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Review Article

Classification of follicular cell tumors of the thyroid gland: Analysis involving Japanese patients from one institute

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Prognostic analyses of thyroid carcinomas of follicular cell origin were carried out on patients treated at Kuma Hospital, Kobe, Japan. A new histopathological classification based on the prognostic evidence is proposed in this study, and it is applicable to the patients treated curatively. Major histological types of papillary carcinoma, follicular carcinoma and poorly differentiated carcinoma were combined into one single entity of follicular cell adenocarcinoma because (i) they have the same cell origin (follicular cell); (ii) clear-cut separation of papillary and follicular carcinoma is not always possible, and 10 year cause-specific survival was essentially similar when the patients were treated curatively; and (iii) poorly differentiated carcinoma usually has a background of either papillary or follicular carcinoma. This adenocarcinoma together with undifferentiated carcinoma was stratified into four prognostic groups using pure morphological criteria of the degree of cellular differentiation and histological grade. They are termed well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated carcinoma and undifferentiated carcinoma of the thyroid. The 10 year disease-free survival rates were 86.3–93.1%, 65.4–78.7%, and 43.0–53.8%, and 0%, respectively. The 10 year cause-specific survival rates were 97.2–100%, 91.5–97.4%, and 71.2–80.0%, and 0%, respectively.

Key words: classification, diagnosis, differentiation, follicular cell, prognosis, thyroid carcinoma

It is well known that the incidence, histological types and even biological behavior of thyroid carcinomas vary among different geographic areas.[1–7] A nationwide cancer registry by the Japanese Society of Thyroid Surgery collected a total of 52 109 patients with thyroid carcinoma who underwent surgery between 1977 and 2005 in Japan. There were 45 683 (87.7%) papillary thyroid carcinomas (PTC), 4910 (9.4%) follicular thyroid carcinomas (FTC), 713 (1.4%) C cell carcinomas (medullary thyroid carcinoma, MTC) and 803 (1.5%) undifferentiated carcinomas (UC).[8] The incidence of histological type of thyroid carcinoma in Japan differs from that in Europe, North America and other geographic areas, and this is postulated to result from iodine intake.[2,4–7,9,10] The different experience of thyroid tumors among pathologists and different prognostic data from different countries may create serious problems when establishing histological criteria in the diagnosis of thyroid carcinomas.[11–17] Although several histological classifications of thyroid carcinomas have been published, a well-accepted classification of differentiated thyroid carcinomas, which links to prognosis, has not been established as yet, partly because of this problem. The comparison of prognostic analyses of different series of thyroid carcinomas from different geographic areas and with different histological criteria may not be adequate, under these circumstances, to reach any valid and definite conclusions on prognostic classification of thyroid carcinomas.[2]

The purpose of the present study was to report on the prognostic analysis and review of patients with thyroid carcinomas treated at a single thyroid hospital, Kuma Hospital, Kobe, in order to eliminate geographic bias or personal philosophy in diagnosis, and to establish a new prognostic classification of thyroid carcinoma of follicular cell origin based on evidence obtained from patients treated at one hospital.

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Figure 1 Low-risk papillary thyroid carcinoma according to Bai *et al.*[18] and well-differentiated adenocarcinoma according to the present proposal. Most of the neoplastic follicular cells are tightly arranged as a single layer (HE).

Figure 2 Loss of cellular polarity/cohesiveness of the high-risk papillary thyroid carcinoma according to Bai *et al.*[18] and moderately differentiated adenocarcinoma according to the present proposal. Papillary structures are covered with tall/columnar cells, but most of them are not tightly arranged (loss of cellular cohesiveness) and their nuclear positions are not basally oriented with hobnail appearance (loss of cellular polarity; HE).

Figure 3 The loss of cellular polarity/cohesiveness of high-risk papillary thyroid carcinoma and moderately differentiated adenocarcinoma. Low cuboidal or flattened neoplastic cells (upper half) become spindle shaped in possible epithelial mesenchymal transition (lower half; HE).

Figure 4 Loss of cellular polarity/cohesiveness of high-risk risk papillary thyroid carcinoma and moderately differentiated adenocarcinoma. The neoplastic papillae are covered with mostly flattened or low cuboidal cells with increased nuclear/cytoplasmic ratio. Note the lack of high-grade nuclear features (HE).

Figure 5 Loss of cellular polarity/cohesiveness of high-risk risk papillary thyroid carcinoma and moderately differentiated adenocarcinoma. Papillary structures are covered with columnar cells of higher nuclear grade when compared with Figs 1–4. The nuclear position becomes more pseudostratified and sometimes piled up (loss of cellular polarity). Note that the upper left field contains a small focus of spindle-shaped neoplastic cells (HE).

