolina Memorial Hospitals, 1930–1972, provide the clinical material for this investigation. During this interval, 410 patients with well-differentiated and nine with medullary carcinoma were seen.

The neoplasms are classified on the basis of the predominant histopathologic pattern. In a previous communication evidence was presented which indicated a similar survival of patients with follicular and papillary carcinomas.[7] These lesions are therefore considered as one group and referred to as well-differentiated thyroid carcinomas. The striking statistically significant difference in the survival rate of patients with well-differentiated carcinomas from those with medullary and the other thyroid malignancies, the 107 poorly differentiated neoplasms which provide the clinical material for this investigation, are shown in Figure 1. The apparent "good" survival of patients with medullary carcinoma is so classified because only nine had this lesion, one of whom survives 19 years after diagnosis. Medullary carcinoma is accompanied by a poorer prognosis than well-differentiated neoplasms but better than poorly differentiated carcinomas.[2] Eighty-seven of the patients were seen at the University of Iowa and 20 at North Carolina Memorial Hospitals. Fifty-nine patients included in this investigation, seen at the University of Iowa Hospitals, provided the basis for a previous study of poorly differentiated thyroid neoplasms.[13] The diagnosis was histologically confirmed in all patients included in the

study. If the biopsy or surgical treatment was performed prior to the patient's admission to the University of Iowa or North Carolina Memorial Hospitals, sections of the tissues excised were reviewed by one of the authors or pathologists at either hospital.

There is a thyroid cancer registry functioning in both hospitals. The methods for collecting, processing, and analyzing the data are described in a previous publication.[7] Historical information, physical, laboratory, and X-ray findings, methods of treatment, operative and pathologic findings and follow-up information is collected and coded by secretaries responsible for the two thyroid cancer registries. The data are transferred from the study protocol to punch cards. This procedure and the additional processing and analysis of the data are done at the North Carolina Memorial Hospital. Follow-up information is obtained during return visits to the hospitals, by correspondence with the patients and/or their physicians and from death certificates. Follow-up information is obtained at least once a year. These data, collected and coded by two secretaries is used to update the punch cards on which the data are stored. The computer program developed for analyzing the data makes it possible to correlate all findings and to examine their effect on survivorship.

Survival rates are computed by modification of the method described by Berkson and Gage,[5] which computes survival by use of the end-results group of the National Cancer Institute.[1] An example of the application of this method is given in a previous communication.[7] Survival is computed on a basis of the number of patients subjected to the risk of dying for the time interval of examination, who; (a) survive, (b) are dead, (c) are lost to follow-up. The results are reported in the form of survival graphs. Percentage survival is indicated on the vertical and duration of survival on the horizontal axes of the graphs. The number at the end of each survival curve indicates the number of patients in the group; those in parentheses indicate the number of patients surviving at the end of the indicated survival interval. Differences in survival are examined for statistical significance using the method described by Koch, Johnson, and Tolley[18] which is similar to that of Cutler and Ederer.[9]

Definitive surgical treatment is considered to be partial thyroidectomy, lobectomy, and near-total thyroidectomy. Included in the partial-thyroidectomy group of patients are those treated by unilateral partial thyroidectomy and others treated by bilateral partial thyroidectomy. The lobectomy group includes those with a unilateral lobectomy with or without resection of the isthmus and those with partial resection of the contralateral lobe. Near-total thyroidectomy involves lobectomy on the side of the lesion or the side of the larger lesion in patients with both lobes involved. A subtotal intracapsular lobectomy, leaving 1-2 grams of thyroid tissue posteriorly near the inferior cornu of the thyroid cartilage, is done on the contralateral side. The branches of inferior thyroid artery on that side are ligated intracapsularly as they enter the thyroid rather than ligating the trunk of the vessel extracapsularly. Preservation of functioning parathyroid tissue is the objective of these two technical maneuvers. Radical neck dissection involves incontinuity resection of the regional lymph nodes, the jugular vein, the contents of the anterior and posterior cervical triangles and the sternocleidomastoid muscle. A second group of patients have had partial neck dissections, with excision of nodes along the jugular vein and/or of the anterior cervical triangle. In some patients, not curable by surgical excision because of extensive spread of neoplasm into extra nodal soft tissues of the neck, gross tumor is removed to facilitate postoperative irradiation. These patients are considered to have had partial neck dissection. Because of the advanced stage of the neoplasm, more than one third of the patients were unsuitable for a definitive surgical procedure. A biopsy was performed on all patients. Since irradiation therapy was used after biopsy in most patients, a tracheostomy was often done to assure an adequate airway.

Most of the operative procedures were performed by the attending and resident staff of the University of Iowa and North Carolina Memorial Hospitals. In patients initially treated elsewhere, detailed information

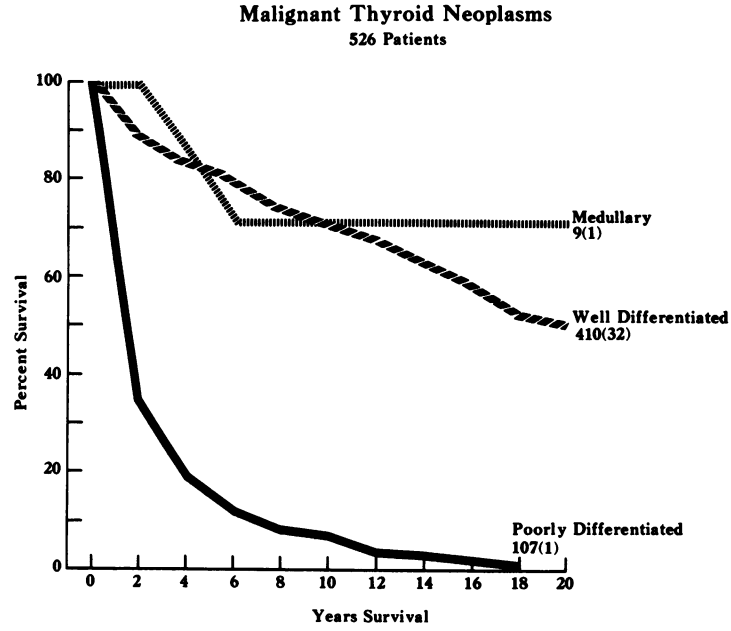

FIG. 1. Survival curves of patients with well differentiated, medullary and poorly differentiated thyroid neoplasms.*

* The survivorship curve for medullary carcinoma differs from that of an earlier article (Fig. 2, Ref. #7). This is due to a computing error in the referenced article.

