# The many appearances of papillary carcinoma of the thyroid

William A. Hawk, M.D.
J. Beach Hazard, M.D.

*Department of Pathology*

The many gross and microscopic appearances of papillary carcinoma of the thyroid have provided some challenges to the field of taxonomy, but more importantly the challenge of correct diagnosis must be met if this cancer is to be properly treated. In most patients, papillary carcinoma is a controllable cancer with a distinctive biologic behavior. Ten- and 20-year survivals are the rule rather than the exception, and indeed when papillary carcinoma is properly treated, even longer periods of survival can be expected. The purpose of this report is to detail the gross and histologic patterns of the disease as they relate to the biologic behavior of this neoplastic group. The principal gross subtypes are summarized in *Table 1*.

In a series of 300 consecutive cases of papillary carcinoma of the thyroid collected from 1921 through 1960, there were 197 for which accurate gross descriptions or photographs were available for assessment. Approximately 78% of the carcinomas fell into the usual or diffuse variety, 12% qualified as small, 8% as encapsulated, and 2% as massive. No massive papillary carcinomas have been seen at the Cleveland Clinic since 1960, but there has been a slight increase in the percentage of small and encapsulated subtypes.

Papillary carcinoma is usually a nonencapsulated tumor mass sharply circumscribed from the adjoining thyroid parenchyma. The margins of the tumor mass may be bosselated or scalloped. It is not uncommon for the neoplasm to extend to the thyroid capsule which it usually does not violate. Typically, the lesions are tan to tan-white, firm to hard, and the cut surface is usually flat or may bulge slightly. Fibrous trabeculation, often with central sclerosis, is common. The neoplasm may replace part or all of the lateral lobe or isthmus (*Fig. 1*). The resemblance of this lesion to granulomatous or subacute thyroiditis on gross examination is striking;

**Table 1.** Gross subtypes of papillary carcinoma

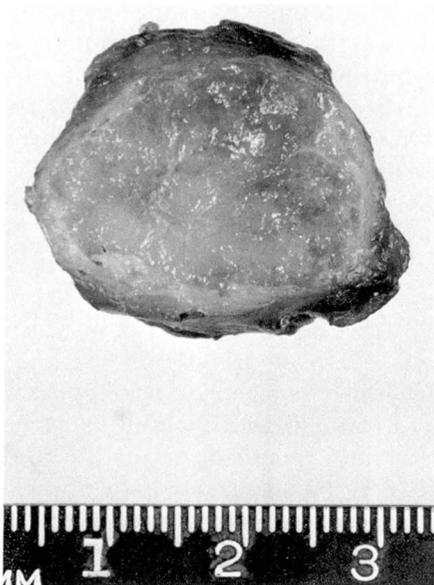|  |
| --- |
| A. Usual or diffuse |
| B. Small |
| C. Encapsulated |
| D. Massive |



**Fig. 1.** This lesion replaced much of the thyroid lobe, resected the thyroidal capsule, and was tan to tan-white.

the mimicry may be so striking that histologic section is required to distinguish between the two lesions.

Small papillary carcinomas have arbitrarily been defined as those which are less than 1.5 cm in their greatest cross diameter. Most of the tumors in this group were smaller than 1.0 cm in diameter (*Fig. 2*). On cross section they resembled a scar or focus of granulomatous inflammation. Such tumors were usually not palpable and were found either incidentally at thyroidectomy performed for another cause or signaled their presence by producing lymph node metastases.

The encapsulated type of papillary carcinoma is deceptive. Grossly, the lesion appeared as an encapsulated mass, the capsule being well-defined and of varying thickness. Even upon close inspection, the capsule appeared intact and gross breaching of this fibrous envelope was not observed in any case. The lesions were tan to tan-white or reddish-brown and often displayed irregular fibrous trabeculation. Cystic degeneration with evidence of old hemorrhage was also observed. None of the neo-



**Fig. 2.** This small papillary carcinoma measures less than 1.0 cm in cross diameter and appears as a sharply circumscribed scar-like area amid otherwise unremarkable thyroidal parenchyma.

plasms displayed the semitranslucent cut surface noted in follicular adenomas.

The rare massive form is quite striking. The lesion was usually larger than 6 cm in cross diameter and frequently involved both thyroid lobes (*Fig. 3*). On cross section, the tumor was grossly papilliferous or granular, often with areas of cystic degeneration. Fusion to proximal cervical lymph node metastases made the clinical presentation of this lesion larger and more grotesque. The histologic patterns of papillary carcinoma are listed in *Table 2*.