Figure 6 The tall/columnar cell group of high-risk papillary thyroid carcinoma belonging to moderately differentiated adenocarcinoma in the present classification. The upper right field contains neoplastic tall cells with basally located nuclei (tall-cell PTC), while the lower left contains tall cells with nuclear stratification (columnar cell PTC; HE).

MATERIALS AND METHODS

Histological risk group analysis of common type PTC

We reviewed patients with primary thyroid carcinoma who underwent primary surgical treatment between 1987 and 2006, at Kuma Hospital, Kobe, Japan. A total of 9500 patients were analyzed in the study. The initial diagnosis was PTC, $n = 8372$ (88.1%); FTC, $n = 586$ (6.2%); MTC, $n = 117$ (1.2%); UC, $n = 53$ (0.56%); malignant lymphoma, $n = 345$ (3.6%); and 'other', $n = 27$ (0.28%). The three principal pathologists responsible for the initial diagnosis were S.K. between 1983 and 1993, K.K. between 1994 and 2005, and M.H. in 2006; all three pathologists are co-authors of the present paper.

Prognosis and risk group classification of PTC patients who underwent primary surgical treatment from 1990 to 1993 were reviewed for analysis of morphological parameters by two pathologists (K.K. and Y.B.). The diagnostic procedure and morphological characteristics to identify low-risk and high-risk patients with PTC were described in detail in our previous reports.[18,19] In brief, low-risk PTC is characterized by either expansive growth with capsulation or invasive growth with well-differentiated cellular characteristics (exclusion of the following high-risk morphology). High-risk PTC is characterized by both invasive growth and at least one of the three less-differentiated cellular morphologies: (i) tall/columnar cell features (≥10%); (ii) solid growth (≥10%); and (iii) loss of cellular polarity/cohesiveness (≥20%). Representative illustrations are shown in Fig. 1 for low-risk PTC, and Figs 2–6 for high-risk PTC. This subclassification is applicable only to adult PTC patients, because age is a strong predictor in thyroid carcinomas and PTC in children has been proved to be low-grade malignancy, even if it has solid growth pattern.[1,2,4,20–22] Microcarcinoma (<10 mm) was not included in the present study because most demonstrated excellent outcomes, and persistent/recurrent disease was identified in only a small number of patients, when they were treated curatively.[23–25] Patients with distant metastasis at surgery were also excluded from the study. Tumors with anaplastic transformation and these with both solid/trabecular/insular carcinoma components and high-grade histology were excluded.[16] Follicular tumor of uncertain malignant potential (FT-UMP) and well-differentiated tumor of uncertain malignant potential (WDT-UMP) were excluded.[26] Malignant lymphoma, squamous cell carcinoma, MTC and intrathyroid epithelial thymoma were also excluded because of their different histogenesis. A total of 476 cases were analyzed for recurrence, and the results are shown in Kaplan–Meier survival curves in Fig. 7; some of the results obtained from a smaller number of patients have been published elsewhere.[18,19] All patients were treated curatively with either total thyroidectomy (including subtotal thyroidectomy) or lobectomy (including lobectomy with isthmectomy) with lymph node dissection. No postoperative chemotherapy, radiation or I^{131} treatment was applied in this series of patients. Microscopy of the dissected lymph nodes confirmed metastasis in 389 patients (81.72%), and no metastatic carcinoma was found in 87 patients (18.28%), as shown in Table 1.

Statistical analysis

Time-independent, categorical and continuous data were evaluated using the χ^2 test or Fisher's exact test as appropriate. The disease-free survival (DFS) and cause-specific survival (CSS) were calculated from the time of primary surgery to the final contact day or the day that recurrence or

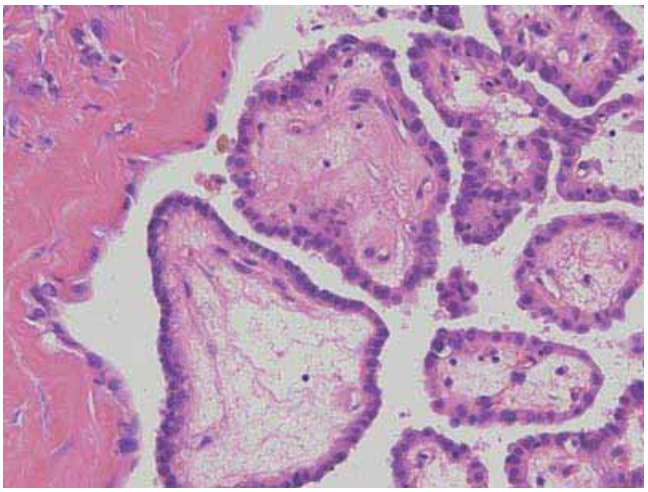
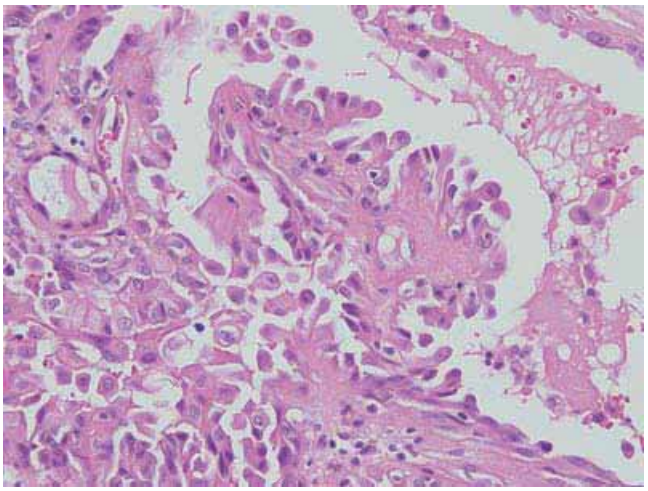


