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Variants of papillary carcinoma of the thyroid: experience at Asir Central Hospital

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Papillary carcinoma of the thyroid is now further subclassifiable into its different variants. We report incidence, clinical behaviour and outcome of rare variants of papillary thyroid cancers at Asir Central Hospital, Saudi Arabia. These variants differ from each other not only on a morphometric basis, but also in clinical behaviour. Accordingly, we report our experience of different variants in a series of 35 papillary carcinomas. These cases were received in the surgical pathology laboratory of Asir Central Hospital from January 1987 to December 1994. We have reviewed clinical charts, microscopic slides and pathological reports of these carcinomas. The following results have been obtained: 20 cases were classical (usual) papillary thyroid carcinomas; seven were follicular variants; three were tall cell/columnar variants; two were oxyphilic variants; and one was a diffuse sclerosing variant. There were two de-differentiated papillary carcinomas (anaplastic carcinomas with foci of well-differentiated papillary carcinomas). These variants were also correlated with clinical parameters such as age, sex and nationality of the patients, aggressiveness of the tumours, types of surgery required, and follow-up when available.

Keywords: papillary carcinoma of thyroid, thyroid cancer.

Until recently, papillary carcinoma of the thyroid was regarded as a single group with indolent clinical course and excellent prognosis. This view is now changing. Recent reports[1] emphasize that papillary carcinoma should be further subclassified into its variants because of prognostic implications. These variants include follicular,[2] tall cell,[3] columnar cell,[4] diffuse sclerosing, oxyphilic (Hurthle cell), cribriform,[5] trabecular,[6] muco-epidermoid,[7] papillary carcinoma with nodular fasciitis-like stroma,[8] and de-differentiated papillary carcinomas.[9] Accordingly, in this report, we have determined the incidence of different types of papillary thyroid neoplasms at Asir Central Hospital, and have correlated this with the clinical findings.

MATERIAL AND METHODS

We searched surgical pathology files that related to goitre specimens received in Asir Central Hospital during a period of 8 years from January 1987 to December 1994. We reviewed only those cases in which a diagnosis of papillary carcinoma was made. The microscopic slides were examined and papillary carcinomas were further subclassified into the following groups based on histological pattern: usual papillary carcinomas; follicular variants of papillary carcinomas; tall cell/columnar variants; diffuse sclerosing variants; oxyphilic variants; and de-differentiated papillary carcinomas. We also reviewed clinical charts to determine such parameters as age, sex and nationality of these patients, aggressiveness of the tumours, types of surgery required and follow-up when available.

RESULTS

Four hundred and seventeen surgically excised thyroid specimens were received in the Department of Pathology of Asir Central Hospital during a period from January 1987 to December 1994. Among these there were 57 cases of different malignancies of the thyroid. Thirty-five of these malignancies were papillary carcinomas. The following results were obtained when these papillary carcinomas were subclassified into the variants: 20 cases of usual type; seven follicular variants; three cases of tall cell/columnar variants; two oxyphilic variants; one diffuse sclerosing variant; and two de-differentiated papillary carcinomas. The age, sex and nationality of these patients are shown in Table 1.

Usual type and follicular variant of papillary carcinoma

There were 20 cases of the classical (usual) type of papillary carcinoma. The histopathology of the usual type of papillary carcinoma is well known. This type features complex papillae, empty-looking ('orphan Annie') nuclei, psammoma bodies, nuclear grooves and cytoplasmic inclusions. We had seven cases of follicular variant. The

Table 1 Histological variants of papillary carcinoma of the thyroid seen in Asir Central Hospital, Abha, Saudi Arabia, over an 8-year period ($n = 35$)

Variant of papillary carcinoma	*n* (%)	Mean age	Females	Saudi
Classic	20 (57)	36	14	15
Follicular	7 (20)	30	6	4
Tall/columnar	3 (8)	65	3	3
Oxyphil	2 (6)	32	2	1
Diffuse sclerosing	1 (3)	46	0	1
De-differentiated	2 (6)	70	2	2

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follicular variant is similar to the usual type except that the cells form follicles instead of papillae (Figure 1). The majority of these carcinomas were seen in women with a mean age of 36 years. When a patient presented with a solitary nodule in the thyroid, the average size of the tumour was 3 cm. Five of these cases, however, presented as multinodular goitres.