On the basis of histologic assessment, cases were assigned to the appropriate subclassification. Thirty-five percent were classified as principally papilliferous, 35% as principally follicular, 11% as equally mixed, 12% as tall cell, and 7% as containing solid areas. From an analysis of each of these subtypes, several observations were made.
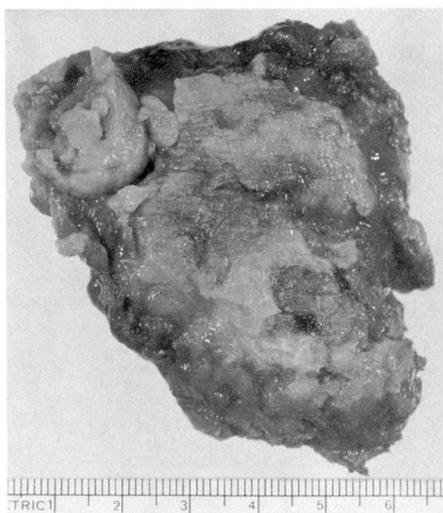
The principally papilliferous var-

**Table 2.** Histologic patterns of papillary carcinoma of the thyroid

A. Principally papilliferous
B. Principally follicular
C. Equally mixed papillary and follicular
D. With solid areas
E. Tall cell

iant presents little difficulty in recognition. The individual papillations are formed of a well-defined, central fibrovascular core covered by neoplastic thyroidal epithelium (*Fig. 4*). These papillae are quite distinct from the papillary infoldings associated with follicular hyperplasia of whatever cause, for the infoldings of follicular hyperplasia lack the central fibrovascular core. The pseudopapillations seen in some follicular adenomas and in nodular goiter are somewhat more difficult to distinguish. These latter structures are formed by the rupture of two adjoining colloid distended follicles. The pseudopapillae are, therefore, covered on both sides by regular epithelium which is identical to that forming the other colloid distended follicles, and the core of the papillation frequently contains microfollicles, a feature not observed in papillary carcinoma.

The principally follicular variant poses more difficulties. In this subtype, the follicles are small to medium sized, often strikingly uniform, and formed of cells identical to those observed covering the papillations of the usual papillary carcinoma. Colloid, or more properly pseudocolloid, was present within these follicles in varying amounts, and the margins of the colloid were frequently scalloped. Only occasional colloid distended follicles were observed. Papillations were absent over many fields, and indeed many blocks were
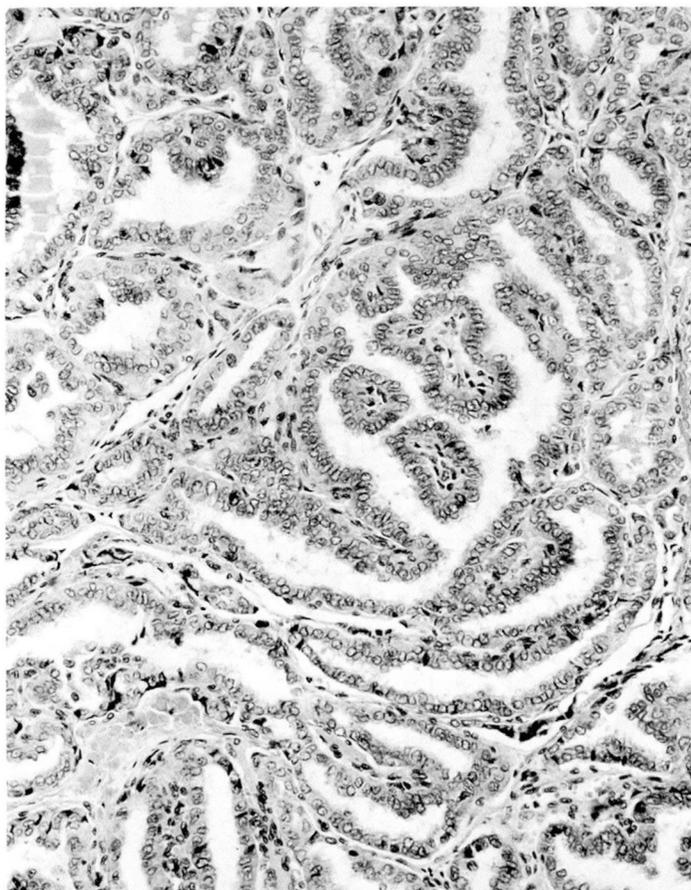


**Fig. 3.** The massive form of papillary carcinoma is of irregular globular shape and despite its large size usually respects the thyroidal capsule.