Figure 1



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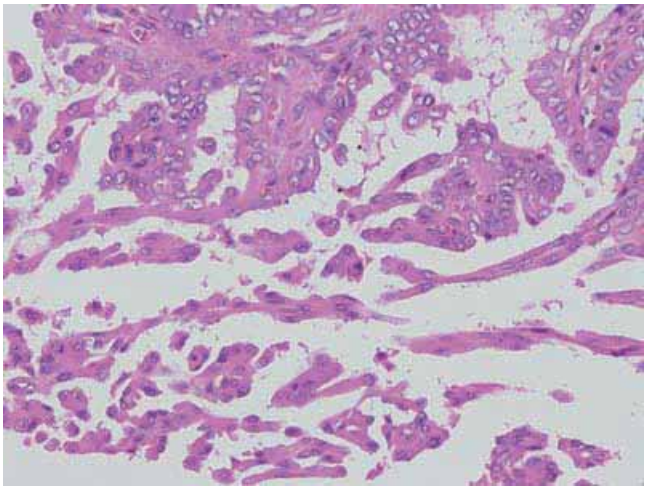

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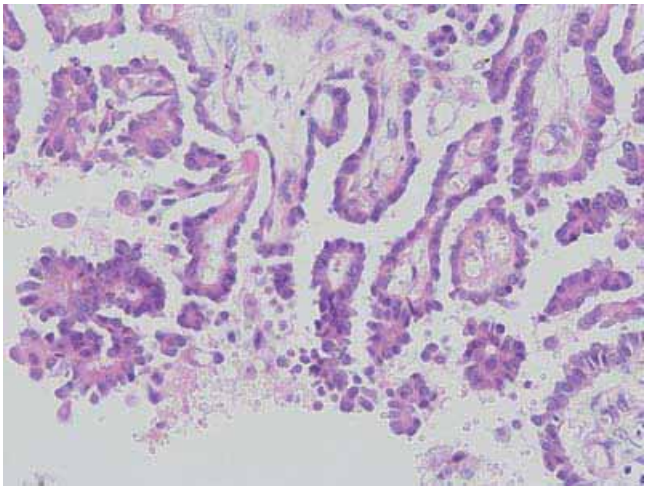

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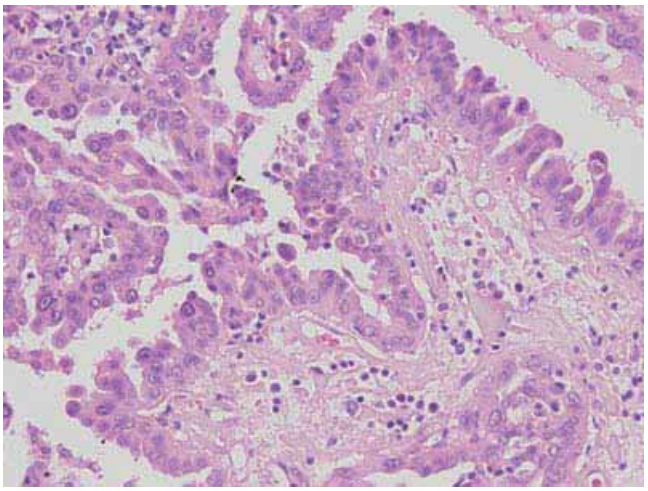

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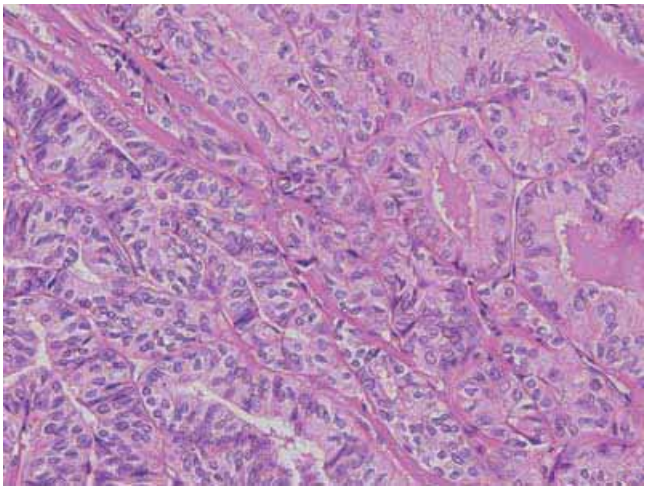