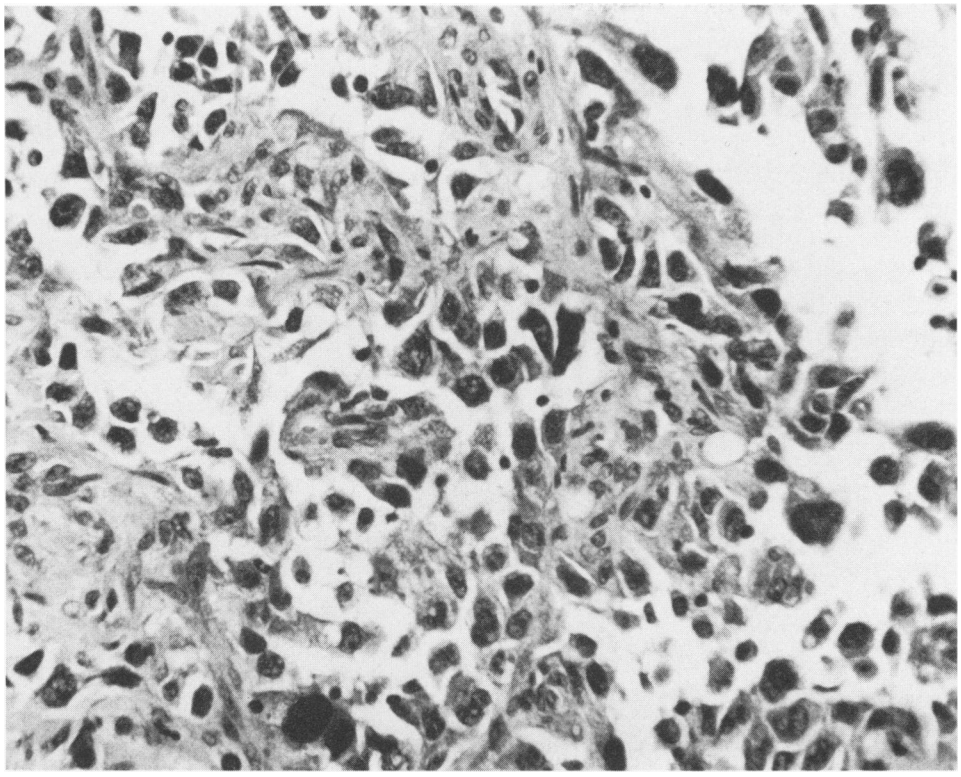

FIG. 2. "Giant cell" variant of anaplastic thyroid carcinoma. (340×).

was obtained concerning the operative procedure, operative and pathologic findings by personal contact, telephone and correspondence.

Results and Discussion

On the basis of the histopathology, the 107 poorly differentiated lesions were classified as either anaplastic or small cell neoplasms. Included in the anaplastic group were those which are sometimes referred to as giant, Hürthle, or spindle cell, and undifferentiated neoplasms (Figs. 2, 3, and 4). The distinction between small cell carcinomas and lymphomas primary occurring in the

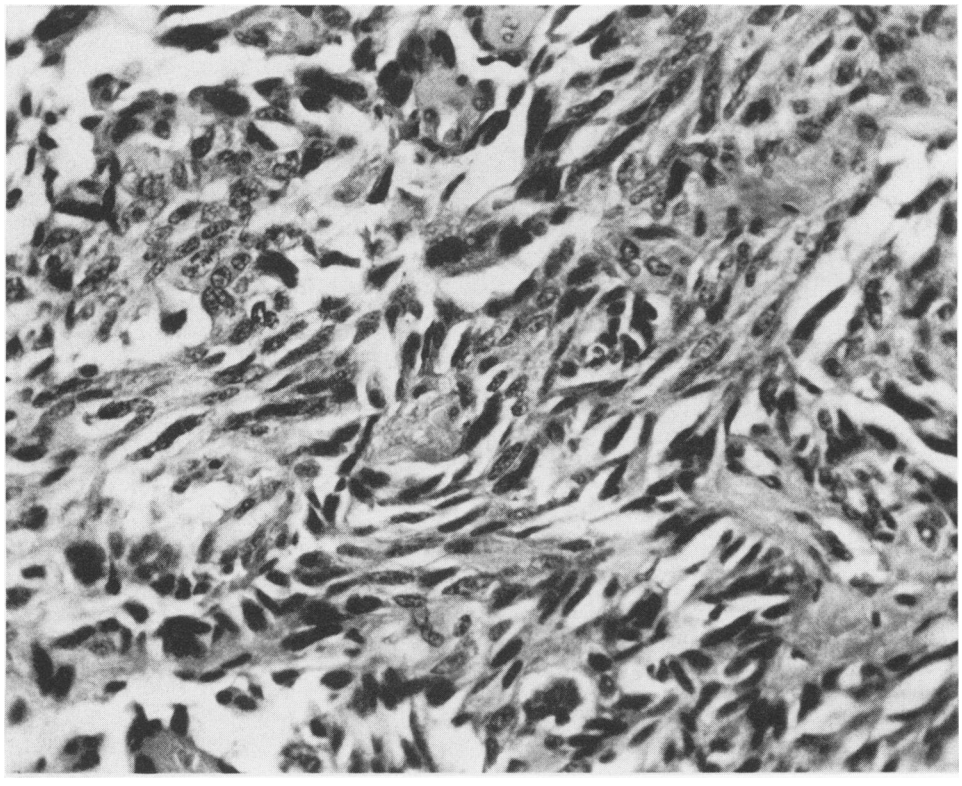

FIG. 3. "Spindle cell" variant of anaplastic thyroid carcinoma. (340×).

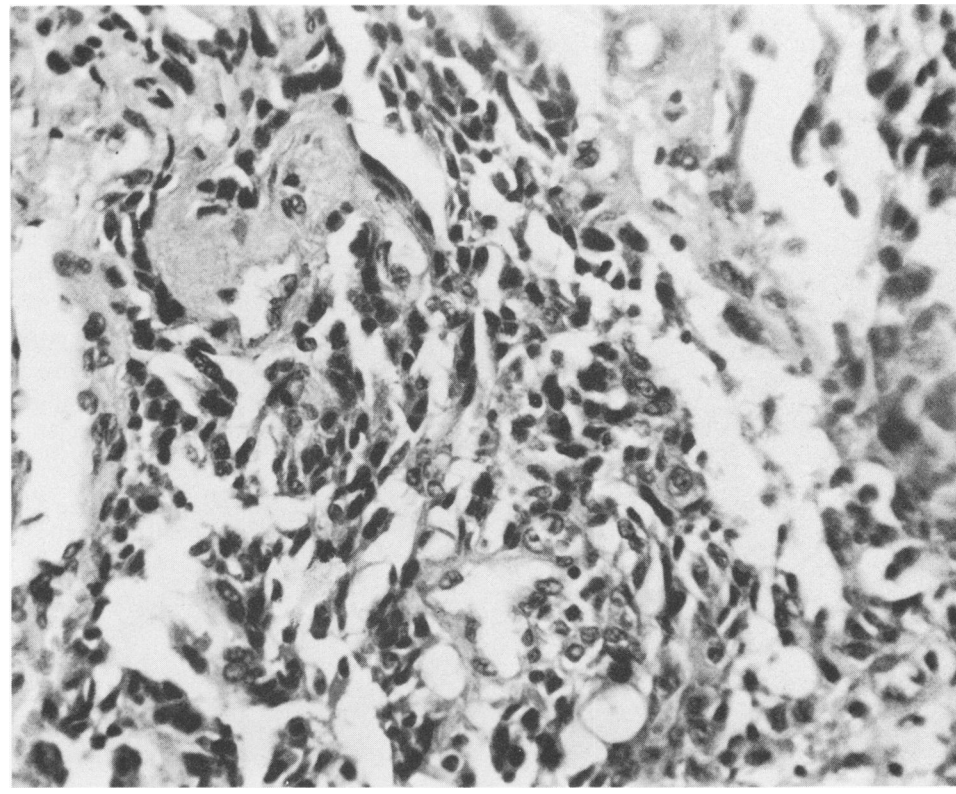

FIG. 4. Undifferentiated or anaplastic thyroid carcinoma. (340×).