**Fig. 4.** Photomicrograph demonstrates the usual papillations which are characteristic of papillary carcinoma. Each papilla is formed of a well-defined fibrovascular core covered by a rather uniform cuboidal epithelium. Also present are well-formed follicles containing variable amounts of pseudo-colloid and lined by an epithelium which is identical to that which covers the papillations (hematoxylin and eosin stain, ×160).

required before papillary areas, the so-called signature of papillary carcinoma, could be identified. In addition, the follicles of papillary carcinoma were quite distinct. The tendency for adjoining follicles to form "party walls" was rarely observed, in contrast to follicular carcinoma of the thyroid where such luminal reduplication is commonly found. A reticulin stain is useful to delineate the well-defined reticulin network that outlines individual follicles and typi-

fies the follicular variant. The well-differentiated nature of these follicles may belie their true nature, which can best be appreciated in areas where these follicles invade the adjoining thyroid parenchyma.

Tumors formed of both papilliferous and follicular elements probably account for the majority of papillary carcinomas of the thyroid. The percentage of each type of component may vary. When either the papilliferous or follicular component predom-

inates, custom awards them to the appropriate respective category. Some neoplasms, however, contain an approximately equal proportion of papillary and follicular elements, and these are considered to be the mixed subtype.

Approximately 7% of papillary carcinomas contain solid areas of varying sizes. Such solid islands are formed of rather uniform, small, well-differentiated cells. These small cells contain nuclei identical with the nuclei of neoplastic elements which form the adjoining follicular or papillary structures and from which they are apparently derived. To warrant inclusion in a separate histologic subtype, the solid areas comprise a conspicuous proportion of the neoplasm ranging from 10% to 80% or more of the neoplasm sample examined histologically. Foci of squamous metaplasia also may be observed within the solid areas. Confusion with medullary carcinoma occasionally arises, since the solid areas may be associated with an unusually abundant pale-staining hyaline stroma suggestive of amyloid. However, we have been unable to demonstrate amyloid in the stroma of any of these carcinomas.

The tall cell variant warrants special consideration (*Fig. 5*). This cell type is distinctive in that the cell itself is of tall columnar shape, the height of the cell being at least twice the breadth. Although this cell type may produce follicles, it is most often found in a highly papilliferous pattern and, in addition, may be strikingly oxyphilic.

The cell type associated with all histologic subtypes or variants other than the tall cell variant can assume at least several appearances. In many papillary carcinomas, the epithelial cell contains a round to slightly ovoid nucleus with a pale or watery center, the so-called "Orphan Annie" eye nucleus. This is characteristic of papillary carcinoma. The cytoplasm of these cells is usually pale pink to amphophilic and finely granular, and the cell is cuboidal. This type of cell is not known to occur in follicular carcinoma of the thyroid. Other papillary carcinomas, however, may be formed of cuboidal to low columnar epithelial cells, in which the nucleus is slightly clefted and nuclear chromatin is finely stippled. The cytoplasm of these cells generally stains pink or amphophilic.

Although the histologic variants are distinctive to the microscopist, the relationship of these subtypes to biologic behavior is of great importance. There were 193 patients available for follow-up; the period ranged from 1 to 32 years (average 7.3 years). Seventeen patients died from the disease, and an additional six patients are living with persistent or recurrent disease. When the several histologic subtypes were matched against the overall biologic behavior of papillary carcinoma, each subtype, with the exception of the tall cell variant, behaved in strikingly similar fashion, with 93% of the patients free of disease for an average period of observation of 7.3 years.