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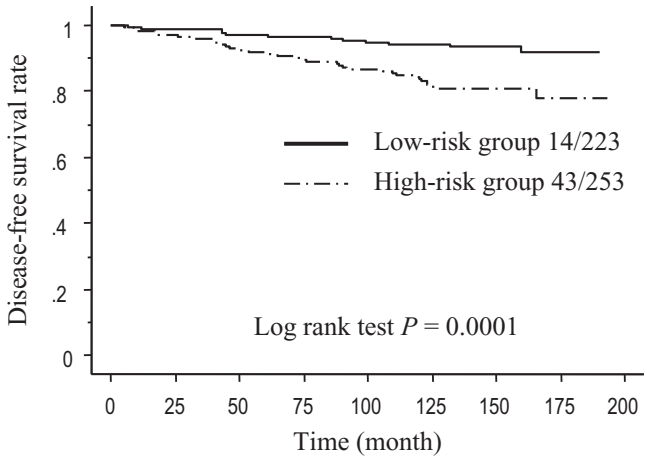

Figure 7 Disease-free survival rates of (—) low-risk ($n = 223$) and (- - -) high-risk ($n = 253$) papillary carcinoma of the thyroid. A total of 476 patients treated curatively at Kuma Hospital Kobe Japan were enrolled. Among them, 14 of 223 low-risk and 43 of 253 high-risk PTC patients developed cancer recurrence. The disease-free survival difference was statistically significant on Kaplan–Meier method and log–rank test ($P = 0.0001$).

cancer-related death was identified. DFS and CSS analyses were performed using the Kaplan–Meier method and the log–rank test. The difference was considered statistically significant for $P < 0.05$. Data analysis was performed using Stat View-J, version 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

Risk group analysis on common type PTC

Thirty-eight (8.0%) male and 438 (92.0%) female patients were enrolled in this analysis of common PTC, and their average age at surgery was 46.9 years old (Table 1). The average follow-up period for DFS was 120.97 ± 39.29 months (mean ± SD). The average follow-up period for CSS was 131.71 ± 35.22 months. Seven patients died of cancer, all of whom belonged to the high-risk group, and seven patients died of other causes, five in the low-risk and two in the high-risk group.

The analysis of recurrence in the 476 cases of PTC confirmed that in our previous report obtained from 263 patients by Bai *et al.*,[18] and the Kaplan–Meier DFS curves of two risk groups in the 476 cases are shown in Fig. 7. The difference of DFS between the low-risk PTC (including encapsulated group and not otherwise specified group, $n = 223$, 10 year DFS, 93.0%) and high-risk PTC (including loss of cellular polarity/cohesiveness group, tall/columnar cell group, and solid type of PTC, $n = 253$, 10 year DFS of 82.5%) was confirmed to be statistically significant ($P = 0.0001$). The correlation between clinicopathological parameters and risk groups of PTC were analyzed and the results are shown in Table 1. More patients with a larger tumor size were observed in the high-risk group than in the low-risk group ($P = 0.0372$), more patients with extrathyroid extension were in the high-risk group than in the low-risk group ($P = 0.0006$), and more patients with advanced pT stage (TNM classification of UICC) were in the high-risk group than in the low-risk group ($P = 0.0144$), and the difference was statistically significant. More lymph node metastasis was observed in the high-risk group than the low-risk group but the difference remained borderline significant.

Table 1 Clinicopathological parameters vs risk group of papillary thyroid carcinoma

Group	Low risk $n = 223$	High risk $n = 253$	P
Age (years)			0.1213
<60	187	198	
≥60	36	55	
Gender			0.2790
Male	21	17	
Female	202	236	
Tumor size (cm)			0.0372‡
<2	96	81	
≥2 and ≤4	98	138	
>4	29	34	
Ex			0.0006‡
0	144	119	
1	56	96	
2	23	38	
pT†			0.0144‡
1	74	54	
2	51	55	
3	75	105	
4a	23	39	
Lymph node metastasis†			0.0629
0	50	37	
1a	32	33	
1b	141	183	
Stage grouping†			0.9075
I	109	119	
II	5	7	
III	30	31	
IVa	79	96	

†TNM classification of International Union against Cancer.

‡χ^2 test.

Ex, extrathyroid invasion, classified according to the 6th edition of *General Rule for the Description of Thyroid Cancer*, Japanese Society of Thyroid Surgery.