Tall/columnar cell variant

There were three cases of the tall/columnar cell variant. The cells were arranged around well-developed papillae. Mitotic figures were easily found, but calcospherites were uncommon. The height of a cell was at least twice its width (Figure 2). In some areas the papillae were lined by a single layer, while in other areas there was nuclear stratification. The tumour was regarded as tall cell variant if papillae were lined by a single layer of the tall cells. It was denoted columnar cell variant if the tall cells showed stratification. Generally these two features co-existed in the same tumour.

The first case was seen in a 70-year-old woman who presented with a right-sided neck mass measuring approximately 6×3 cm^2. The overlying skin was fixed and erythematous but not ulcerated. An attempted total thyroidectomy failed, and therefore a right partial lobectomy was performed. Follow-up of this patient is not available.

The second case occurred in an 80-year-old woman who came with a swelling (10×7 cm^2) of the right side of the neck causing deviation of the trachea. The overlying skin was erythematous with eczematous change but without ulceration. A right total lobectomy

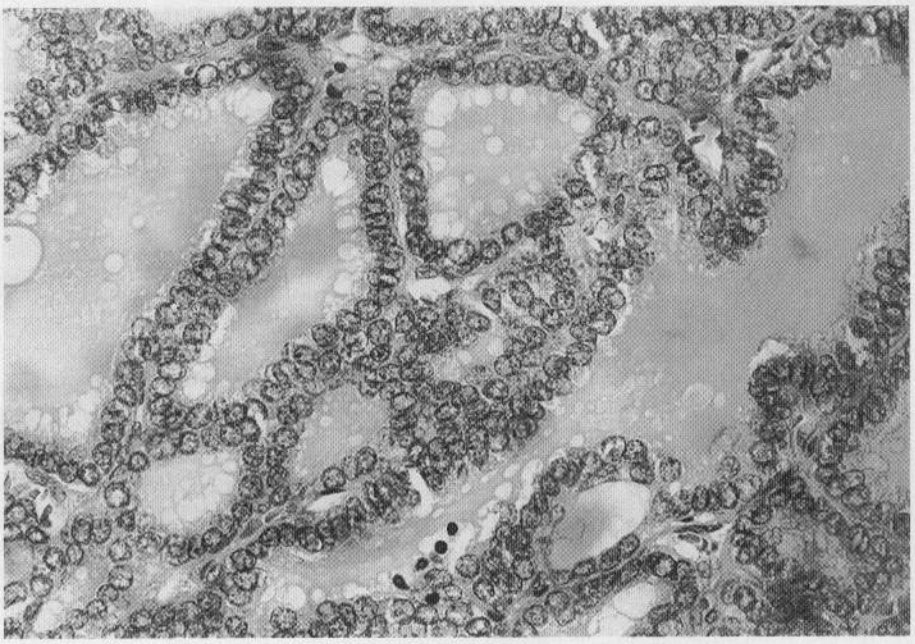

Figure 1 Follicular variant of papillary carcinoma of the thyroid. Neoplastic cells are arranged in follicles. Large, crowded, overlapping and empty-looking ('orphan Annie') nuclei are the characteristic features. (Haematoxylin and eosin; original magnification × 250.)