Eighteen patients were designated as belonging to the tall cell subtype. These patients averaged 57 years of age at the time of diagnosis in contrast to an average age of 36 years for the overall group. As indicated previously, the tall cell variant is associated with strikingly papilliferous architecture and with the production of rather large bulky lesions. Virtually
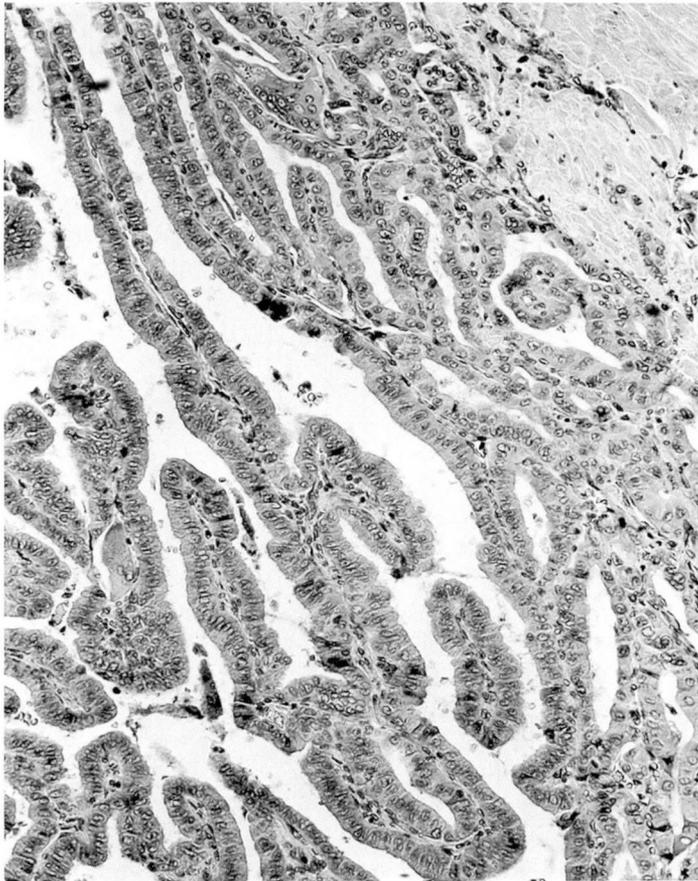
**Fig. 5.** Photomicrograph shows the typical appearance of the tall cell variant. The epithelial cells covering the papillation are of tall columnar type, the height of the cell exceeding the width by a ratio of at least 2:1 (hematoxylin and eosin stain, ×160).

all massive tumors were of this histologic cell type. More importantly, an excessive mortality was associated with this group. Four of the 18 patients died of the disease within a few years after diagnosis; the longest interval between diagnosis and death was 7 years.

The encapsulated gross subtype merits further discussion. This is a small but important subgroup of papillary carcinoma, of which 15 cases in the present series were available for analysis; eleven of these were women and four were men. The av-

erage age of patients in this series was 40 years and the median age 37 years. The sex ratio (3:1) was identical to that for papillary carcinoma in general in the 15- to 45-year age group. Lymph node metastases developed in only three of the 15 (20%), in contrast to approximately 54% of the overall series as observed at the time of primary operation. There has been but one death in the series; this was one of the earliest patients who died with lymph node and bony metastases 9 years after the disease was diagnosed. The remaining patients in this series

have survived free of disease for as long as 18 years. These factors suggest that the encapsulated form of papillary carcinoma has a better prognosis than papillary carcinoma in general. The prognosis for this small series is so unusually good that it suggests an error in diagnosis. However, these cases of encapsulated or principally encapsulated papillary carcinoma of the thyroid were based on histologic evidence of penetration through the capsule or the production of lymph node metastases or both (*Fig. 6*). Also the grossly encapsulated forms, except the tall cell variant, were of the histologic subtypes.

Size appears to be an important determinant of the biologic behavior of papillary carcinomas of the thyroid. Fifty-four tumors could be clas-