Review of publications on prognostic analyses of thyroid carcinomas treated at Kuma Hospital, Kobe, Japan

Prognosis on PTC patients and poorly differentiated carcinoma of PTC background

Ito *et al.* analyzed 1680 cases of PTC without distant metastasis at diagnosis from 1987 to 1995 including small carcinoma (<10 mm) and the results were published elsewhere.[27] In brief,

Table 2 DFS and CSS of thyroid carcinomas, Kuma Hospital, Kobe, Japan

	10 year DFS % (*n*)	10 year CSS % (*n*)
FTC†		
Minimally invasive	86.3 (*n* = 224)	97.2 (*n* = 224)
Widely invasive	65.4 (*n* = 56)	97.4 (*n* = 56)
PTC†		
Low risk	93.0 (*n* = 223)	100 (*n* = 223)
High risk	82.5 (*n* = 253)	91.5 (*n* = 253)
PDC		
PTC type (WHO)	53.8 (*n* = 14)	80.0 (*n* = 15)
PTC type (Sakamoto)	77.0 (*n* = 182)	94.2 (*n* = 189)
PTC type (Turin)	25.0 (*n* = 4)	60.0 (*n* = 5)
FTC type (WHO)	43.0 (*n* = 36)	71.2 (*n* = 44)

†Patients with distant metastasis at surgery were not included in calculations of the 10 year CSS.

CSS, cause-specific survival; DFS, disease-free survival; FTC, follicular thyroid carcinoma; PDC, poorly differentiated carcinoma; PTC, papillary thyroid carcinoma; WHO, World Health Organization.

there were only 14 (0.8%) poorly differentiated carcinoma (PDC) according to the World Health Organization (WHO) definition (PDC-WHO: solid/trabecular/insular growth pattern in the majority of tumor together with an infiltrative growth, necrosis and vascular invasion) and four (0.2%) according to the Turin proposal definition (PDC-Turin: solid/trabecular/insular carcinoma with increased mitosis or necrosis).[4,16,28,29] There were 182 (10.8%) PDC according to the Sakamoto definition (PDC-S: solid/trabecular/schirrous growth regardless of high grade histology)[30] and 61 cases (3.6%) tall cell variant of PTC according to the WHO definition (tall cell feature >50%) among 1680 PTC.[27] The prognostic data were incorporated into Table 2. In brief, the 10 year DFS of PDC-S was 77.0%, PDC-WHO, 53.8%; and PDC-Turin, 25%, while the 10 year DFS of common type and non-solid type PTC ($n = 1498$) was 88.8%, and the 10 year DFS of tall cell variants of PTC was 75.5%. The CSS was evaluated for 1707 PTC patients, including 27 with distant metastasis at diagnosis. The difference of CSS between PDC-S ($n = 189$) and other PTC ($n = 1518$) was significantly different ($P = 0.0001$), and the 10 year CSS rates were 94.2% and 98.4%, respectively. The 10 year CSS of PDC-WHO ($n = 15$) was 80% and that of PDC-Turin ($n = 5$) was 60%, while that of PTC of the tall cell variant ($n = 63$) was 90.5%.

Prognosis on FTC patients and PDC of FTC background

For analysis of FTC, 280 FTC patients (including 224 with minimally invasive and 56 with widely invasive disease) who were receiving curative surgery at Kuma Hospital, Japan from 1983 to 2004 in addition to 10 FTC patients (five with minimally invasive and five with widely invasive disease) with distant metastasis at surgery in the same period were analyzed and the details were published elsewhere by Ito *et al*.[31] The mean follow-up period of 290 patients was 73.8 months, and 36 patients developed recurrence, including distant metastases in 29 patients. The prognostic data are incorporated into Table 2. In brief, the 10 year DFS rate was 86.3% in 224 patients with minimally invasive FTC, in comparison with 65.4% in 56 patients with widely invasive FTC, and the DFS difference was statistically significant between the two groups of FTC patients ($P = 0.0319$, Kaplan–Meier). The 10 year CSS of all 229 patients with minimally invasive FTC was 97.2% and that of all 61 patients with widely invasive FTC was 84.2%, and the CSS difference was statistically significant between the two groups of FTC patients ($P = 0.0113$, Kaplan–Meier). The 10 year CSS, however, of 224 patients with minimally invasive FTC receiving curative surgery was 97.2% and that of 56 patients with widely invasive FTC receiving curative surgery was 97.4%, and the significant difference vanished in the survival analysis of patients with curative surgery.[29]

PDC-WHO were collected from the aforementioned review, and the data from 36 patients receiving curative surgery and eight patients with non-curative surgery were analyzed, and the details reported by Ito *et al*.[31] In brief, the 10 year DFS of PDC-WHO patients receiving curative surgery ($n = 36$) was 43.0% and the 10 year CSS of all PDC-WHO patients ($n = 44$) was 71.2%.