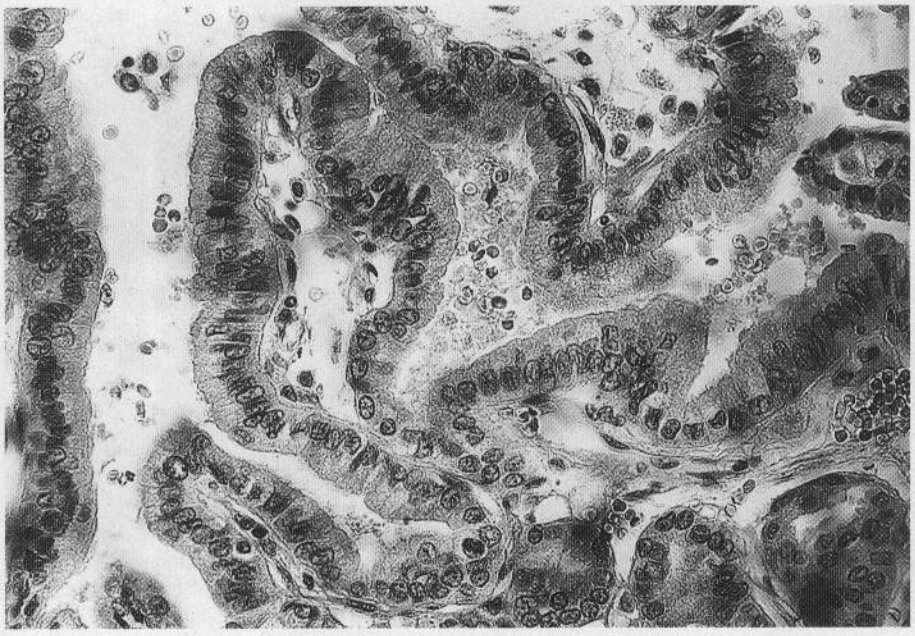

Figure 2 Tall/columnar cell variant of papillary carcinoma of the thyroid. The cells are arranged around well-developed papillae. The height of the cells is at least twice their width. In some areas the papillae are lined by a single layer, while in other areas there is nuclear stratification. The former areas are regarded as an example of the tall cell variant, and the latter areas as an example of the columnar cell variant. (Haematoxylin and eosin; original magnification × 250.)

was performed. Multiple lymph nodes were also involved. The tumour recurred 2 years later, when debulking was undertaken. She was alive and well when seen 1 year after the second operation.

The third case was seen in a 45-year-old man who also presented with a neck mass and hoarseness of voice due to right-sided vocal cord paralysis. A total thyroidectomy was performed along with lymph node dissection. Follow-up of this patient is not available.

Diffuse sclerosing papillary carcinoma

We had one case of diffuse sclerosing papillary carcinoma. This 46-year-old male patient was referred to us with a 3-year history of swelling of the neck. The thyroid gland was considerably enlarged in a diffuse form. There were several lymph nodes palpable in both cervical areas. A total thyroidectomy was performed with bilateral lymph node dissections. Seven lymph nodes were positive for metastatic carcinoma on histological examination. Histopathological examination of the resected specimen of the thyroid revealed extensive sclerosis in the stroma around the small island of tumour cells (Figure 3). The tumour had spread widely in the thyroid parenchyma and also had extended outside the capsule. There was patchy lymphocytic infiltrate and numerous psammoma bodies. Post-operatively, the patient received radiation treatment and thyroxine replacement. No recurrence was noted in a follow-up period of 2 years.

Oxyphilic variant

There were two cases of oxyphilic papillary carcinomas. One was in a 15-year-old Saudi boy who was admitted with swelling of the right side of the neck. Cervical lymph nodes were not palpable. Thyroid function tests including T-4, T-3 and thyroid-stimulating hormone (TSH) were within normal limits. A right lobectomy was performed. The tumour was well circumscribed with an intact capsule. The post-operative course was uneventful.

The second case of oxyphilic papillary carcinoma was found in a 50-year-old who had history of cerebral infarct and hemiplegia. She presented with a well-deliniated nodule in the thyroid. The tumour was encapsulated.

Microscopically, both these neoplasms were predominantly composed of gnarled, complex branching papillae having slender fibrovascular stalks. Fillicular structures and the amount of fibrosis were not significant. Solid foci were not evident. The cells lining these papillae contained abundant eosinophilic cytoplasm, at least twice as much, or more, as for the usual type of carcinoma (Figure 4). The nuclei were round or ovoid. The nuclear chromatin was finely speckled. The position of the nuclei was quite variable but many were apical.

Foci of differentiated papillary carcinoma among undifferentiated carcinoma

We had two cases of de-differentiated carcinoma. One occurred in an 85-year-old woman and the other in a 55-year-old woman. Both the women presented with an extensive neck mass in which the tumour was so extensive that complete resection was not possible. Microscopically, the tumour was composed of anaplastic cells, among which small foci of well-differentiated papillary carcinoma were visible (Figure 5). These foci would have been missed if the sampling obtained for microscopic examination were not enough. The undifferentiated carcinomas consisted of solid patterns of growth, often containing many mitoses and zones of necroses.