thyroid gland, is a difficult one to make (Fig. 5). The absence of follicular or acinic formation by the neoplastic cells is the criterion most often used as the basis for establishing the diagnosis of a lymphoma primary occurring in the thyroid gland. Therefore, the number of small cell lesions of the thyroid gland which are classified as lymphomas is in large measure a function of, (a) the number of sections of neoplasm which are

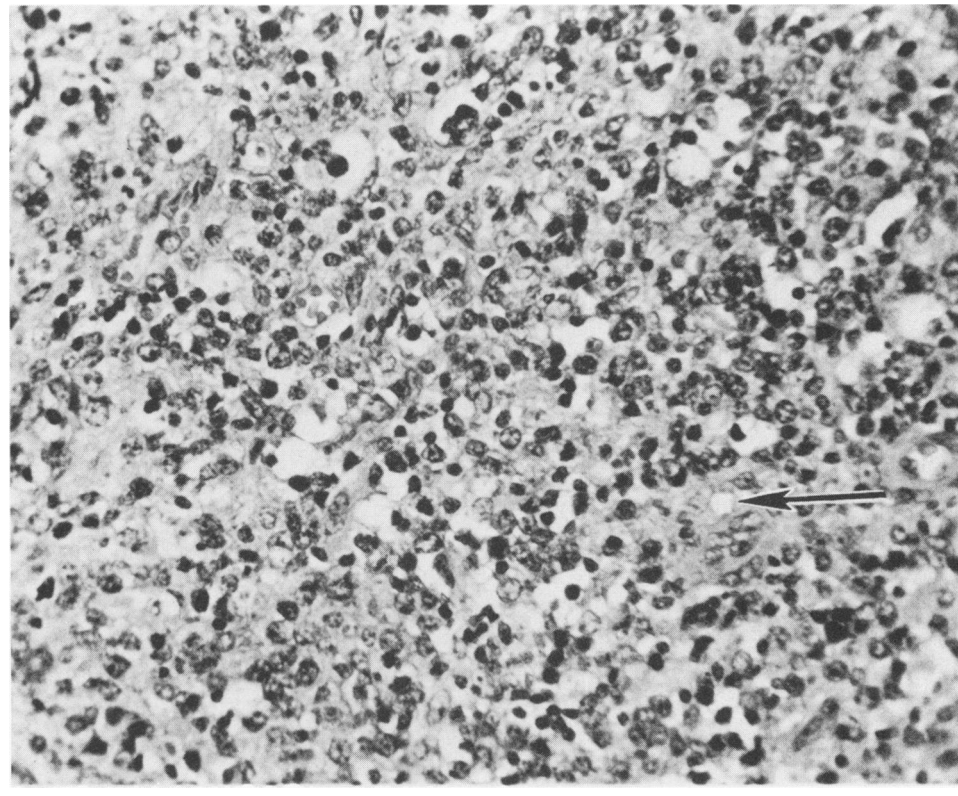

FIG. 5. Small cell carcinoma of the thyroid gland. Note "follicle" indicated by arrow. (340×).

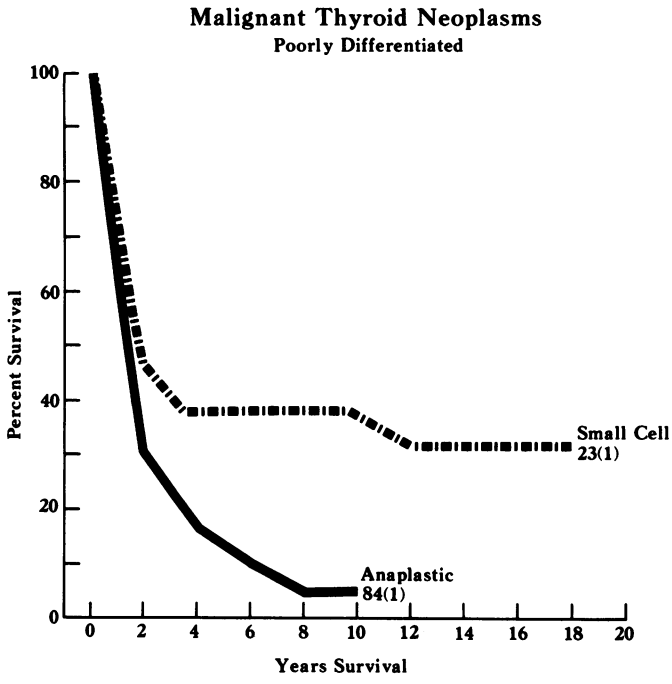

FIG. 6. Survival curves of patients with anaplastic carcinomas and small cell neoplasms of the thyroid gland.

examined and (b) the criteria accepted as evidence of follicular formation. Electron miscoscopy, not used in this study, may possibly be helpful in differentiating between small cell carcinomas and lymphomas of the thyroid. The results of this investigation suggest that the differentiation of small cell carcinoma from lymphoma primary in the thyroid gland, may not be of clinical significance. Such differentiation might assume significance if the diagnosis of lymphoma were to be followed by staging as in lymphomas occurring elsewhere. Lymphoma and small cell carcinoma of the thyroid gland appear to have a similar biologic behavior and response to treatment. In this report the two patients who are considered to have lymphomas are included with the 21 regarded as having small cell carcinomas. The survival curves shown in Figure 6 indicate statistically significant differences ($p < 0.05$) between the survival of the 84 patients with anaplastic lesions and 23 patients with small cell neoplasms.

In Figure 7 is indicated the extent of disease in patients with anaplastic and small cell neoplasms based on clinical, operative, and pathologic findings at the time of diagnosis: Stage I, disease limited to the thyroid gland; Stage II, extension of the neoplasm to regional lymph nodes; Stage III, extension of the neoplasm beyond regional lymph nodes. As shown in Figure 8, patients with anaplastic lesions with Stage I and II disease have similar survival which is better than that of patients with Stage III disease. The differences between the survival curves are not statistically significant. Because of the small number of patients available for study, comparison of the survival curves of patients with small cell lesions with Stage I, II, and III disease is meaningless.

The average age at the time of diagnosis of the 84 patients with anaplastic lesions was 60.5 years, 53.9 years for those 23 with small cell lesions, compared with 44.3 years for the 410 patients with well differentiated carcinomas. Of 65.6% patients with anaplastic lesions, 60.8% of those with small cell carcinomas were women compared with 70.0% of patients with well differentiated carcinomas. In contrast to well differentiated carcinoma, neither age or sex was found to influence survivorship in patients with either type of poorly differentiated neoplasms.

Sixty-five (77.3%) patients with anaplastic lesions and all 23 with small cell lesions had histories of goiter. In 28 (33.3%) of the patients with anaplastic lesions and in six (26.1%) of those with small cell lesions, the goiter had been present for more than 1 year at the time of diagnosis. Recent growth of the goiter was reported by all 65 of the patients with anaplastic lesions and in 19 of those with small cell neoplasms. The history of recent growth of the goiter is more often associated with poorly differentiated than with well differentiated neoplasms.[6]

One patient with a small cell neoplasm and none with anaplastic lesions, had undergone irradiation of the head or neck during infancy or adolescence.