Table 3 New classification of thyroid follicular cell carcinomas

Benign:
- Follicular adenoma

Borderline:
- Follicular tumor of uncertain malignant potential†
- Well-differentiated tumor of uncertain malignant potential†

Malignant:
1. Well-differentiated adenocarcinoma (low-risk PTC and minimally invasive FTC)
   Subtype: PTC and FTC
2. Moderately differentiated adenocarcinoma (high-risk PTC, aggressive variants of PTC and widely invasive FTC)
   Subtype: PTC and FTC
3. Poorly differentiated carcinoma
   Subtype: PTC background and FTC background
4. Undifferentiated carcinoma

†reported by Williams.[26]
FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma.

New classification of thyroid tumors of follicular cell origin and proposal of well differentiated and moderately differentiated adenocarcinoma

Minimally invasive FTC and the low-risk group (encapsulated group and NOS group) of PTC have and excellent prognosis, as shown in the present study and by others.[20,31–33] It is our proposal that these two histotypes of thyroid carcinoma can be grouped together in one comprehensive category, because of their excellent prognosis and the same cell origin (Table 3). This group was designated as well-differentiated

adenocarcinoma (WDA) of follicular cell origin (well-differentiated follicular cell carcinoma of the thyroid) whose 10 year DFS rate was 86.3–93.1% and 10 year CSS rate was 97.2–100% in Japan. Concerning the intermediate risk group between WDA and PDC, we propose to set up a new group of carcinoma of follicular cell origin, a moderately differentiated adenocarcinoma (MDA; moderately differentiated follicular cell carcinoma of the thyroid). In our proposal, MDA includes widely invasive FTC and high-risk PTC, including aggressive variants of PTC.[1,4,34,35] Solid-type (solid area ≥10%) PTC in adult patients had a higher recurrence rate, as clarified by Bai *et al.*,[18] and solid variant (solid area ≥70%) of PTC in adult patients also had a slightly worse (90%) mortality rate reported by Nikiforov *et al.*[21] Although conflicting data on solid variant (solid area ≥50%) of PTC in adult cases exist, for example, Carcangiu *et al.* reported that it did not have an aggressive prognosis,[36] and Noguchi *et al.* reported no prognostic difference between well-differentiated carcinomas and their solid/trabecular carcinomas.[37] It is our proposal that PTC with solid growth (solid area: both ≥10% and ≥50%) without high-grade histology should be included in the MDA category. A borderline lesion of follicular cell tumor, between benign follicular adenoma and malignant tumors, has been proposed by Williams, and we also recommend this terminology in our classification shown in Table 3.[26,38]

DISCUSSION

There are many reports on the prognostic factors of differentiated thyroid carcinomas in the literature, particularly on PTC. Some included histological parameters, such as histological grade and cellular differentiation, and immunohistochemistry, in addition to well established clinical parameters, such as age and gender of patients, size of tumors, extrathyroid extension, completeness of surgery and distant metastasis and so on.[1,5,22,39–44] All of the prognostic stratifications of patients before surgical treatment (exclusion of parameters obtainable from histological examination of surgical samples) are useful in predicting low-, intermediate- and high-risk groups of patients. Unfortunately, some patients in the low-risk group still develop recurrence and/or metastasis, and eventually die of so-called differentiated thyroid carcinoma. Therefore, tissue-based prognostic predictors are obviously necessary, particularly for the low-risk and common-type differentiated carcinoma.[15] For pathologists, the most promising predictors were histopathological parameters, such as growth pattern, cellular differentiation and histological grade and so on, because all of them are established prognostic parameters in the other organs. Tscholl-Ducommun and Hedinger claimed that their PTC subtypes, based on their grade of differentiation, correlated well with prognosis,[45] and Schelfhout *et al.* also reported that their histological differentiation was an independent prognostic factor.[46] As far as we can judge from the illustrations and description, the Tscholl-Ducommun and Hedinger undifferentiated papillary carcinoma in their fig. 11 was non-solid type PTC different from the PDC-WHO or UC, and was an example of MDA of high-risk PTC in our classification, as shown in Fig. 5 of the present study. Histological grading using the Broders' classification was reported by McConahey *et al.* to be a cause-specific important prognostic factor in PTC.[41] Akslen compared the prognostic significance of morphological subclassification of PTC with histological grade using combined assessment of marked nuclear atypia, tumor necrosis and vascular invasion.[47] The histological grade proved to be a strong prognostic factor whereas morphological subclassification of PTC had only minor impact.[47,48] D'Avanzo *et al.* divided 132 FTC patients into three groups using their terminology, minimally invasive, moderately invasive and widely invasive FTC defined by invasive patterns, and showed difference in recurrence and mortality among the three groups.[49] In the present group a poorly differentiated category was proposed for medullary (C cell) carcinoma of the thyroid with ultrastructural features, doubling time and prognostic data.[50] The histological grade and differentiation classification of thyroid carcinomas had been introduced by several groups but this approach did not become popular and has not been widely used. Only small numbers of differentiated carcinomas were routinely graded in diagnosis, because the majority of differentiated carcinomas were grade 1.[4,9,41] The other approach to identify aggressive carcinoma in PTC and FTC was PDC, which was applied to solid carcinoma with or without high grade histology,[15,16,30,36,51] and it was incorporated in the 2004 edition of the WHO classification of thyroid tumors.[4] It was not applicable, however, to non-solid type aggressive PTC or FTC. Alternatively several aggressive variants of PTC are well known to have prognostic significance, such as tall cell variant, columnar cell variant and solid variant and so on.[1,4,28,29,31,35,52,53] These variants are grouped as intermediate differentiated, moderately differentiated or poorly differentiated carcinoma in various manners by various authors.[34,35,54–56] The diagnosis of aggressive variants is sometimes difficult because of the presence of composite tumors with different components.[57] To solve these issues, we proposed here our new classification and new histological criteria, which can classify prognostically different thyroid carcinomas into WDA, MDA, PDC and UC. This classification is applicable to all follicular cell tumors and had a significant prognostic impact on tumor recurrence for patients treated curatively.