DISCUSSION

In our evaluation of our 35 cases, we found that the majority of our papillary neoplasms fell into either the classical or the follicular type, thus ensuring good prognosis. Twenty-seven of our cases belonged to the classical or follicular variants. The usual papillary carcinoma is characterized by five well-known histopathological features: i.e. papillae; empty-looking nuclei; calcospherites; nuclear grooves; and nuclear pseudo-inclusions.[10] The follicular variant[2]

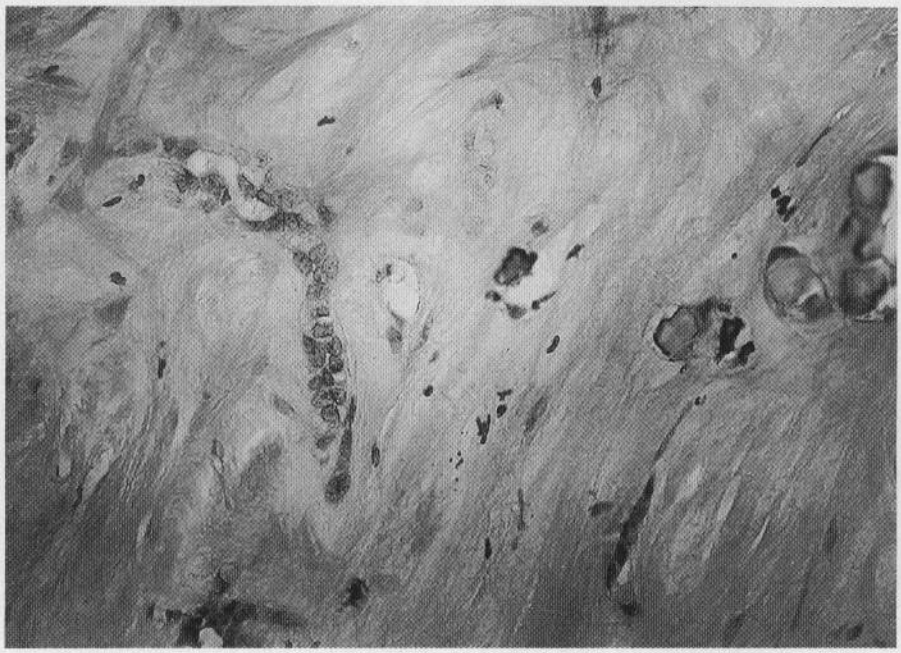

Figure 3 Diffuse sclerosing papillary carcinoma of the thyroid. The photomicrograph shows extensive sclerosis in the stroma around the small island of tumour cells. Many psammoma bodies are seen in the left half of the field. (Haematoxylin and eosin; original magnification × 250.)

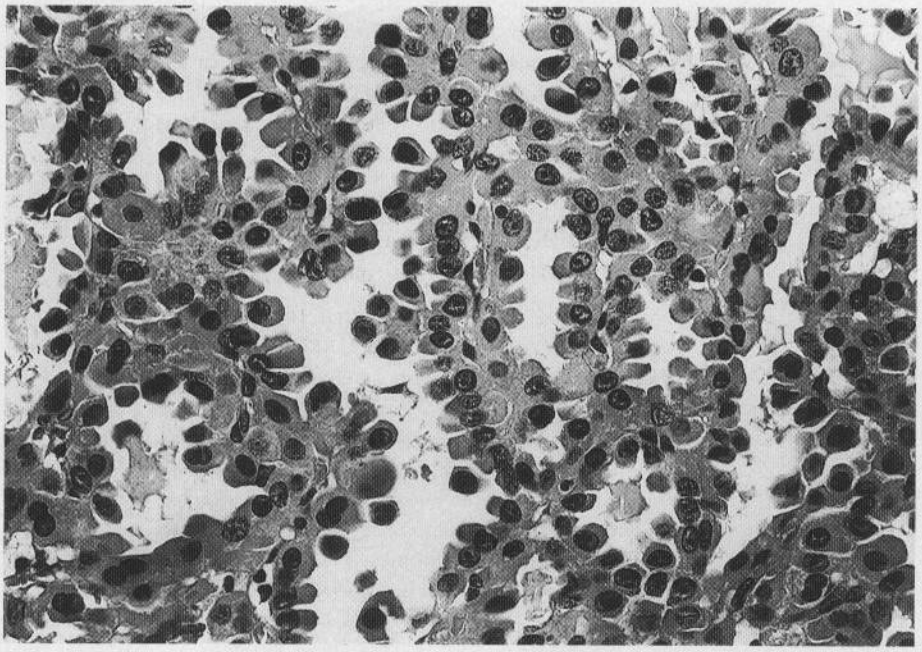

Figure 4 Oxyphilic variant of papillary carcinoma of the thyroid. This photomicrograph shows complex branching papillae with slender fibrovascular stalks. The cells lining these papillae contain abundant eosinophilic cytoplasm, at least twice as much, or more, as for the usual type. The nuclei are round or ovoid. The nuclear chromatin is finely speckled. The position of the nuclei is quite variable, but many are apical. (Haematoxylin and eosin; original magnification × 250.)