The more common symptoms occurring in the 107

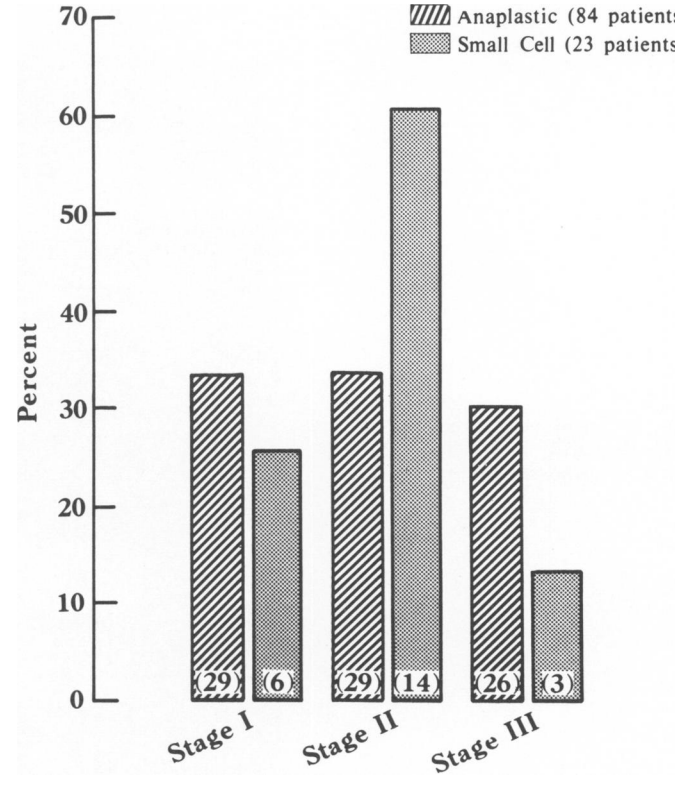

FIG. 7. Extent of disease in patients with poorly differentiated thyroid neoplasms.

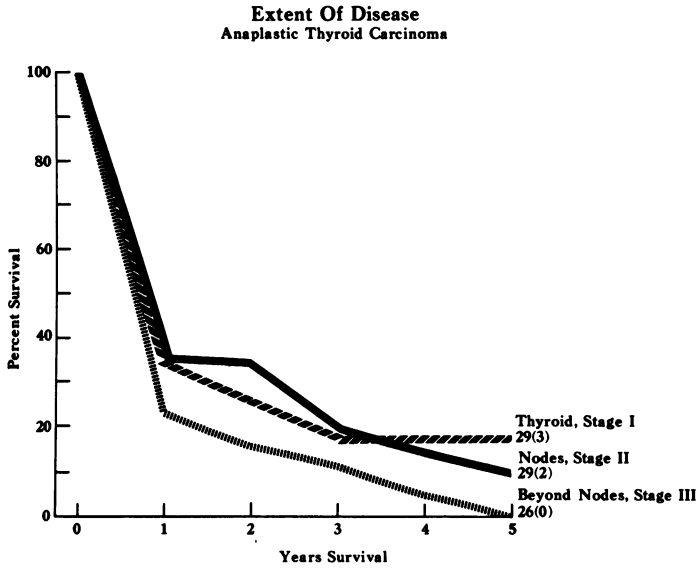

FIG. 8. Survival curves of patients with anaplastic thyroid carcinomas with Stage I, II and III disease.

patients with poorly differentiated neoplasms are indicated in Figure 9. Note that hoarseness, dyspnea, and dysphagia occurred in about one third of the patients with both anaplastic and small cell neoplasms. This is in striking contrast to patients with well differentiated lesions in whom these symptoms rarely occur. These manifestations are related to the biologic behavior of poorly differentiated lesions characterized by early local extension in the neck. These neoplasms invade through the thyroid capsule, rapidly spread beyond the regional lymph nodes to involve the muscles and other soft tissues.

In Table 1 are listed the more common physical and

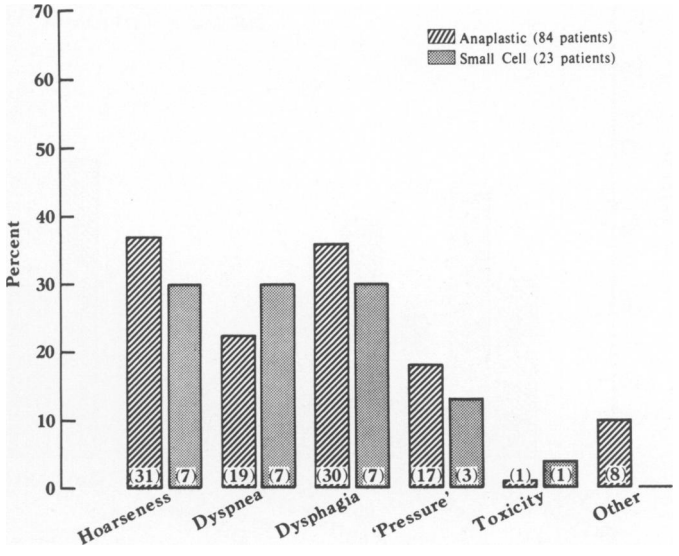

FIG. 9. Symptoms experienced by patients with poorly differentiated thyroid neoplasms.

TABLE 1. *Clinical Findings in Patients with Poorly Differentiated Thyroid Neoplasms*

	Anaplastic 84 Patients	Small Cell 23 Patients
Single nodule	17.1% (16)	21.7% (5)
One lobe enlarged	25.5% (23)	21.7% (5)
Both lobes enlarged	26.7% (24)	26.0% (6)
Isthmus enlarged	4.5% (4)	— —
Normal thyroid	3.6% (3)	4.3% (1)
Tender thyroid	9.5% (8)	— —
Soft tissue extension	4.5% (4)	— —
Pulmonary metastases	19.0% (16)	8.7% (2)
Unilateral neck nodes	13.0% (11)	34.8% (8)
Bilateral neck nodes	13.0% (11)	8.7% (2)
Vocal cord paralysis	17.1% (16)	13.0% (3)
Other soft tissue metastases	7.1% (6)	8.7% (2)
Bone metastases	7.1% (6)	— —

radiologic findings. Nodal involvement was suspected on physical examination in patients with small cell lesions almost twice as frequently as in patients with anaplastic lesions.

Ten ^{125}I scans were done in patients with anaplastic lesions and three in those with small cell neoplasms. Three $^{75}Selenomethionine$ scans were done in patients with anaplastic lesions and two in patients with small cell lesions. In the five patients who had both scans, there was a decreased uptake of ^{125}I and increased uptake of $^{75}Selenomethionine$ in the area of the neoplasm. In the additional seven patients with anaplastic lesions who had only a ^{125}I scan, there was reduced uptake consistent with the diagnosis. This good correlation between both scans and the pathologic findings is more characteristic of poorly than well differentiated thyroid carcinoma.[24]

The diagnoses which were based on the clinical findings prior to definitive surgery, biopsy or post-morterm examination are shown in Figure 10. The diagnosis was established at the time of post-mortem examination in four patients with anaplastic lesions, who clinically were not suspected of having a poorly differentiated thyroid carcinoma. In three of these patients with metastatic spread beyond the neck, the anaplastic thyroid carcinoma was the principle cause of death. The clinical findings more frequently suggest the correct diagnosis in patients with small cell than anaplastic carcinomas.