In the present paper we have described four important recommendations and proposals. The first was that PTC (>87% of all thyroid carcinomas in Japan) could be divided into high-risk and low-risk groups for recurrence using morphological features alone. In the Bai *et al.* study their low-risk group had a 10 year DFS of 93.1%, and there were no cancer-related deaths among the 151 patients during a >150 month

mean follow-up period, while in their high-risk group, the 10 year DFS was 78.7% and tumor death occurred in six (10 year CSS, 91.5%) of 71 patients.[18] Their results were confirmed in the present study using a larger number of patients. Low-risk PTC comprised 223/476 patients (46.8%) and had a 10 year DFS of 93.0%, while high-risk PTC comprised 253/476 patients (53.2%) and had a 10 year DFS of 82.5%.

The second was differential diagnostic criteria that define high-risk PTC, and they were (i) tall/columnar features; (ii) solid growth; and (iii) loss of cellular polarity/cohesiveness in addition to capsulation and invasiveness. Epithelial–mesenchymal transition (EMT) is a common event in thyroid carcinoma and it is characterized by loss of epithelial properties and acquisition of mesenchymal properties. They include the loss of apical-basal polarity, loss of cell–cell adhesion, loss of E-cadherin expression and overexpression of vimentin in the tumors.[58] One of these EMT-related features, loss of cellular polarity/cohesiveness, was first applied by our group in the histological criteria to differentiate low-risk and high-risk PTC.[19] The tall/columnar cell features and loss of cellular polarity/cohesiveness are often seen in adencarcinomas of various organs, and they are usually not in a category of poorly differentiated adenocarcinoma.[52,57] It is our conclusion that thyroid carcinomas with these features should be included in MDA rather than PDC, because they form papillary, tubular or follicular structures morphologically and retain follicular cell differentiation, such as the production of thyroid hormone and uptake of radioiodine functionally.

The third important point was that less-differentiated morphology in a minority of tumor area is already an indicator for lower DFS (i.e. higher chance of recurrence), while most textbooks use the majority of tumor area for the diagnostic threshold.[1,4] Bai *et al.* showed that their PTC with tall/columnar cell feature involved lower DFS of 63.2% in a 113 month follow-up period, and CSS of 78.9%, even though the feature were defined by the lowest cut-off value (≥10% in tumor area).[18]

The fourth was unification of PTC and FTC as a single entity of follicular cell carcinoma, although our current understanding of the genetics of thyroid tumors failed to support this proposal.[59,60] The classification of tumors is primarily morphological but usually it reflects current concepts of embryogenesis and histogenesis of the organs in which tumors occur. Traditionally, it has not been fully applied to the classification of thyroid tumors and examples were FTC and PTC. FTC and PTC are both low-grade differentiated carcinomas and have the same histogenesis, but they are distinct entities in thyroid pathology and separately classified in diagnosis, due to differences in clinical management and in pattern of metastasis, greater lymphatic spread in PTC and greater hematogenous spread in FTC.[1,4,5,7,40,61] The classification proposed here combined all carcinoma of follicular cell phenotype into one comprehensive diagnostic category of follicular cell carcinoma and tried to subdivide this carcinoma into WDA, MDA and PDC according to different prognosis and cellular differentiation (Table 3). The distinction of PTC and FTC was not emphasized in the present classification, and they were one of the subtypes of WDA, MDA and PDC. This is because the two subtypes had an essentially similar 10 year CSS rate in the present study when the patients were treated curatively, which has also been reported by others,[20,37,43,62,63] although many conflicting data have been published, which included significant numbers of patients with advanced stages.[5,7,9,40,61,64–66] There is no definitive reason why PTC and FTC subtypes must be separated into two distinct entities in the classification of thyroid carcinomas. Many pathologists are aware that the distinctions between FTC and PTC are not always clear-cut, and Williams proposed new diagnostic terminology for a group of carcinomas with definite capsular invasion and questionable PTC-type nuclear changes, as well-differentiated carcinoma not otherwise specified (WDC-NOS), and LiVolsi and Asa referred to such cases as hybrid tumors.[13,26,38] Those studies showed that significant numbers of thyroid carcinomas had both FTC and PTC characteristics and the distinction between FTC and PTC was not always possible under current diagnostic criteria.[1,4,11,14,26] The current proposal in the classification of thyroid follicular cell carcinoma solved this issue differently, needless to say FTC and PTC were subtypes of WDA, MDA or PDC, and are not essential in diagnosis when the distinction is not clear-cut.

