Papillary Thyroid Carcinoma with Different Histological Patterns

Jen-Der Lin, MD; Chuen Hsueh[1], MD; Bie-Yu Huang, MD

Tumor-node-metastasis (TNM) staging is the most commonly used model for evaluating therapeutic strategies for papillary thyroid cancer (PTC). Additionally, different histopathological patterns and variants of PTC have been reported to influence the prognosis of these patients. We reviewed the clinical presentation, cancer recurrence, and cancer-specific mortality of the most frequent histological patterns, including the follicular variant (FVPTC), insular pattern, tall cell pattern, diffuse sclerosing type, PTC with Hashimoto's thyroiditis, and multicentric PTC. The tall cell variant of PTC is a more aggressive variant than classical PTC and has a poor prognosis. The high expression of Muc1 and type IV collagenase in these tumors may facilitate stromal degradation and increase the invasive potential. In contrast, approximately 18% of PTC patients have been identified as having FVPTC. FVPTC patients have a better survival rate than those with follicular thyroid cancer, and fewer instances of lymph node or soft tissue invasion than control patients with classical PTC. The diffuse sclerosing variant of PTC predominantly observed in young patients is a rare aggressive tumor that requires intensive treatment. Despite characteristic clinical and histological features that facilitate easy diagnosis, pre-operative fine needle aspiration cytological diagnosis of this variant is often challenging. Different histological variants of PTC with other histological patterns are important for predicting cancer recurrence. In addition to TNM staging, high-risk histological patterns of PTC require more aggressive follow-up examinations and postoperative adjuvant therapies. *(Chang Gung Med J 2011;34:23-34)*

Dr. Jen-Der Lin

Key words: total thyroidectomy, thyroglobulin, cancer recurrence, poorly differentiated thyroid cancer

Papillary thyroid carcinoma (PTC) is the most commonly observed well-differentiated thyroid cancer in endocrine clinics. Most PTC patients have a good prognosis and long-term survival without distant metastasis. Tumor-node-metastasis (TNM) staging is most commonly used for the initial evaluation of thyroid cancer before and after thyroid surgery.[1] Furthermore, different histopathological patterns and variants of PTC have been reported to influence the prognosis of these patients.[2-4] During the last 10

From the Division of Endocrinology and Metabolism, Department of Internal Medicine; [1]Department of Pathology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan.
Received: Sep. 9, 2010; Accepted: Dec. 2, 2010
Correspondence to: Dr. Jen-Der Lin, Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital at Linkou. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel.: 886-3-3281200 ext. 8821; Fax: 886-3-3288257;
E-mail: einjd@cgmh.org.tw

years, data have accumulated from long-term follow-up studies of different histological patterns and variants of PTC.

As indicated in a recent investigation, new variants of PTC or other histological patterns may correlate with patient prognosis.[5] The most frequent histological patterns such as the follicular variant, insular pattern, columnar, tall cell pattern, diffuse sclerosing type, Hashimoto's thyroiditis, and multicentric PTC were categorized. The purpose of this review is to stratify the prognosis concerning cancer recurrence and cancer mortality in PTC patients with different histopathological patterns compared with those with classical PTC. Different variants or histological patterns may co-exist in a patient.

We have not had sufficient information about different histological variants of PTC in reports from different populations and countries. The biological behaviors of PTC variants differ from that of classical PTC. A recent report observed follicular, tall cell, and oncocytic variants at comparably high rates of 6.6%, 3.9%, and 1.9%, respectively.[4] Disease-free survival and cause-specific survival rates in patients with the tall cell variant were significantly worse than those in patients with classical PTC. Inconsistent data concerning variants of PTC may have been generated by inconsistent diagnostic criteria and differences in characteristics, such as the gender age, geographic location and ethinc background, of subjects enrolled in analyses. The reported histological variants of PTC in children and adolescents differ from those in adults.[6] A series of 42 PTC patients found 8 (19%) with non-specified PTC, 12 (29%) with the solid/trabecular variant, 7 (16%) with the microcarcinoma variant, 6 (14%) with the diffuse sclerosing variant, 4 (10%) with the follicular variant, 2 (5%) with the encapsulated follicular variant, and 3 (7%) with the tall cell variant.[6]

Different histological patterns with papillary thyroid cancer

Tall cell variant

The tall cell variant of PTC is defined by cells that are at least twice as high as they are wide.[7-9] Histopathological findings show the tumors to be extremely papillary, and the papillae are elongated and occasionally coalescent (Fig. 1A). The low-power microscopic appearance may resemble a trabecular pattern in parts of the tumor.[10] Since the first report of the variant by Hawk and Hazard in 1976, clinicians have struggled with this variant because pathologists have had difficulty in recognizing the tumor and misdiagnosing this variant. In a study performed in a large academic center, 12% of classical PTC patients without extra-thyroid extension were reclassified as having the tall cell variant.[11] The major discrepancy in the diagnosis among pathologists is the percentage of tall cells in pathological slides.[10] In previous studies, rates of 10 to 70% were reported.[8,12,13] Patients diagnosed with the tall cell variant of PTC were older at presentation and had large tumors with extra-thyroid extension compared with those with classic PTC.[14] Indeed, in one study, 80% of the patients with the tall cell variant showed some degree of extra-thyroid extension, and the mean age at presentation was 53 years.[11] A diagnosis of the tall cell variant of PTC is made when ≥ 50% of cells are tall cells. As mentioned previously, the cells should have a height that is at least twice their width, an eosinophilic cytoplasm, and the nuclear features of PTC.[10]

Although fine needle aspiration cytology (FNAC) is of limited value in typing the variants of PTC because of overlapping morphological features, it can provide clues for diagnosing certain aggressive variants.[15] Cytological features of the tall cell variant included cleaved nuclei with fine powdery chromatin, small nucleoli, and a dense oxyphilic cytoplasm.[16] Nuclear grooves and intranuclear cytoplasmic pseudoinclusions are rare. The striking cytological features are "tail-like cells" that contain tall, columnar, and oxyphilic cytoplasmic regions with eccentric nuclei located adjacent to the basement membrane (Fig. 1B). The reported differential diagnosis of the tall cell variant of PTC includes Hürthle cell lesions, oncocytic PTC, Warthin-like papillary carcinoma, and breast cancer.[16-18] There is overlap in the morphologic features of the tall cell and Hürthle cell variants, and in one study, cytology correctly identified 60% and 76.4% of these cases, respectively.[15]