In Figure 11 are indicated the definitive operations which have been used. An operation to excise all gross neoplasm, was performed in 58.1% of patients with anaplastic lesions and 78.2% of patients with small cell neoplasms. This did not include all the patients with Stage I or II disease who theoretically could have had all gross neoplasm excised. The poor condition of the patient or the extent of local disease in the thyroid gland or lymph nodes, precluded definitive operation in 10.9% of patients with anaplastic lesions and 8.7% of patients

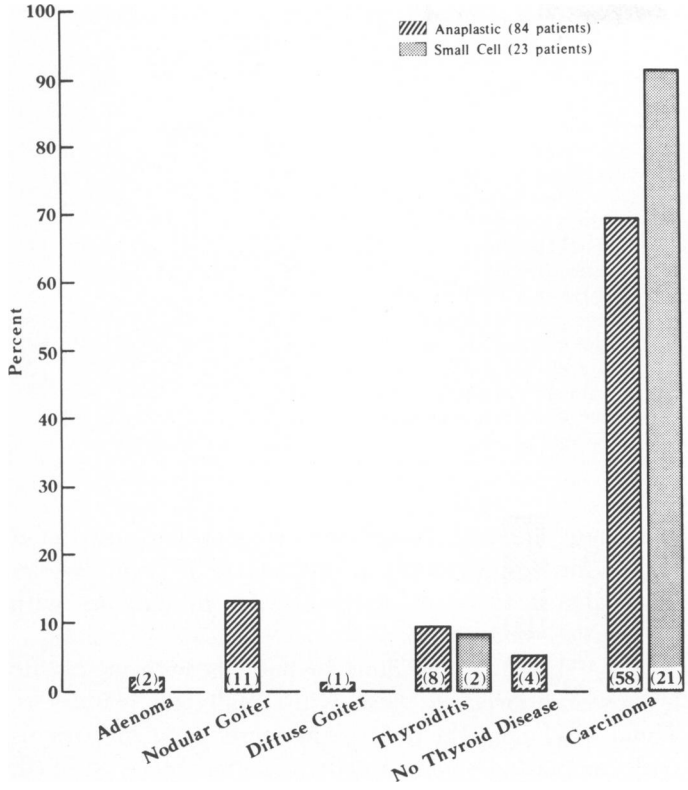

FIG. 10. Preoperative diagnoses in patients with poorly differentiated thyroid neoplasms.

with small cell neoplasm with Stage I and II disease. In Figure 12 are indicated the palliative methods of treatment which were used.

Comparison of survival curves for anaplastic and small cell lesions indicates no significant differences related to the type of definitive operation which was performed. The better survival of patients after definitive or curative operations, probably reflects less extensive disease rather than more effective treatment. Based upon the course of individual patients after operation, it is our opinion that the procedures should be tailored to the findings. Lobectomy is indicated in the unusual patient in whom an early small lesion is limited to one lobe. Near-total thyroidectomy is more often indicated in poorly differentiated carcinomas; partial resection of one lobe would be unjustified. Because poorly differentiated thyroid carcinomas tend to invade adjacent soft tissues, the strap muscles overlying the lesions should be excised incontinuity with the thyroid tissue. Radical neck dissection should be done when the findings indicate that all gross neoplasm can be excised. Commonly there is spread beyond the thyroid and/or lymph nodes into the muscles or other soft tissues of the neck. In these circumstances all gross neoplasm should be removed with preservation of the parathyroid glands and recurrent laryngeal nerve on one side. In this instance, the operation is palliative and should serve only to facilitate the use of postoperative irradiation therapy. The degree to which this latter objective is achieved depends upon the completeness of excision and the radiosensitivity of the lesion.

The best survivorship is experienced by patients who undergo operation without irradiation. Patients who undergo operation and postoperative irradiation respond better than those who are treated with irradiation alone. Supervoltage has been used during the last 10 years. Survivorship was compared in patients with anaplastic carcinoma with Stage I and II disease who underwent operation and irradiation. Again, the patients who underwent operation alone responded the best. These findings do not signify that irradiation results in poorer survival, but with case selection patients with more advanced disease receive irradiation therapy. Regression or arrest of neoplasms which occurs occasionally in advanced anaplastic lesions, indicates use of high voltage irradiation therapy to maximum dosage. In some patients the quality of survival as well as its duration is improved as a result of irradiation therapy.

The numbers of patients with small cell lesions are too few to meaningfully compare survival rates of those treated with and without surgical treatment and irradiation. However, observation of patients with small cell carcinoma indicates that these lesions are in general more radiosensitive than the anaplastic lesions. Very striking regression has been observed in some patients, some of whom remain free of disease 5 or more years after therapy. Because the lesion may be radiosensitive, all patients with small cell neoplasms in whom residual neoplasm is suspected after surgical excision,

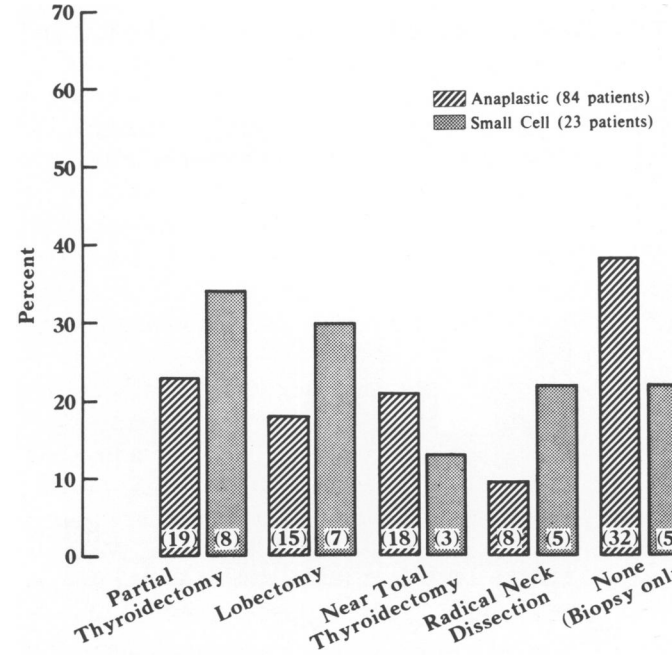

FIG. 11. Definitive operations in patients with poorly differentiated thyroid neoplasms.

should receive postoperative irradiation. In practice this means those patients who have direct or lymphatic extension of the neoplasm beyond the thyroid gland.

Intravenous nitrogen mustard, adrenal cortical steroids and ^{131}I have been used without any indication of favorable effect in patients with advanced anaplastic and small cell neoplasms. Most patients with both types of neoplasms have received suppressive thyroid hormone therapy. There is no evidence that this therapy has controlled the neoplasm.