sified as small (less than 1.5 cm in diameter) among the 193 patients for whom follow-up was available. There were no deaths from disease in this group, but one patient, a 10-year-old boy has survived 10 years with the disorder. In addition, one patient died from other cause. This contrasts rather sharply with the mortality observed among the other gross forms of papillary carcinoma, in which 17 patients have died and five are living with known disease. Nine patients died from other causes, a proportionately higher number. As reported previously by one of us (JBH), the small papillary carcinomas that showed a scalloped fibrous border without detectable invasion of the thyroid parenchyma by papillary carcinoma cells never produced distant
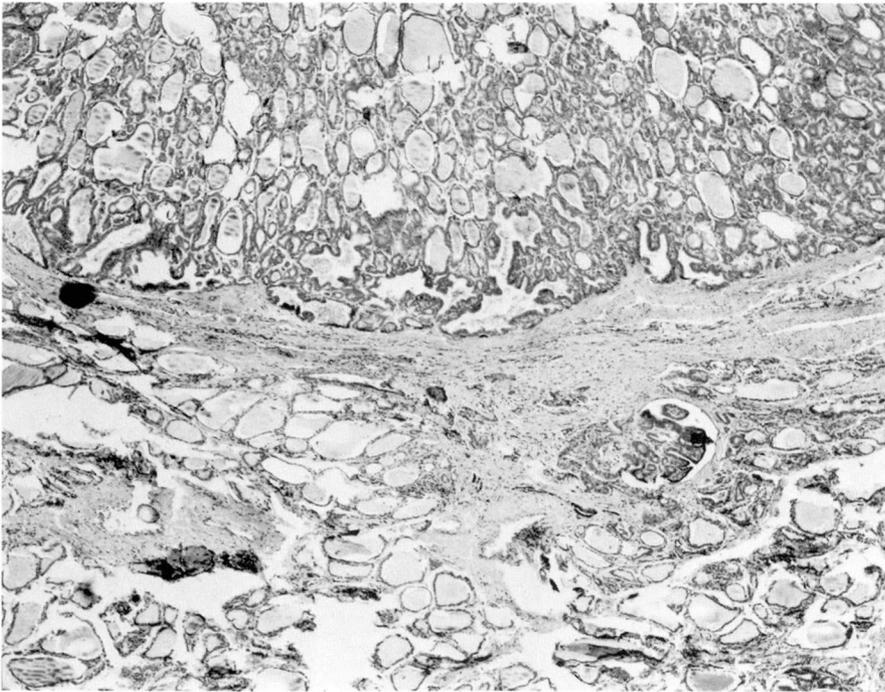


**Fig. 6.** Photomicrograph of a principally encapsulated papillary carcinoma of thyroid demonstrates the extension of the neoplastic elements through the capsule wall into the adjoining thyroid parenchyma (hematoxylin and eosin stain, ×40).

or lymph node metastases, and such a lesion was usually found at thyroidectomy done for other cause (*Fig. 7*).[1] However, in those microcarcinomas in which neoplastic elements had access to adjoining thyroid plates or lobules, lymph node deposits occurred in direct proportion to the area at risk, and in several examples the lymph node deposits were the clue to the presence of the small papillary carcinoma. The clinical behavior of this latter type is identical to that of the more usual forms. These observations are similar to those of Woolner.[2]

In the overall series, approximately 82% of the papillary carcinomas were solitary lesions within the lobe or isthmus of the thyroid and 18% were multicentric. When multicentricity occurred, both lobes were involved in slightly more than 50% of the patients. In the overall series, secondary tumor was found at the primary operation in lymph nodes in 54% of cases. In the majority of cases, node involvement was ipsilateral, but in approximately 25% of cases bilateral lymph node metastases were observed. This finding almost always coincided with involvement of the
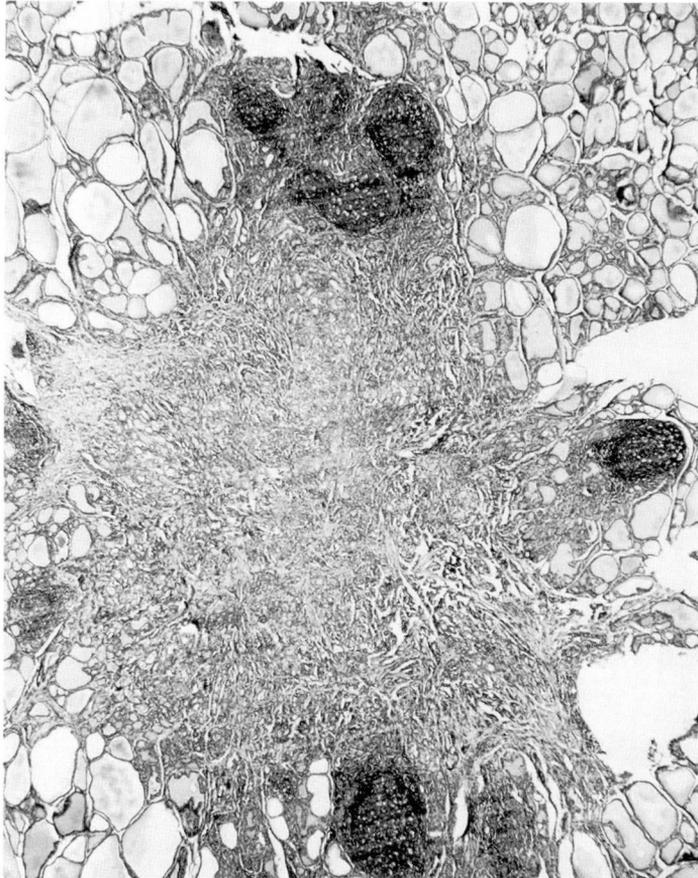