Ghossein et al. reported that the gland-confined tall cell variant of PTC without extrathyroid extension has a more aggressive behavior than conventional intrathyroidal PTC. Patients with the tall cell variant without extrathyroidal extension were shown to have a significantly higher nodal metastatic rate than patients with classical PTC patients without

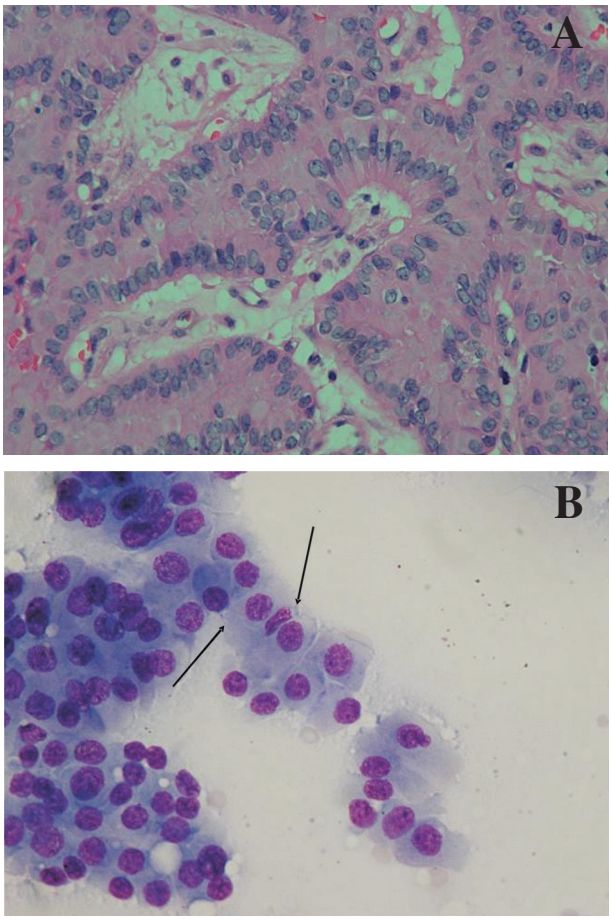

Fig. 1 Histopathological characteristics (A) and fine needle aspiration cytology (B) of the tall cell variant of papillary thyroid carcinoma. (H & E stain; Liu's stain; x 200)

extrathyroidal extension, independent of age, gender, and tumor size ($p = 0.004$).[11] In that same study, 3 of 47 (6%) patients with the tall cell variant without extrathyroidal extension developed distant metastases, while none of the 62 patients with classical PTC had recurrence at a distant site ($p = 0.07$). In a recent study at the Memorial Sloan-Kettering Cancer Center, 278 patients with the tall cell variant presented at an older age (54.3 years vs. 46.3 years, $p < 0.0001$) and had a higher rate of extrathyroidal extension (53.6% vs. 30.2%, $p < 0.0001$) and poorer 5-year disease-specific survival (81.9% vs. 97.8%, $p < 0.0001$) than 2,522 classical PTC patients with sufficient information for analysis.[19] Patients with the tall cell variant had poorer 5-year disease-specific survival (81.9% vs. 91.3%, $p = 0.049$) and a higher number of deaths ($p = 0.043$) than a matched PTC cohort.

There is still a paucity of information from long-term follow-up cases of small tumors and the tall cell variant confined to the lymph node. The implications of tall cell microcarcinoma have not been addressed in the literature, as these tumors are extremely rare and long-term follow-up data on large numbers of patients are not available. No study has addressed the prognostic impact of cervical nodal metastases comprised of tall cells in patients whose primary tumor is of the classical type.

Although there are several reports on the association between the molecular profile of these tumors and the aggressive behavior of the tall cell variant of PTC, host factors, other tumor factors and tumor–tall cell variant-host interactions remain unknown. Some data appear to indicate that molecular factors intrinsic to the tall cell variant are responsible for its aggressive biological and clinical behavior. The aggressive behavior of the tall cell variant could be related to certain factors elaborated by the tumor. The high expression of Muc1 and type IV collagenase (matrix metalloproteinase-2) in these tumors may allow for stromal degradation and greater invasive potential.[20,21] The high Ki-67 (MIB-1) labeling index noted in an immunohistochemistry study, suggesting higher proliferation activity of the tall cell variant than classical PTC, has been investigated in cases of extrathyroidal invasion.[16] The aggressive behavior of the tall cell variant may also be related to the higher prevalence of activating point mutations of BRAF in the tall cell variant than in classical PTC.[21] Indeed, papillary cancers of any subtype that have BRAF mutations have a higher frequency of extraglandular extension and nodal metastases. The incidence of the tall cell variant is accentuated by the fact that it is over- represented in thyroid carcinomas that are refractory to radioactive iodine (RAI) therapy. Recently, Rivera et al. found that 20% of fluorodeoxyglucose positron-emission tomogram (FDG-PET)-positive/RAI refractory tumors were the tall cell variant type.[22]

Follicular variant

In 1977, Chen et al. observed a follicular variant of PTC (FVPTC) exhibiting the characteristic biological behavior and morphological features of PTC.[23] Approximately 18% (42 of 227 patients) of

patients with PTC were identified as having FVPTC.[24] Clinical and laboratory analyses have indicated the existence of separate mechanisms and routes for distant metastasis and either extrathyroidal growth or lymph node metastasis of thyroid cancer. A high proportion of PTC patients have extrathyroidal growth or lymph node metastasis; conversely, follicular thyroid cancer results in more distant metastases than PTC.[25,26] FVPTC patients have a better survival rate than follicular thyroid cancer patients and fewer instances of lymph node and soft tissue invasion than control patients with classical PTC.