The natural history of poorly differentiated thyroid neoplasms involves widespread distant metastases which is well demonstrated by the post-mortem findings in our patients. In Table 2 are indicated the tissues or organs found to be involved by metastatic neoplasm at the time of post-mortem examination. In this small number of patients there is no apparent difference in the pattern of metastases occurring with anaplastic and small cell neoplasms. Differences between the biologic behavior of poorly differentiated and well differentiated neoplasms, is reflected by the finding that the former much more frequently produce metastatic disease involving multiple systems. In contrast, well differentiated lesions have a long course characterized by spread to regional lymph nodes and late distant extension to bone and/or lungs.

In 67 of 75 (89.3%) of patients dying with anaplastic carcinoma the neoplasm was the cause of death. In 12 of the 15 (80.0%) of patients dying with small cell lesions, the neoplasm was the cause of death. In contrast, death was caused by the neoplasm in 67 (41.0%) of 139 patients dying with well differentiated thyroid carcinoma.[7]

Small cell neoplasms of the thyroid are lesions that on the basis of their biologic behavior, clinical course and response to treatment can and should be clearly distinguished from anaplastic thyroid carcinomas. The diagnosis in patients with small cell neoplasms is made about a decade earlier than with anaplastic carcinoma and about a decade later than with well differentiated carcinomas. The predeliction for the female in small cell lesions is less striking than with well differentiated and anaplastic carcinomas.

The morphologic differences have already been described. The genesis of these neoplasms also appear to differ. In contrast to anaplastic carcinomas, an admixture of well differentiated and small cell neoplasms is essentially unknown. In a collected series of 40 patients,[19,20,25] no patient was reported to have both lesions. We have seen one such case (Fig. 13). Well differentiated carcinoma, on the other hand, has been reported to co-exist in 5 to 10% of patients with anaplastic carcinoma.[3,16,23] In a carefully studied group of patients at M. D. Anderson Hospital the majority with anaplastic carcinomas

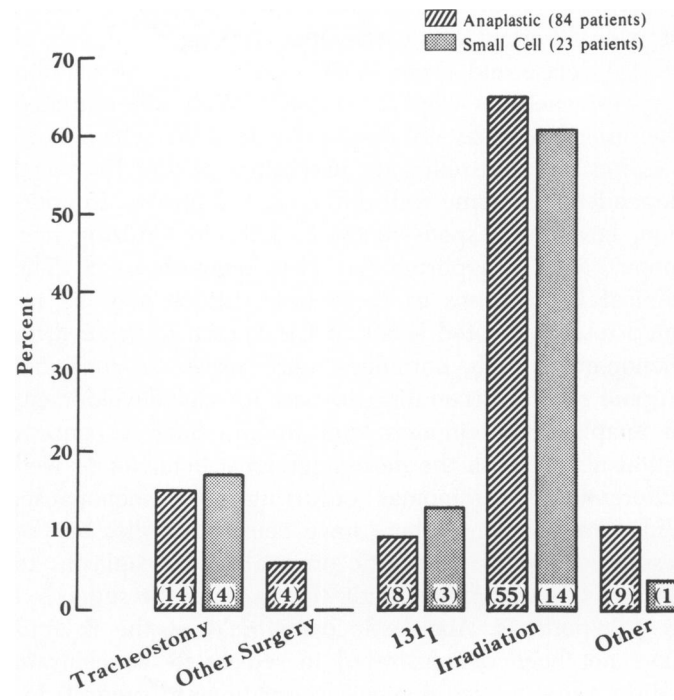

FIG. 12. Palliative treatment in patients with poorly differentiated thyroid neoplasms.

had co-existent well differentiated carcinomas.[14] This finding is relevant to the pathogenesis of anaplastic carcinomas. The coincidental finding of well differentiated and anaplastic thyroid cancer does not necessarily establish an etiologic relationship between these two lesions. However, it suggests the possibility that well differentiated carcinoma may be transformed into anaplastic carcinoma. This concept is supported by experimental and clinical evidence that the genesis of well differentiated carcinoma may be a two-phase phenomenon involving initiating and promoting factors. For instance, irradiation of the thyroid during infancy or childhood may alter the genetic composition of a cell with concomitant alteration in morphology and biologic potential. Subsequent stimuli which increase cell division or function—promoting factor—may enhance the development of cancer in a cell with this genetic change.[4] TSH (thyroid stimulating hormone) may effect such a promoting action on the thyroid gland. Furthermore, the biologic characteristics of a tumor may not necessarily be permanent, but may be altered by processes of mutation and selective survival. Progression to a more undifferentiated neoplasm might be anticipated to follow continual growth stimulus by TSH as would occur with concomitant hypothyroidism. Although the incidence of well differentiated thyroid carcinoma progressing to anaplastic carcinoma is low, it apparently may be increased by the use of irradiation, external or radioiodide, with or without stimulation by way of hypothyroidism.[8,23]

Pertinent to these concepts are recent *in vitro* studies of well differentiated carcinoma utilizing the levels of adenylcyclase and cyclic AMP as a measure of cellular responsiveness to trophic stimuli.[15] Well differentiated thyroid carcinomas are responsive to TSH which is in keeping with the clinical observation of the hormonal dependency of some well differentiated tumors. In addition, however, responsiveness to LH (leuteinizing hormone) and epinephrine has also been observed. The clinical implications of these observations may be related to the elevated levels of LH known to occur after menopause. Such hormones may serve as continual trophic stimuli accounting in part for the development of anaplastic carcinomas later in life. Such a concept might also explain the more aggressive behavior of well differentiated carcinomas occurring after menopause. Unfortunately, since there have been no studies on the responsiveness of anaplastic or small cell neoplasms to TSH or other trophic stimuli, this can only be suggested as a hypothesis. Anaplastic carcinomas of the thyroid have not been demonstrated to selectively concentrate iodide; there are no clinical observations to suggest dependence upon TSH. Consequently, there would seem to be little role for therapy with either of these methods in the management of anaplastic thyroid carcinoma.

The cell of origin of small cell neoplasms has not been established. There are no similar neoplasms in animals. It is possible that most or all of these lesions are variants of lymphomas. This view is also shared by others.[20] Their radio responsiveness is consistent with such a thesis. Due to the absence of distinguishing, consistent morphologic characteristics which separate small cell carcinomas from lymphomas of the thyroid, the clinical course of patients is the only method available to differentiate between the two types of neoplasms. Walt[25] indicated that the prognosis of lymphoma, particularly if well localized, is more favorable than that of small cell carcinoma. Our findings suggest that differentiation of small cell carcinoma from lymphoma of the thyroid, is of more academic than practical interest. Currently, the management of these lesions is similar.