**Fig. 7.** This low-power photomicrograph shows a small microcarcinoma with the characteristic scalloped border. Infiltration of adjoining thyroid parenchyma occurred in only a few microfoci (hematoxylin and eosin stain, ×16).

thyroidal isthmus. Angioinvasion in the primary tumor was observed in 7.4% of the small papillary carcinomas and in 18% of the other gross subtypes. The importance of vascular invasion as a biologic determinant is difficult to assess. In a report by Franssila,[3] vascular invasion was regarded as important in determining survival. In that report of 97 patients, 19 died from carcinoma of the thyroid. Vascular invasion was noted in six patients and was associated with distant metastases in five patients, three observed at the time of operation, and two occurring later. In the present series, angioinvasion was noted in only four of the 17 patients who died of the disease. Because the frequency of angioinvasion increases with the size of the tumor, it would seem that this finding is probably not a major determinant of the biologic behavior of papillary carcinoma.

Psammoma bodies are a common finding in papillary carcinoma of the thyroid and were observed in approximately 50% of cases in the present series. The number of psammoma bodies in any given neoplasm varies. When present, psammoma bodies are very useful in the diagnosis of papillary carcinoma, since these structures occur extremely rarely in other thyroid disorders. In our experience, psammoma bodies have been observed in follicular carcinoma and in nodular goiter, but the total incidence of psammoma bodies in these groups is less than 1%. Klinck and Winship,[4] in a report on psammoma bodies and thyroid cancer, made similar observations and noted that psammoma bodies are best observed in association with solid masses of tumor cells projecting into cystic spaces.

The association of papillary carcinoma of the thyroid with struma lymphomatosa is not a strong one and occurred in only seven of 209 consecutive patients with papillary carcinoma examined here. In one of these patients, papillary carcinoma occurred first and struma lymphomatosa developed in the contralateral lobe 1 year after definitive thyroid surgery. Struma lymphomatosa must be distinguished from focal lymphocytic thyroiditis which is a most common concomitant of papillary carcinoma of the thyroid. The histologic features of focal lymphocytic thyroiditis are similar to those of struma lymphomatosa, but the process differs sharply in the extent and diffuseness of involvement and by the absence of goitrous changes attributable to thyroiditis. In many instances, papillary carcinomas may also be associated with foci of focal lymphocytic infiltration in the absence of significant follicular epithelial alteration. Patients with focal lymphocytic thyroiditis usually do not have the hypometabolic state associated with struma lymphomatosa and, therefore, do not have increased levels of thyrotropin which theoretically may be important in those cases of struma lymphomatosa associated with papillary carcinoma. It should also be pointed out that in a series of 287 patients with struma lymphomatosa followed for a similar period of time, none have developed papillary carcinoma.

The clinical and histopathologic observations on papillary carcinoma of the thyroid seem to establish certain important facts. The tumor appears to occur in many gross and histologic subtypes, only one of which seems to alter its good biologic behavior. The tall cell histologic variant is

associated with higher mortality, but also occurs in an older age group and in a principally papilliferous form. If anything, the principally encapsulated papillary carcinoma tends to produce fewer lymph node metastases and to be associated with the same general prognosis as for papillary carcinoma. The prognosis for small papillary carcinomas is also excellent, and those which have the scalloped sclerotic border and no contact with the adjoining thyroid plates are benign clinically and rarely, if ever, produce lymph node metastases. Because papillary carcinoma of the thyroid is a controllable cancer, it is important that all of its gross and microscopic subtypes be recognized and that this type of cancer not be confused with other forms of carcinoma of the thyroid, for which the prognosis tends to be less than excellent.

## References

1. Hazard JB: Small papillary carcinoma of the thyroid. A study with special reference to so-called nonencapsulated sclerosing tumor. Lab Invest 9: 86–97, 1960.
2. Woolner LB: Thyroid carcinoma; pathologic classification with data on prognosis. Semin Nucl Med 1: 481–502, 1971.
3. Franssila K: Value of histologic classification of thyroid cancer. Acta Pathol Microbiol Scand (A) Suppl 225: 1–76, 1971.
4. Klinck GH, Winship T: The psammoma bodies and thyroid cancer. Cancer 12: 656–662, 1959.