The preoperative diagnosis of FVPTC has been investigated and analyzed in recent decades.[27-31] The diagnostic features revealed by FNAC are thick eosinophilic colloid balls in the background, multilayered microfollicles (rosettes), numerous grooves, and inclusions in follicular cell monolayers (Fig. 2). All cytological analyses of FVPTC, including those by Goodell et al. from the US,[27] Nair et al from India,[29] Fulciniti et al from Italy,[32] and Kumar et al from Iran were retrospective studies that attempted to identify the cytopathological correlation between FVPTC and other thyroid malignancies with small sample sizes.[28]

A cross-sectional population analysis of a national cancer database in the U.S.A. that examined the prevalence and extent of disease characteristics of FVPTC and the survival impact of its histopathological diagnosis compared to classical PTC illustrated that age at presentation and sex distribution were similar between FVPTC (47.9 years; 79.3% female) and classical PTC patients.[33] Although the prevalence of lymph node metastasis was significantly lower in FVPTC than classical PTC (14.8% vs. 27.8%, respectively; $p < 0.001$), the T stage was not significantly different ($p = 0.450$). The mean overall survival rates for patients with FVPTC (204.5 months) and classical PTC (205.3 months) were not significantly different ($p = 0.373$). Most long -term follow-up studies in other populations showed similar survival rates for these two diseases;[34,35] in addition, the aggressive macrofollicular variant of PTC was reported in limited cases.[36]

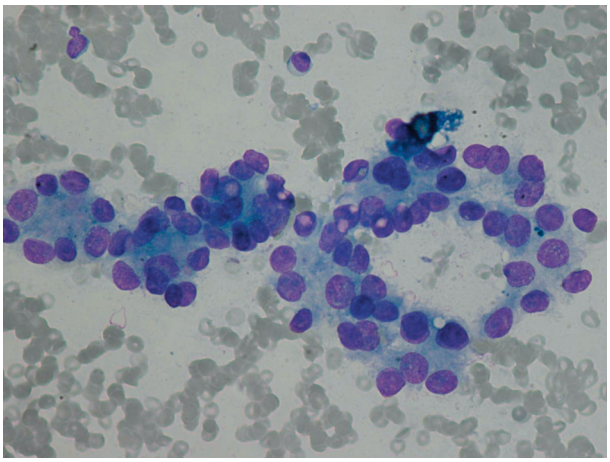

Fig. 2 Fine needle aspiration cytology of the follicular variant of papillary thyroid carcinoma. (Liu's stain; x 200)

Despite the good prognosis of FVPTC compared with the classical form of PTC, the pre-operative diagnosis and diagnosis of FVPTC from frozen sections are still challenging.[37,38] Before the histopathologic criteria for FVPTC were utilized universally, there was controversy concerning the diagnostic criteria for minimally invasive follicular thyroid cancer, FVPTC, and follicular adenoma.[31,39,40] After a review of previous pathological findings in one study, 25% of patients had a change in diagnosis.[39] Theoretically, there is a possibility of FVPTC or minimally invasive follicular thyroid cancer being diagnosed as benign lesions; additionally, some distant metastases are found years later in follow-up evaluations. For these patients, additional histological analysis using frozen sections or final histopathological diagnoses is recommended.

Diffuse sclerosing pattern

The diffuse sclerosing type of PTC is characterized by diffuse involvement of 1 or both lobes of the thyroid, marked squamous metaplasia, numerous psammoma bodies, extensive interstitial fibrosis, and heavy lymphocytic infiltration with formation of germinal centers.[41] The diffuse sclerosing variant of PTC is a rare and aggressive tumor that requires intensive treatment. Despite characteristic clinical and histological features that permit easy diagnosis, pre-operative FNAC diagnosis is often challenging and inexperienced cytopathologists can delay the diagnosis.[42]

Fig. 3 illustrates a 25 year-old woman who presented with a left thyroid nodule. The thyroid ultrasound showed a hypoechoic nodule with an ill-defined margin (Fig. 3A). A previous imaging inves-

tigation of 8 patients revealed the following ultrasound features (7/8) of the diffuse sclerosing variant of PTC: heterogeneous echotexture (7/7), solid composition (7/7), ill-defined margins (4/7), scattered microcalcifications with a snowstorm appearance (7/7), and various echogenicities. CT findings (6/8) revealed numerous microcalcifications and multiple enlarged nodes in all of the patients.[43] These imaging studies are not specific for the diffuse sclerosing variant of PTC.[44] Further cytological examination was important in this woman. FNAC demonstrated monolayer cells with anisocytosis and mitotic figures in a Liu stain (Fig. 3B). After a total thyroidectomy with lymph node dissection, an RAI whole-body scan revealed lung metastases in the patient. Evaluation of this patient showed that the diffuse sclerosing variant is a major subtype of PTC in the young, as was also shown in a recent report.[3] The histology of this tumor is characterized by diffuse involvement of 1 or both lobes of the thyroid, with many psammoma bodies, dense lymphocytic infiltrates and scattered lymphoid follicles (Fig. 3C, D).[41,45]

Because the diffuse sclerosing variant of PTC is not common, it was not until about 10 years ago that long-term treatment results could be analyzed.[46-48] In 1990, 14 patients treated between 1958 and 1988 for the diffuse sclerosing variant of PTC were shown to be alive without metastasis.[49] The study concluded that complete resection did not result in later recurrence in any of the patients; therefore, cosmetic and complication-free surgery should be considered. Further investigation illustrated cancer mortality was not changed; additionally, the rates of recurrence and distant metastases were increased compared with those for classical PTC patients.[46-48] A large series study consisting of 83 patients with the diffuse sclerosing variant of PTC and 168 patients with classical PTC illustrated that the incidence of laterocervical lymph node pathology at diagnosis was significantly higher for the diffuse sclerosing variant ($p < 0.05$). Recurrences in regional lymph nodes were observed in 3.6% and 15.7% ($p < 0.001$), and distant metastases in 1.2% and 7.2% ($p < 0.05$) of classical PTC and the diffuse sclerosing variant of PTC, respectively. One patient with classical PTC (0.6%) and 3 with the diffuse sclerosing variant (3.6%) died from tumor-related causes ($p < 0.05$).[47] In summary, the diffuse sclerosing variant of PTC is an uncommon