The limited experience in the management of thyroid carcinomas with chemotherapy is documented by a few case reports and the observations of Silverberg *et al.*[21]

TABLE 2. *Tissues Found Involved by Metastatic Neoplasm at Post mortem Examination*

Involved Tissues	Anaplastic 15 Patients	Small Cell 4 Patients
Thyroid	46.6% (7)	100% (4)
Trachea	26.6% (4)	75% (3)
Neck nodes	80.0% (12)	100% (4)
Neck other	60.0% (9)	100% (4)
Gastrointestinal tract	0% (0)	100% (4)
Pulmonary	100.0% (15)	75% (3)
Bone	80.0% (12)	25% (1)
Other soft tissue	53.3% (8)	50% (2)

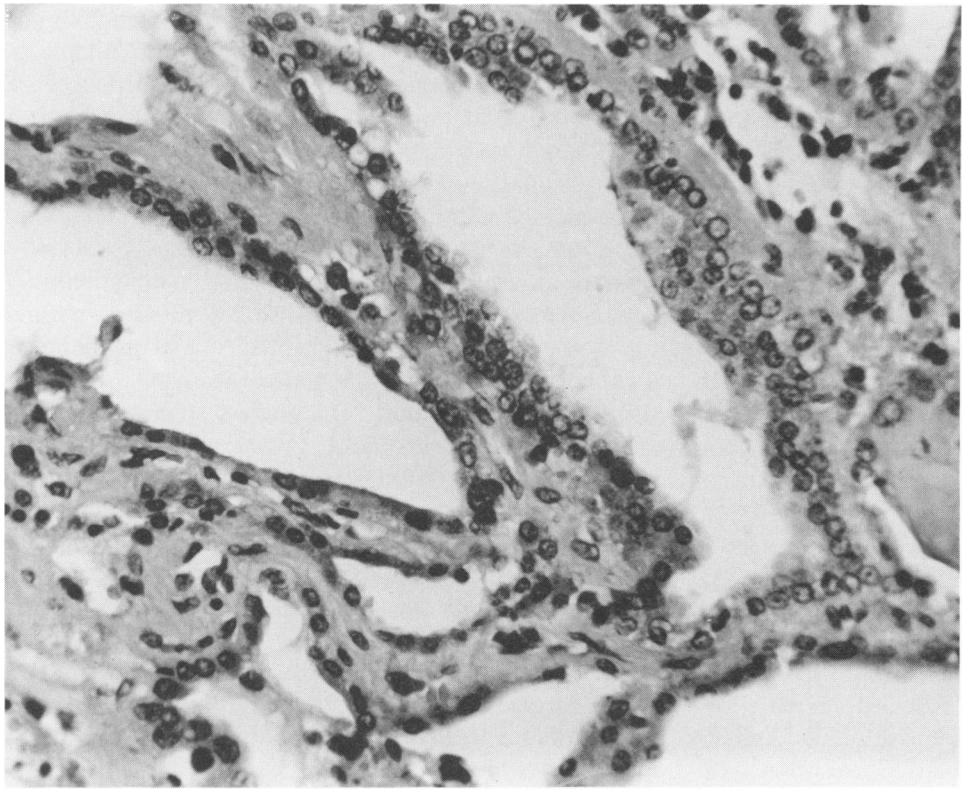

FIG. 13. Follicular carcinoma occurring with small cell carcinoma shown in Fig. 5. (340×).

and Gottlieb *et al.*[12] Well differentiated thyroid cancers which generally grow slowly, have a metabolism similar to the normal thyroid and are not particularly sensitive to available carcinolytic drugs. Treatment of the more aggressive poorly differentiated cancers is in keeping with cancer chemotherapy in general. Patients with generalized disease or distant metastases or radio resistant tumors may be candidates for chemotherapy. Nitrogen mustard, 5 fluorouracil, cyclosphosphamide, hydroxyurea, adriamycin, and bleomycin have all been utilized[11,12,21] but their usefulness has not been established. An encouraging report cites the benefits of combination chemotherapy of cyclosphosphamide, 5 fluorouracil, methotrexate, vinblastine and rufocromomycin in one patient.[17]

The most extensive experience is that from the M. D. Anderson Hospital.[12] In 37 patients with both well differentiated and anaplastic carcinomas treated with a wide variety of drugs, there were five who had partial remission of the disease. One patient with a giant and spindle cell carcinoma responded to methotrexate, one with medullary carcinoma to phenylalanine mustard, and one each of medullary, Hürthle, and papillary-follicular carcinoma to adriamycin. Based upon this experience, a number of patients were treated with adriamycin.[11] Adriamycin is a fermentation product of the mold *streptomyces peucetius var caesius* and although the exact mechanism of action is unclear, it appears to bind nucleic acids, thereby inhibiting replication. In 17 patients treated over an 18-month period, improvement was observed in seven with either well differentiated or anaplastic neoplasms. One of four patients with a giant-spindle cell carcinoma had a response longer than 12 months. At the present adriamycin is the most promising of the chemotherapeutic agents against thyroid cancer. Because of the limited number of observations, however, its use must be regarded as investigational.

Summary and Conclusions

The experience with 107 patients with poorly differentiated neoplasms of the thyroid gland seen at the University of Iowa and North Carolina Memorial Hospitals during the past 42 years has been reviewed. The following conclusions emerge from the findings of this investigation:

(1) The clinical course of the patients indicate that important differences exist between the biologic behavior of lesions with anaplastic and those with small cell histopathologic characteristics. The latter are more responsive to surgical and irradiation therapy and have a better prognosis.

(2) Small cell neoplasms include carcinomas and lymphomas which cannot be differentiated on the basis of morphology. The findings suggest that both types of lesions have a similar response to therapy and survival. More sophisticated technics and study of larger numbers of cases may take it possible to differentiate these lesions; our experience indicates this is of academic rather than practical importance.

(3) Complete excision of the gross neoplasm, feasible in about one third of the cases, is the treatment of choice. The operative procedure should be tailored to the gross and microscopic findings.

(4) When complete excision of neoplasm is not possible, as much gross neoplasm should be removed as consistent with preservation of parathyroid, recurrent nerve and other vital functions. Residual neoplasm should be treated with high voltage irradiation. This therapeutic approach will result in significant palliation in some patients with advanced anaplastic carcinomas, and in most patients with small cell lesions.

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References

1. American Joint Committee for Cancer Staging and End Results Reporting: "Reporting of Cancer Survival and End Results." Bethesda, Maryland, National Cancer Institute, 1963.
2. Beahrs, O. H. and Pasternak, B. M.: Cancer of the Thyroid Gland. Curr. Probl. Surg., 1969.
3. Beemer, R. K. and Baker, H. W.: Anaplastic Carcinoma of the Thyroid. Northwest Med., **69**:417, 1970.
4. Berenblum, L.: A Speculative Review. The probable Nature of Promoting Action and Its Significance, Understanding the Mechanism of Carcinogenesis. Cancer Res., **14**:471, 1954.
5. Berkson, J. and Gage, R. P.: Calculation of Survival Rates for Cancer. Proc. Mayo Clinic, **25**:270, 1950.
6. Buckwalter, J. A., Mason, E. E., Rowley, R. D. and Broer, R. A.: Thyroid Cancer Biology. *Arch. Surg.*, **76**:667, 1958.
7. Buckwalter, J. A. and Thomas, C. G., Jr.: Selection of Surgical Treatment for Well Differentiated Thyroid Carcinomas. Ann. Surg., **176**:565, 1972.
8. Crile, G., Jr.: The Endocrine Dependency of Certain Thyroid Cancers and the Danger That Hypothyroidism May Stimulate Their Growth. Cancer, **10**:1119, 1957.
9. Cutler, S. J. and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chronic Dis., **8**:699, 1958.
10. Doniach, I.: Etiological Considerations of Thyroid Cancer *in* Tumors of the Thyroid Gland. (Ed.) Sir David Smithers, E. and S. Livingstone, Edinburgh and London, 1970, p. 55.
11. Gottlieb, J. A. and Hill, C. S., Jr.: Treatment of Thyroid Cancer with Adriamycin. Presented at the American Thyroid Association Meeting, October, 1972. Chicago, Illinois.
12. Gottlieb, J. A., Hill, C. S., Ibanez, M. L. and Clark, R. L.: Chemotherapy of Thyroid Cancer—An Evaluation of Experience with 37 Patients. Cancer, **30**:853, 1972.
13. Granner, D. K. and Buckwalter, J. A.: Poorly Differentiated Carcinoma of the Thyroid Gland. Surg. Gynecol. Obstet., **116**:650, 1963.
14. Hill, S., Jr.: Personal Communication.
15. Hinshaw, H. T., Schorr, I., Thomas, C. G., Jr., Cooper, M. A.

and Ney, R. L.: Inappropriate Adenylcyclase Hormone Response of Certain Endocrine Tumors. Proc. Fourth Int. Congress Endocrinol., 1972.