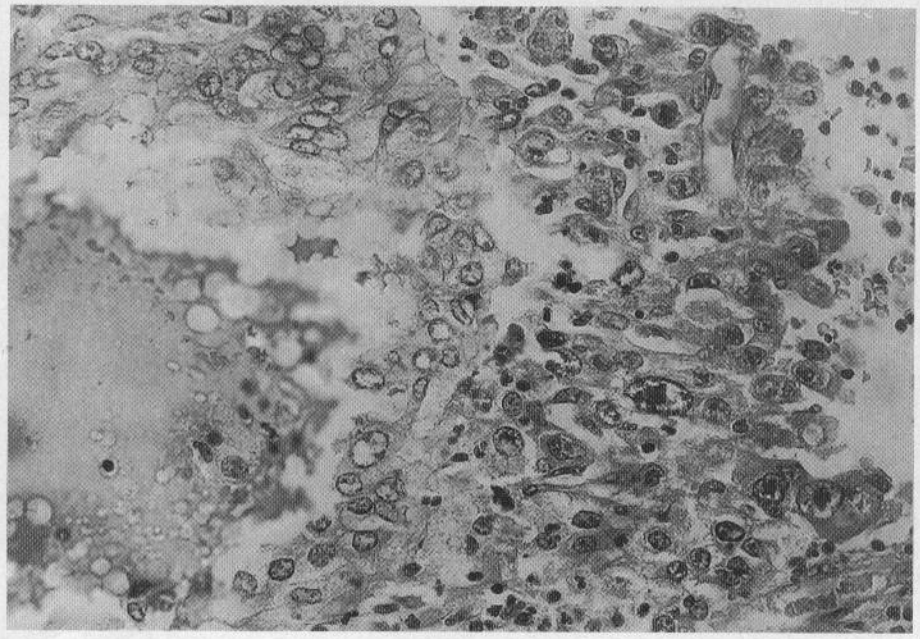

Figure 5 Differentiated papillary carcinoma among undifferentiated carcinoma. The photomicrograph shows sheets of anaplastic cells in the right half of the field. The nuclei are large and variable, and contain coarse chromatin. The nucleoli are also large and prominent. The left half of the field shows a follicle containing homogeneous colloid. The follicle is lined by the cells containing empty-looking nuclei that are characteristically seen in the well-differentiated follicular variant of papillary carcinoma of the thyroid. (Haematoxylin and eosin; original magnification × 250.)

has all the features of a papillary tumour except the presence of papillae. This means that the tumour has empty-looking nuclei, calcospherites, nuclear grooves, and nuclear pseudo-inclusions, but instead of forming papillae the cells are arranged in follicles. Fortunately, the prognosis of both of these variants is good.

Tall/columnar cell variant

At the time of initial reporting, our three cases of tall cell were considered as the usual type of papillary carcinoma. It was thus axiomatic to assume that these tumours would have a similar presentation and outcome to the usual papillary neoplasm. In fact, there were remarkable differences. Two of the tall cell variant cases had extension beyond the thyroid capsule with involvement of overlying skin. The third case also had several metastatic lesions in the lymph node. The surgeons had to face many difficulties during removal of the growth, and only partial removal was possible.

The tall cell variant of papillary carcinoma was first described by Hawk & Hazard[3] in 1976. This is a rare tumour and is seen in approximately 10% of cases of papillary carcinomas. This pattern is seen in the older age group, and behaves more aggressively when compared with the classical group. These patients tend to suffer local recurrences in the neck, often with invasion of the trachea, and many would succumb to this complication.[11] The tumour was extensive, involving neck muscles and subcutaneous tissue in two cases. Microscopically, the tall cell carcinoma was highly papillary and was composed of cells that were twice as tall as they were wide, and the cytoplasm was quite eosinophilic. Mitotic figures were