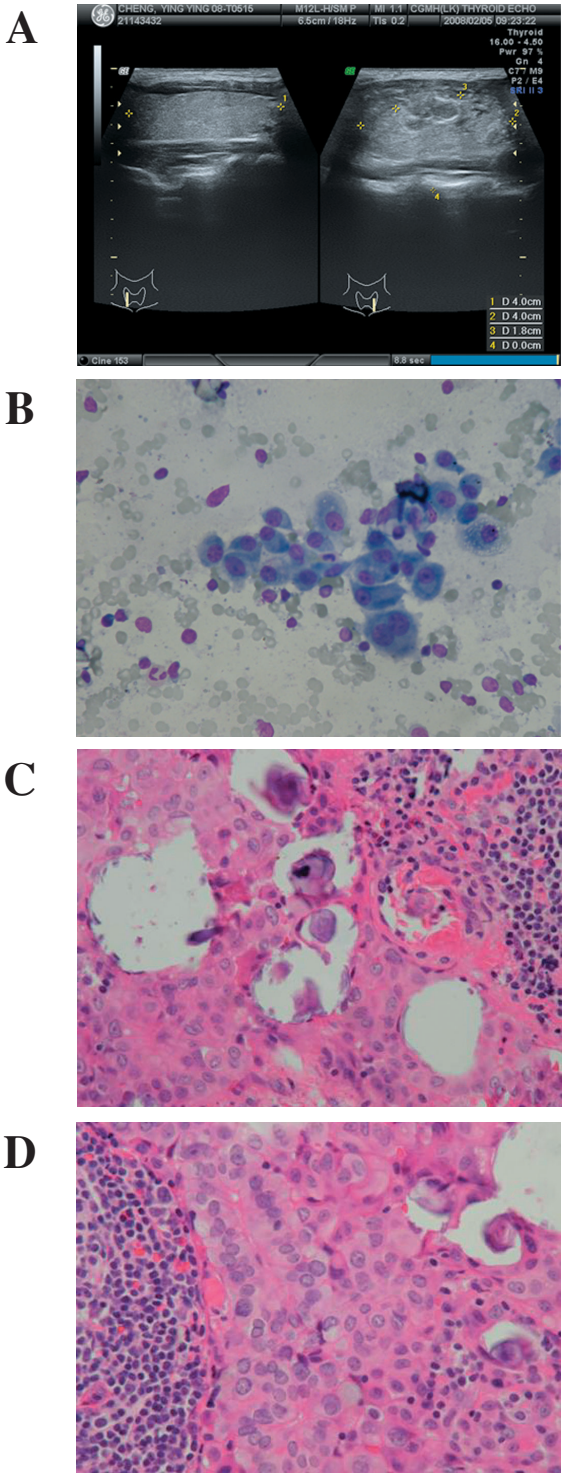

Fig. 3 Thyroid ultrasonography (A), fine needle aspiration cytology (B) with Liu's stain and histopathological findings (C, D) in a 25 year-old woman histologically diagnosed with the diffuse sclerosing variant of papillary thyroid carcinoma.

thyroid cancer that is predominantly diagnosed in young patients, but its clinical behavior is highly aggressive Therefore, more aggressive surgical treatment with appropriate postoperative ^{131}I therapy is recommended.

Papillary thyroid carcinoma with chronic lymphocytic thyroiditis

Both PTC and chronic lymphocytic thyroiditis or Hashimoto's thyroiditis are commonly observed in endocrine clinics. The interrelationship between these disorders concerning their occurrence, clinical presentation, diagnosis, and therapeutic results has been presented by several centers.[2,50-53] Asymptomatic and subclinical chronic thyroiditis are not generally detected early except in subjects who have health screenings. Imaging analysis including thyroid ultrasonography is used less frequently in patients diagnosed with chronic lymphocytic thyroiditis. For these reasons, the association of chronic lymphocytic thyroiditis with PTC was only revealed a decade ago. In addition, the diffuse hypoechogenecity of chronic lymphocytic thyroiditis in thyroid ultrasound imaging makes the diagnosis of malignant lesions in the thyroid difficult.[54]

There are ethnic, geographic, and gender differences in the prevalence of PTC with chronic lymphocytic thyroiditis.[2] After the first documentation by Dailey et al. in 1955, the reported rate of coexistence of these 2 diseases ranged from 0.3 to 38%.[55-58] The relationship between thses two conditions remains unclear because it is controversial whether chronic lymphocytic thyroiditis is induced secondarily by the neoplasm or whether it predisposes the patient to development of thyroid carcinoma.[59,60] Despite the difference in etiology of these 2 disorders, the prevalence and severity of chronic lymphocytic thyroiditis combined with 3 other diseases was defined by examination of surgically resected materials from 3 ethnic groups. The incidence of autoimmune thyroiditis was significantly higher in patients with PTC than in those with adenomatous goiters or follicular adenoma.[61] Most studies have shown better clinical presentations, less frequent recurrences, and lower cancer mortality in PTC patients with coexisting chronic lymphocytic thyroiditis than in those without it. PTC associated with chronic lymphocytic thyroiditis is associated with a smaller primary tumor size at presentation. It is also associated with a reduced risk of recurrence during follow-up, although this was not significant after adjustment for other prognostic factors.[53] A BRAF (V600E) mutation in PTC cells was revealed as a factor that facilitates tumor cell growth and progression. The mutation results in a more advanced clinical presentation and poor prognosis for PTC patients after treatment.[62] The prevalence of activating point mutations in BRAF is much higher (73 - 86%) in Korea than in Western countries (29-69%), and these mutations are associated with a poor prognosis in PTC patients.[63] Further investigation is required to determine the frequency of the BRAF (V600E) mutation in PTC patients with and without coexisting chronic lymphocytic thyroiditis and the clinical and pathological features associated with concomitant chronic lymphocytic thyroiditis and PTC.[64] Previous findings revealed that the BRAF (V600E) mutation was present in 27 (72.9%) patients with and 61 (95.3%) patients without chronic lymphocytic thyroiditis (p = 0.01). The low mutation frequency partially explains the better prognosis in PTC patients with chronic lymphocytic thyroiditis.

Poorly differentiated pattern of papillary thyroid cancer

Poorly differentiated thyroid carcinoma, an undifferentiated carcinoma similar to medullary carcinoma, is a lethal invasive thyroid cancer.[65,66] Histopathological examination of PTC and follicular thyroid cancer may reveal poorly differentiated thyroid carcinoma in a primary thyroid operation or tissues with recurrence. These dedifferentiations may result in a poor prognosis for patients.[67,68] Characteristic histological patterns such as trabecular insular and solid areas, growth patterns of atypias and necrosis, and high mitotic counts have been used as diagnostic criteria.[69,70] Few reports and studies of poorly differentiated thyroid carcinoma pathogenesis have been published. A recent examination of 111 differentiated thyroid carcinoma patients with distant metastases identified poor differentiation as an independent factor associated with poor outcome.[67,71] Foci of poorly differentiated tumors have been identified through pathological analysis in cases of thyroid carcinoma that are predominantly well-differentiated.[69]