16. Ibanez, M. L., Russell, W. O., Albores-Saavedra, J., Lampertico, P., White, E. C. and Clark, R. L.: Thyroid Carcinoma—Biologic Behavior and Mortality. Cancer, **19**:1039, 1966.
17. Israel, L., DePierre, A. and Chahinian, P.: Combination Chemotherapy for 418 Cases of Advanced Cancer. Cancer, **27**:1089, 1971.
18. Koch, G. G., Johnson, W. D. and Tolley, H. D.: A Linear Model's Approach to the Analysis of Survival and Extent of Disease in Multi-Dimensional Contingency Tables. J. Am. Stat. Assoc., **67**:783, 1972.
19. Meissner, W. A. and Phillips, M. J.: Diffuse Small Cell Carcinoma of the Thyroid. Arch. Pathol., **74**:41, 1962.
20. Rayfield, E. J., Nishiyama, R. H. and Sisson, J. C.: Small Cell Tumors of the Thyroid. Cancer, **28**:1023, 1971.
21. Silverberg, S. G., Hutter, R. V. P. and Foote, F. W., Jr.: Fatal Carcinoma of the Thyroid: Histology, Metastases and Causes of Death. Cancer, **25**:792, 1970.
22. Staunton, M. D. and Martin, M.: An Analysis of the Results of Initial Treatment for Patients With Malignant Tumors of the Thyroid Seen at the Royal Marsden Hospital 1945–1963. *In* Tumors of the Thyroid Gland, Edited by Sir David Smithers, E. and S. Livingstone, Edinburgh and London, 1970.
23. Thomas, C. G., Jr.: Progression in Thyroid Cancer. Clin. Endocrinol., **2**:262, 1968.
24. Thomas, C. G., Jr., Pepper, F. D. and Owen, J.: Differentiation of Malignant from Benign Lesions of the Thyroid Gland Using Complementary Scanning with 75Selenomethionine and Radioiodide. Ann. Surg., **170**:396, 1969.
25. Walt, A. J., Woolner, L. B. and Black, B. M.: Small cell Malignant Lesions of the Thyroid. *In* Trans. Am. Goiter Assoc., Charles C Thomas, Springfield, Illinois, 1956.

Discussion

Dr. W. Coupery Shands (Jackson): I enjoyed Dr. Thomas' and Dr. Buckwalter's paper very much. I thought it was a splendid paper, with a 40-year follow-up.

Three years ago, before this Association, we presented a small series of 107 thyroid carcinomas followed for 15 years in three Jackson hospitals, and in this group there were 17 cases of anaplastic carcinomas. As Dr. Thomas pointed out, it seems well established that well-differentiated thyroid carcinomas may become transformed into the anaplastic group, particularly giant and spindle cell carcinomas.

In our group of 17, Dr. Gatlin, the co-author, a pathologist, was able to identify this change histologically, in that papillary elements were present with either the spindle or the giant cell in three cases. Clinically, it is impossible to separate this group, because all of these patients have had long-standing goiters and have recent growth; but, of course, the outlook in this group is dismal, as pointed out by Dr. Thomas.

As far as the small cell lymphoma controversy, this sometimes will pose a problem at the operating table on frozen section, because even an experienced pathologist may be unable to differentiate between the diagnosis of reticulum cell lymphoma versus small cell carcinoma. In fact, we have deferred to Dr. Hazard's opinion on this on two occasions.

The only point of practical importance is that, or course, if the lymphoma is confined to the thyroid, as pointed out by Woolner and others, the prognosis is substantially better, I believe, in reticulum cell than in small cell carcinoma of the thyroid. If there is extension beyond the thyroid, the surgeon is then faced with the dilemma of how aggressive to be in the surgical treatment at the moment, and, of course, would usually defer for a permanent section. It might be pointed out that Dr. Thomas and Dr. Buckwalter have an excellent survival record in small cell carcinomas of the thyroid; but in general, most reported series of cases do not indicate this high survival, and there would be more reliance on irradiation in the lymphoma group than in the small cell carcinomas.

Dr. Joseph A. Buckwalter (Closing): I thank Dr. Shands for his kind and thoughtful remarks. This case emphasizes two important aspects of small cell neoplasms of the thyroid: First, the difficulty of distinguishing between reticulum cell neoplasms, lymphomas and small cell carcinomas of the thyroid gland; secondly, the importance of an aggressive, positive approach to therapy in these patients.

[Slide] The patient, a 48-year-old woman, was initially treated with lobectomy and radical neck dissection. The initial impression was that this was a small cell carcinoma of the thyroid gland. At the time of the initial treatment she was given an inadequate dose of the low voltage irradiation.

Three years later, a second course of irradiation was given again, a relatively modest dose, for possible residual neoplasm.

Six years after diagnosis, she was seen for the first time at the University of Iowa Hospital. At this time it was felt she had no evidence of residual neoplasm. Three years later, examination revealed recurrent neoplasm in the neck. At operation, because the neoplasm had invaded the trachea, the esophagus, and incorporated the major vessels and nerves in the neck, it was decided that she was inoperable.

Three years later, a more aggressive surgeon performed a laryngectomy, esophagectomy, and superior mediastinal dissection. She has had no additional irradiation therapy.

Eighteen years after the original diagnosis, the patient, now 66 years of age, is free of gross evidence of recurrent or residual neoplasm. Reevaluation of the multiple sections of tissues obtained indicates that this may have been a reticulum cell neoplasm rather than a small cell carcinoma of the thyroid. It seems possible, in retrospect, that supervoltage full therapy irradiation at the time of the initial therapy might have eradicated the neoplasm.

Consistent with current concepts of the mechanism of the action and experience with cancer chemotherapy, poorly differentiated than well differentiated thyroid neoplasms should be more responsive. Nitrogen mustard, 5-fluorouracil, cyclophosphamide, hydroxyurea, adriamycin, bleomycin, methotrexate, vinblastin, and rufocromomycin have all been used to treat patients with advanced thyroid neoplasms. The most extensive experience of which we are aware is at the M. D. Anderson Hospital. This experience suggests that adriamycin is the most promising chemotherapeutic agent for the use in advanced, poorly differentiated thyroid neoplasms.