easily found. A tumour closely related to the tall cell was later described by Evans[4] as the columnar cell variant of papillary carcinoma. The tumour is histologically similar to the tall cell variant, except that stratification is noted among columnar cells lining the papillae. The tumour has the same aggressive behaviour as the tall cell variant. Generally both these variants are lumped together as the tall cell/columnar cell variant.[12] Akslen & Varhaug[13] have also described a case in which tall cell carcinoma and columnar cell carcinoma co-existed. Bronner & LiVolsi[14] have described five cases of spindle cell squamous carcinomas found in association with tall cell papillary carcinoma. Flint *et al.*[15] carried out DNA and morphometric analysis in the tall cell variant, and then compared these with the classical variant. They did not observe significant differences regarding nuclear DNA content, chromatin texture or nuclear size and shape between the two varieties. It is possible that the aggressive behaviour of this type of tumour might be due to the excessive number of mitoses.

Diffuse sclerosing papillary carcinoma

We had one case of the diffuse sclerosing variant of papillary carcinoma which occurred in a middle-aged man. Despite the short history of swelling in the neck, the tumour had behaved aggressively, extending outside the thyroid capsule, and had metastasized to several of the cervical lymph nodes. A similar aggressive behaviour has been reported by Vickery *et al.*,[11] Hedinger *et al.*[16] and Rosai.[12] Contrary to this, however, Fujimoto *et al.*[17] reported a favourable prognosis in 14 young female patients with this type of neoplasm. Since in most cases of diffuse sclerosing variant, the cancer cells have invaded almost the whole thyroid gland and many of the regional lymph nodes, the treatment recommended for such a variant is total thyroidectomy along with bilateral modified neck dissection. In patients having only unilateral involvement, however, a subtotal thyroidectomy may be carried out.[17] The diffuse sclerosing variant has to be differentiated from focal fibrosis, Hashimoto's thyroiditis and Riedel's thyroiditis. Focal fibrosis (as opposed to diffuse fibrosis) can be seen in the usual type of papillary carcinoma as well. Isarangkul[18] recorded dense focal fibrosis within tumour masses in 89% of his 37 cases of papillary carcinoma. However, the abundant psammoma bodies, the patchy lymphocytic infiltrates and the diffuse nature of the fibrosis that are characteristic of the diffuse sclerosing variant were absent in the focal fibrosis.

Oxyphilic variant

The oxyphilic variant is very rare. We encountered two such examples. We used papillae as our selection criterion, although oxyphilic papillary carcinoma may include neoplasms that lack papillae but have nuclear features characteristic of papillary carcinomas.[19] We did not include in this series any tumour in which oxyphilic cells constituted a minor component. Small areas of oxyphilic cells can normally be found in an otherwise classic papillary carcinoma. The interesting feature in our series was that both these neoplasms were well circumscribed, encapsulated and without metastatic lymph node involvement. There were no recurrences in the post-operative course of several years. However, there was a considerable age discrepancy between our two cases, one occurring in a 15-year-old boy and the other in a 50-year-old woman. The age range in the reported series was 10 to 70 years. The size of the neoplasm and the presence or absence of encapsulation appear to be more important in determining the patient's prognosis than is the oxyphilic nature of the neoplastic cells found in this variant of papillary thyroid carcinoma.

Foci of differentiated papillary carcinoma among undifferentiated carcinoma

Nishiyama *et al.*[9] have suggested that all undifferentiated carcinomas arise from well-differentiated tumours. Our two cases were seen in the older age group: one women was 85 years old and the other was 55 years old. These findings may suggest that the well-differentiated component which is usually seen in the younger age group might have been there for a considerable length of time and then de-differentiated into anaplastic carcinomas. Our finding is also supported by Carcangiu *et al.*,[20] who reported a study of 70 cases of anaplastic carcinomas. The age at the time of initial diagnosis in 67 of these cases was above 50 years.

CONCLUSIONS

In conclusion, we emphasize that a histopathological report of papillary carcinoma of the thyroid should indicate whether the tumour is of the usual type or belongs to an unusual variant which may have an adverse prognosis. This may ease the tension of the surgeon who might have faced difficulties during removal of the neoplasm, and might have been considering a more aggressive neoplasm than the usual type of papillary carcinoma. Some of the subtypes that have a worse prognosis than the classical type, such as the tall cell variant, should be identified on the microscopic slides. The age of the patient can also be an important clue. The tall cell variant is usually seen in the older age group. Similarly, highly aggressive anaplastic carcinomas also occur in the older age group, and, if diligently searched for on the microscopic slides, small foci of the well-differentiated component of papillary cancer can be identified.

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