Immunohistochemical investigation of poorly differentiated thyroid carcinoma illustrates a follicu-

lar-derived tumor, with thyroglobulin (Tg) production in intracellular paranuclear vacuoles and TTF-1 expression. Poorly differentiated thyroid carcinoma is classified based on the assumption that a lack of follicles is synonymous with a loss of normal thyroid structure. From a functional or endocrine point of view, the majority of poorly differentiated thyroid carcinomas maintain their capacity to produce hormones, and Tg is an important immunohistochemical marker for the differential diagnosis from other trabecular lesions of the thyroid gland, as well as a useful post-operative serum marker for patient follow-up.[72] Markers of malignancy in follicular tumors (such as HBME-1 and galectin-3) may also be expressed in poorly differentiated thyroid carcinoma but have no practical diagnostic application, as morphological signs of malignancy (i.e. vascular invasion) are unequivocally present in all patients.[73]

RAI uptake by cancer cells of poorly differentiated thyroid carcinomas is associated with successful ^{131}I radiotherapy.[67,74] In contrast, poorly differentiated thyroid carcinoma has been reported to be RAI - refractory and FDG-PET - positive.[22] This difference reflects geographical variations in terms of different tumor stages at the time of ^{131}I treatment and different timings and dosages for RAI administration. A recent investigation illustrated the high prevalence of the poorly differentiated thyroid carcinoma histotype in a series of ^{131}I - refractory metastatic thyroid cancers, and in this specific subgroup of patients, the presence of necrosis and extrathyroidal extension was associated with shorter disease-specific survival.[22] Early cytological diagnosis of poorly differentiated thyroid carcinoma followed by total thyroidectomy with tumor removal was the most effective therapy.[71,75] Long-term follow-up studies revealed a 10-year cause-specific survival rate of 31% in poorly differentiated thyroid carcinoma patients. Age and TNM staging at the time of surgery were significant indicators of patient survival and mortality.[67,71]

Multicentric papillary thyroid cancer

In PTC, multicentric lesions are not unusual findings. It is unlcear whether tumor foci result from intraglandular metastases from a single dominant tumor or unrelated neoplastic clones.[76] Clinical information concerning presentation and prognosis is needed, and long-term follow-up studies after treatment for multicentric PTC must be performed to determine the appropriate therapy.[77]

Patients with multicentric PTC in previous studies were older and had more advanced clinical presentations and higher recurrence rates than patients with unifocal PTC.[77-79] Multicentric PTC in association with radiation exposure and a familial history of Gardner's syndrome results in a poorer prognosis than that observed for classical unifocal PTC.[80,81] Over 30% of PTC was found to be multicentric and most may be associated with papillary microcarcinoma.[82,83] According to previous data, 3.5% - 6.2% of PTC patients have a family history of thyroid cancer.[80,84] Most multicentric PTC cases are sporadic and cannot be associated with previous radiation exposure. The preoperative diagnosis of multicentric PTC by thyroid ultrasonography with FNAC from multiple foci was evaluated in one study.[85] Because these are high-risk patients, total thyroidectomy followed by ^{131}I therapy and close follow-up of serum Tg levels is recommended for these multifocal small thyroid cancers. When lymph node metastases are identified during initial thyroid surgery, high rates of recurrent lymph node metastasis can be expected.[86] Routine lymph node dissection or modified radical neck dissection is reported to reduce recurrence in these patients.[87,88] ^{131}I therapy is less effective for local neck recurrence.

Multicentric PTC presents with high recurrence rates and advanced TNM staging compared with unifocal PTC. Microcarcinoma in multicentric PTC should be treated as high-risk tumors. Persistentmulticentric PTC results in high rates of recurrence and distant metastasis in patients and warrants aggressive therapeutic modalities.[77]

Conclusions

TNM staging is still the most important guideline to determine postoperative therapy and follow-up for PTC. However, histological variants and a combination of PTC with other histological patterns have been shown to be important predictors of cancer recurrence.

Acknowledgements

The authors would like to thank Dr. WH Chen for cytological photographic contributions, Miss ML Perng for preparing the manuscript and Chang Gung Medical Center for supporting this research through

grant CMRPG380691.

REFERENCES

1. TNM Classification of Malignant Tumors (UICC). In: Sobin LH, Wittekind C, eds. 6th ed. New York: Wiley-Liss, 2002:52-6.
2. Loh KC, Greenspan FS, Dong F, Miller TR, Yeo PP. Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 1999;84:458-63.
3. Koo JS, Hong S, Park CS. Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. Thyroid 2009;19:1225-31.
4. Ito Y, Hirokawa M, Uruno T, Kihara M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A. Prevalence and biological behaviour of variants of papillary thyroid carcinoma: experience at a single institute. Pathology 2008;40:617-22.
5. Rufini V, Salvatori M, Fadda G, Pinnarelli L, Castaldi P, Maussier ML, Galli G. Thyroid carcinomas with a variable insular component: prognostic significance of histopathologic patterns. Cancer 2007;110:1209-17.
6. Collini P, Mattavelli F, Pellegrinelli A, Barisella M, Ferrari A, Massimino M. Papillary carcinoma of the thyroid gland of childhood and adolescence: Morphologic subtypes, biologic behavior and prognosis: a clinicopathologic study of 42 sporadic cases treated at a single institution during a 30-year period. Am J Surg Pathol 2006;30:1420-6.
7. Pathology and Genetics of Tumours of Endocrine Organs (The International Agency for Research on Cancer. WHO Classifiacation of Tumours) In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. 1st ed. Lyon: WHO, 2004.
8. Johnson TL, Lloyd RV, Thompson NW, Beierwaltes WH, Sisson JC. Prognostic implications of the tall cell variant of papillary thyroid carcinoma. Am J Surg Pathol 1988;12:22-7.
9. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. Cleve Clin Q 1976;43:207-15.
10. Ghossein R, Livolsi VA. Papillary thyroid carcinoma tall cell variant. Thyroid 2008;18:1179-81.
11. Ghossein R, Leboeuf R, Patel KN, Rivera M, Katabi N, Carlson DL, Tallini G, Shaha A, Singh B, Tuttle RM. Tall cell variant of papillary thyroid carcinoma without extrathyroid extension: biologic behavior and clinical implications. Thyroid 2007;17:655-61.
12. Nishida T, Katayama S, Tsujimoto M, Nakamura J, Matsuda H. Clinicopathological significance of poorly differentiated thyroid carcinoma. Am J Surg Pathol 1999;23:205-11.
13. Ostrowski ML, Merino MJ. Tall cell variant of papillary thyroid carcinoma: a reassessment and immunohistochemical study with comparison to the usual type of papillary carcinoma of the thyroid. Am J Surg Pathol 1996;20:964-74.
14. Michels JJ, Jacques M, Henry-Amar M, Bardet S. Prevalence and prognostic significance of tall cell variant of papillary thyroid carcinoma. Hum Pathol 2007;38:212-9.
15. Gupta S, Sodhani P, Jain S, Kumar N. Morphologic spectrum of papillary carcinoma of the thyroid: role of cytology in identifying the variants. Acta Cytol 2004;48:795-800.
16. Urano M, Kiriyama Y, Takakuwa Y, Kuroda M. Tall cell variant of papillary thyroid carcinoma: Its characteristic features demonstrated by fine-needle aspiration cytology and immunohistochemical study. Diagn Cytopathol 2009;37:732-7.
17. Köybaşioğlu F, Simşek GG, Onal BU. Tall cell variant of papillary carcinoma arising from a thyroglossal cyst: report of a case with diagnosis by fine needle aspiration cytology. Acta Cytol 2006;50:221-4.
18. Tosi AL, Ragazzi M, Asioli S, Del Vecchio M, Cavalieri M, Eusebi LH, Foschini MP. Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: report of 4 cases with evidence of malignant potential. Int J Surg Pathol 2007;15:14-9.
19. Morris LG, Shaha AR, Tuttle RM, Sikora AG, Ganly I. Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. Thyroid 2010;20:153-8.
20. Wreesmann VB, Sieczka EM, Socci ND, Hezel M, Belbin TJ, Childs G, Patel SG, Patel KN, Tallini G, Prystowsky M, Shaha AR, Kraus D, Shah JP, Rao PH, Ghossein R, Singh B. Genome-wide profiling of papillary thyroid cancer identifies MUC1 as an independent prognostic marker. Cancer Res 2004;64:3780-9.
21. Campo E, Merino MJ, Liotta L, Neumann R, Stetler-Stevenson W. Distribution of the 72-kd type IV collagenase in non neoplastic and neoplastic thyroid tissue. Hum Pathol 1992;23:1395-401.
22. Rivera M, Ghossein RA, Schoder H, Gomez D, Larson SM, Tuttle RM. Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. Cancer 2008;113:48-56.
23. Chen KT, Rosai J. Follicular variant of thyroid papillary carcinoma: a clinicopathologic study of six cases. Am J Surg Pathol 1977;2:123-30.
24. De Micco C, Vassko V, Henry JF. The value of thyroid peroxidase immunohistochemistry for preoperative fine-needle aspiration diagnosis of the follicular variant of papillary thyroid cancer. Surgery 1999;126:1200-4.
25. Schelfhout LJ, Creutzberg CL, Hamming JF, Fleuren GJ, Smeenk D, Hermans J, van de Velde CJ, Goslings BM. Multivariate analysis of survival in differentiated thyroid cancer: the prognostic significance of the age factor. Eur J

Cancer 1988;24:331-7.
26. Lin JD, Chao TC. Follicular thyroid carcinoma: diagnosis to treatment. Endocr J 2006;53:441-8.
27. Goodell WM, Saboorian MH, Ashfaq R. Fine-needle aspiration diagnosis of the follicular variant of papillary carcinoma. Cancer 1998;84:349-54.
28. Kumar PV, Talei AR, Malekhusseini SA, Monabati A, Vasei M. Follicular variant of papillary carcinoma of the thyroid. A cytological study of 15 cases. Acta Cytol 1999;43:139-42.
29. Nair M, Kapila K, Karak AK, Verma K. Papillary carcinoma of the thyroid and its variants: a cytohislogical correlation. Diagn Cytopathol 2001;24:167-73.
30. Sorrenti S, Trimboli P, Catania A, Ulisse S, De Antoni E, D'Armiento M. Comparison of malignancy rate in thyroid nodules with cytology of indeterminate follicular or indeterminate Hürthle cell neoplasm. Thyroid 2009;19:355-60.
31. Liu FH, Liou MJ, Hsueh C, Chao TC, Lin JD. Thyroid follicular neoplasm: Analysis by fine needle aspiration cytology, frozen section, and histopathology. Diagn Cytopathol 2010;38:801-5.
32. Fulciniti F, Benincasa G, Vetrani A, Palombini L. Follicular variant of papillary carcinoma: cytologic finding on FNAB samples-experience with 16 cases. Diagn Cytopathol 2001;25:86-93.
33. Lin HW, Bhattacharyya N. Clinical behavior of follicular variant of papillary thyroid carcinoma: presentation and survival. Laryngoscope 2010;120:712-6.
34. Chang HY, Lin JD, Chou SC, Chao TC, Hsueh C. Clinical presentations and outcomes of surgical treatment of follicular variant of the papillary thyroid carcinomas. Jpn J Clin Oncol 2006;36:688-93.
35. Lang BH, Lo CY, Chan WF, Lam AK, Wan KY. Classical and follicular variant of papillary thyroid carcinoma: a comparative study on clinicopathologic features and long-term outcome. World J Surg 2006;30:752-8.
36. Cardenas MG, Kini S, Wisgerhof M. Two patients with highly aggressive macrofollicular variant of papillary thyroid carcinoma. Thyroid 2009;19:413-6.
37. Lin HS, Komisar A, Opher E, Blaugrund SM. Follicular variant of papillary carcinoma: the diagnostic limitations of preoperative fine-needle aspiration and intraoperative frozen section evaluation. Laryngoscope 2000;110:1431-6.
38. Tielens ET, Sherman SI, Hruban RH, Ladenson PW. Follicular variant of papillary thyroid carcinoma. A clinicopathologic study. Cancer 1994;73:424-31.
39. Widder S, Guggisberg K, Khalil M, Pasieka JL. A pathologic re-review of follicular thyroid neoplasms: the impact of changing the threshold for the diagnosis of the follicular variant of papillary thyroid carcinoma. Surgery 2008;144:80-5.
40. Elsheikh TM, Asa SL, Chan JK, DeLellis RA, Heffess CS, LiVolsi VA, Wenig BM. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. Am J Clin Pathol 2008;130:736-44.
41. Chan JK, Tsui MS, Tse CH. Diffuse sclerosing variant of papillary carcinoma of the thyroid: a histological and immunohistochemical study of three cases. Histopathology 1987;11:191-201.
42. Bongiovanni M, Triponez F, McKee TA, Kumar N, Matthes T, Meyer P. Fine-needle aspiration of the diffuse sclerosing variant of papillary thyroid carcinoma masked by florid lymphocytic thyroiditis; A potential pitfall: A case report and review of the literature. Diagn Cytopathol 2009;37:671-5.
43. Lee JY, Shin JH, Han BK, Ko EY, Kang SS, Kim JY, Oh YL, Chung JH. Diffuse sclerosing variant of papillary carcinoma of the thyroid: imaging and cytologic findings. Thyroid 2007;17:567-73.
44. Kwak JY, Kim EK, Hong SW, Oh KK, Kim MJ, Park CS, Cheong WY. Diffuse sclerosing variant of papillary carcinoma of the thyroid: ultrasound features with histopathological correlation. Clin Radiol 2007;62:382-6.
45. Ohori NP, Schoedel KE. Cytopathology of high-grade papillary thyroid carcinomas: tall-cell variant, diffuse sclerosing variant, and poorly differentiated papillary carcinoma. Diagn Cytopathol 1999;20:19-23.
46. Lam AK, Lo CY. Diffuse sclerosing variant of papillary carcinoma of the thyroid: a 35-year comparative study at a single institution. Ann Surg Oncol 2006;13:176-81.
47. Falvo L, Giacomelli L, D'Andrea V, Marzullo A, Guerriero G, de Antoni E. Prognostic importance of sclerosing variant in papillary thyroid carcinoma. Am Surg 2006;72:438-44.
48. Chow SM, Chan JK, Law SC, Tang DL, Ho CM, Cheung WY, Wong IS, Lau WH. Diffuse sclerosing variant of papillary thyroid carcinoma--clinical features and outcome. Eur J Surg Oncol 2003;29:446-9.
49. Fujimoto Y, Obara T, Ito Y, Kodama T, Aiba M, Yamaguchi K. Diffuse sclerosing variant of papillary carcinoma of the thyroid. Clinical importance, surgical treatment, and follow-up study. Cancer 1990;66:2306-12.
50. Repplinger D, Bargren A, Zhang YW, Adler JT, Haymart M, Chen H. Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer. J Surg Res 2008;150:49-52.
51. Cipolla C, Sandonato L, Graceffa G, Fricano S, Torcivia A, Vieni S, Latteri S, Latteri MA. Hashimoto thyroiditis coexistent with papillary thyroid carcinoma. Am Surg 2005;71:874-8.
52. Del Rio P, Cataldo S, Sommaruga L, Concione L, Arcuri MF, Sianesi M. The association between papillary carcinoma and chronic lymphocytic thyroiditis: does it modify the prognosis of cancer? Minerva Endocrinol 2008;33:1-5.
53. Kim EY, Kim WG, Kim WB, Kim TY, Kim JM, Ryu JS, Hong SJ, Gong G, Shong YK. Coexistence of chronic lymphocytic thyroiditis is associated with lower recur-

rence rates in patients with papillary thyroid carcinoma. Clin Endocrinol 2009;71:581-6.
54. Liu FH, Chang HY, Huang BY, Liou MJ, Hsueh C, Lin JD. Sonography and fine-needle aspiration biopsy in the diagnosis of benign versus malignant nodules in patients with autoimmune thyroiditis. J Clin Ultrasound 2009;37:487-92.
55. Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto's disease of the thyroid gland. Arch Surg 1955;70:291-7.
56. Matsubayashi S, Kawai K, Matsumoto Y, Mukuta T, Morita T, Hirai K, Matsuzuka F, Kakudoh K, Kuma K, Tamai H. The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. J Clin Endocrinol Metab 1995;80:3421-4.
57. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.
58. Woolner LB, McConaley WM, Beahrs OH. Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroid disorders. J Clin Endocrinol Metab 1959;19:53-83.
59. Kamma H, Fujii K, Ogata T. Lymphocytic infiltration in juvenile thyroid carcinoma. Cancer 1988;62:1988-93.
60. Okayasu I, Saegusa M, Fujiwara M, Hara Y, Rose NR. Enhanced cellular proliferative activity and cell death in chronic thyroiditis and thyroid papillary carcinoma. J Cancer Res Clin Oncol 1995;121:746-52.
61. Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans. Cancer 1995;76:2312-8.
62. Xing M, Clark D, Guan H, Ji M, Dackiw A, Carson KA, Kim M, Tufaro A, Ladenson P, Zeiger M, Tufano R. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. J Clin Oncol 2009;27:2977-82.
63. Kim TY, Kim WB, Rhee YS, Song JY, Kim JM, Gong G, Lee S, Kim SY, Kim SC, Hong SJ, Shong YK. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol 2006;65:364-8.
64. Kim SK, Song KH, Lim SD, Lim YC, Yoo YB, Kim JS, Hwang TS. Clinical and pathological features and the BRAF (V600E) mutation in patients with papillary thyroid carcinoma with and without concurrent Hashimoto thyroiditis. Thyroid 2009;19:137-41.
65. Konrad HR, Canalis RF. Lethal thyroid carcinoma. Arch Otolaryngol 1978;104:454-5.
66. Valenta LJ, Michel-Bechet M, Mattson JC, Singer FR. Microfollicular thyroid carcinoma with amyloid rich stroma, resembling the medullary carcinoma of the thyroid (MCT). Cancer 1977;39:1573-86.
67. Lin JD, Chao TC, Hsueh C. Clinical characteristics of poorly differentiated thyroid carcinomas compared with classical papillary thyroid carcinomas. Clin Endocrinol 2007;66:224-8.
68. Sugitani I, Toda K, Yamamoto N, Sakamoto A, Fujimoto Y. Re-evaluation of histopathological factors affecting prognosis of differentiated thyroid carcinoma in an iodine-sufficient country. World J Surg 2010;34:1265-73.
69. Volante M, Landolfi S, Chiusa L, Palestini N, Motta M, Codegone A, Torchio B, Papotti M. Poorly differentiated carcinoma of the thyroid with trabecular, insular, and solid patterns. Cancer 2004;100:950-7.
70. Hiltzik D, Carlson DL, Tuttle RM, Chuai S, Ishill N, Shaha A, Shah JP, Singh B, Ghossein RA. Poorly differentiated thyroid carcinomas defined on the basis of mitosis and necrosis: a clinicopathologic study of 58 patients. Cancer 2006;106:1286-95.
71. Haq M, Harmer C. Differentiated thyroid carcinoma with distant metastases at presentation: prognostic factors and outcome. Clin Endocrinol 2005;63:87-93.
72. Volante M, Papotti M. A practical diagnostic approach to solid/trabecular nodules in the thyroid. Endocr Pathol 2008;19:75-81.
73. Volante M, Papotti M. Poorly differentiated thyroid carcinoma: 5 years after the 2004 WHO classification of endocrine tumours. Endocr Pathol 2010;21:1-6.
74. Jung TS, Kim TY, Kim KW, Oh YL, Park do J, Cho BY, Shong YK, Kim WB, Park YJ, Jung JH, Chung JH. Clinical features and prognostic factors for survival in patients with poorly differentiated thyroid carcinoma and comparison to the patients with the aggressive variants of papillary thyroid carcinoma. Endocr J 2007;54:265-74.
75. Bongiovanni M, Bloom L, Krane JF, Baloch ZW, Powers CN, Hintermann S, Pache JC, Faquin WC. Cytomorphologic features of poorly differentiated thyroid carcinoma: a multi-institutional analysis of 40 cases. Cancer Cytopathol 2009;117:185-94.
76. Giannini R, Ugolini C, Lupi C, Proietti A, Elisei R, Salvatore G, Berti P, Materazzi G, Miccoli P, Santoro M, Basolo F. The heterogenous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma. J Clin Endocrinol Metab 2007;92:3511-6.
77. Lin JD, Chao TC, Hsueh C, Kuo SF. High recurrent rate of multicentric papillary thyroid carcinoma. Ann Surg Oncol 2009;16:2609-16.
78. Grant CS, Stulak JM, Thompson GB, Richards ML, Reading CC, Hay ID. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg 2010;34:1239-46.
79. Lin JD, Kuo SF, Chao TC, Hsueh C. Incidental and non-incidental papillary thyroid microcarcinoma. Ann Surg Oncol 2008;15:2287-92.
80. Simonowitz D, Thomsen S, Moossa AR, Block GE. The treatment of incidental papillary thyroid cancer. Arch Surg 1976;111:477-83.

81. Miyaki M, Iijima T, Ishii R, Hishima T, Mori T, Yoshinaga K, Takami H, Kuroki T, Iwama T. Molecular evidence for multicentric development of thyroid carcinomas in patients with familial adenomatous polyposis. Am J Pathol 2000;157:1825-7.
82. Gerfo PL, Chabot J, Gazetas P. The intraoperative incidence of detectable bilateral and multicentric disease in papillary cancer of the thyroid. Surgery 1990;108:958-62.
83. Kebebew E. Heraditary non-medullary thyroid cancer. World J Surg 2008;32:678-82.
84. Stoffer SS, Van Dyke DL, Bach JV, Szpunar W, Weiss L. Familial papillary carcinoma of the thyroid. Am J Med Genet 1986;25:775-82.
85. Kuo SF, Chao TC, Chang HY, Hsueh C, Yang CH, Lin JD. Prognostic evaluation of patients with multicentric papillary thyroid microcarcinoma. J Formos Med Assoc (in press)
86. Bardet S, Malville E, Rame JP, Babin E, Samama G, De Raucourt D, Michels JJ, Reznik Y, Henry-Amar M. Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. Eur J Endocrinol 2008;158:551-60.
87. Perrino M, Vannucchi G, Vicentini L, Cantoni G, Dazzi D, Colombo C, Rodari M, Chiti A, Beck-Peccoz P, Fugazzola L. Outcome predictors and impact of central node dissection and radiometabolic treatment in papillary thyroid cancers ≤ 2 cm. Endocr Relat Cancer 2009;16: 201-10.
88. Noguchi S, Yamashita H, Uchino S. Modified radical neck dissection is better than partial dissection of lymph nodes. World J Surg 2009;33:394-6.

不同組織亞型之乳突狀甲狀腺癌

林仁德 薛 純[1] 黃碧玉

腫瘤—淋巴—轉移 (TNM) 之分期，目前在乳突狀甲狀腺癌之臨床分期上是最常用的方式，在評估治療效果也較爲客觀。在此客觀分期背後並未把不同甲狀腺乳突癌組織亞型包含在內。在過去報告中不同組織亞型治療之預後差異極大。本文對乳突狀甲狀腺癌較常見之亞型或合併甲狀腺乳突癌之甲狀腺組織特殊型態如：濾泡型乳突癌，島嶼亞型 (Insulin Pattern) 之未分化乳突癌，高細胞亞型及瀰漫硬化性亞型，與橋本氏甲狀腺炎並存之乳突癌，與多發性甲狀腺乳突癌等。在臨床表徵，甲狀腺癌再發，或癌症之死亡率有回溯性之資料分析並提供台灣一醫學中心之資料，以供比較。高細胞亞型在臨床上是較有侵犯性且預後較差之甲狀腺乳突癌。此亞型之癌細胞在 Mucl 及第 IV 型之 collagenase 之基因表達較強因而也使癌細胞對細胞外基質之穿透力增加且有較強之軟組織侵犯性。相對地，有 18% 之乳突狀甲狀腺癌是屬於濾泡狀亞型。濾泡狀亞型乳突癌治療之預後比濾泡狀甲狀腺癌佳，同時診斷時淋巴腺轉移或軟組織之侵犯比率比典型之乳突癌較少。瀰漫性硬化亞型之乳突癌較常發生在年輕人之侵犯性乳突癌，因而須較積極治療。儘管不同乳突癌之亞型臨床特徵及組織學特性差異很大，但手術前細針穿刺細胞學檢查並非容易診斷。不同組織亞型組織型態之病理學診斷在病人治療預後之判斷是非常重要指標。因而在甲狀腺癌病人治療之建議上除在 TNM 分期外，組織亞型之判讀對術後積極性之輔助性療法是很重要的。(長庚醫誌 2011;34:23-34)

關鍵詞：甲狀腺全切除術，甲狀腺球蛋白，癌死亡，分化不良甲狀腺癌

長庚醫療財團法人林口長庚紀念醫院 內科部 內分泌及新陳代謝科，[1]病理科；長庚大學 醫學院
受文日期：民國99年9月9日；接受刊載：民國99年12月2日
通訊作者：林仁德醫師，長庚醫療財團法人林口長庚紀念醫院 內科部 內分泌及新陳代謝科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉8821; Fax: (03)3288257; E-mail: einjd@cgmh.org.tw