Another reason as to why we combined FTC and PTC into one diagnostic category, was that iodine supplementation in food led to a corresponding decrease of the incidence of FTC.[2,6,7,67] This finding indicates that both types of thyroid carcinoma may be two phases of one low-grade carcinoma, because the incidences of each were inversely influenced by environmental factors. The occurrences of PTC and FTC are usually mutually exclusively present but, interestestingly, a few cases of PTC in the bone associated with origin of FTC in the thyroid have been found.

In our new classification, both FTC and PTC are core members of WDA, MDA and PDC. It is recommended that a low-grade PTC should be diagnosed with additional comments as a WDA, papillary type. For minimally invasive FTC, it should be WDA, encapsulated FTC type, with or without capsular invasion. PTC with tall/columnar cell features, solid growth or loss of cellular polarity/cohesiveness should be MDA, PTC type. For widely invasive FTC, it should be MDA, widely invasive FTC with angioinvasion etc.

The prevalence of FTC, PTC, PDC and UC seems to vary among different geographic areas.[1,4,5,7,8,10,66] An example is PDC, and its incidence was reported as 2–3% in North America and 15% in North Italy,[10] but it was extremely rare in Japan, in <1% of the present patients. It may be a rare tumor in some other geographic areas and we doubt that there are sufficient numbers of patients to form a distinct diagnostic

entity in such countries. We agree that solid/trabecular/insular growth with high-grade histology is an important morphological feature to predict patient prognosis,[16,27,31,51,63] but we suspect that PDC is a transient form of carcinoma from differentiated carcinoma to UC rather than a stable form of carcinoma, because we often found this feature focally in advanced stage tumors, and sometimes with anaplastic transformation. Usually PDC cases show a mixture of different histological features, such as PTC, FTC or UC in addition to PDC, because the definition of PDC applies to the cases whose majority of tumor area contain PDC features. No one case had pure PDC features throughout in all of the tumor samples from the primary lesion, recurrent lesion, and metastatic lesion in our experience. Some authors believe that the vast majority of PDC are in fact examples of PTC or FTC with unusual growth pattern.[52,57] We agree that this type of carcinoma has more aggressive biological behavior than WDA and MDA, and have retained it as a subtype of follicular cell carcinomas in the present classification to reflect the WHO classification (Table 3).

In conclusion, we have proposed here a new prognostic classification of the thyroid follicular cell carcinomas. It is based on pure histopathological parameters and applicable to patients at curative stages. The low-risk follicular cell carcinoma is termed WDA and it is characterized by capsulation with or without minimal invasion, or invasive carcinoma without less differentiated morphology. The intermediate-risk group between WDA and PDC is named MDA and this carcinoma was defined as invasive carcinoma with less-differentiated morphology, published in detail in our previous studies.[18,19] Although different types of follicular cell origin carcinoma harbor different genetic background, the present subclassification was proved to be significant on prognostic analysis, and it will demonstrate its value in determination of patient prognosis. In Japan, most thyroid carcinomas are differentiated carcinomas and are treated with curative surgery. Therefore this subclassification of early-stage differentiated thyroid carcinoma is extremely important for patient care in countries where most patients are treated curatively.

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REFERENCES

1 Rosai J, Carcangiu M, Delellis R. *Atlas of Tumor Pathology: Tumors of the Thyroid Gland*. Washington, DC: Armed Forces Institute of Pathology, 1992.
2 Cady B. Comparative analysis of thyroid carcinoma in Germany and the U.S. *Cancer* 2000; **89**: 1–4.
3 Clark OH. Predictors of thyroid tumor aggressiveness. *West J Med* 1996; **165**: 131–8.
4 DeLellis R, Lloyd R, Heitz P, Eng C. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of Endocrine Organs*. Lyon: International Agency for Research on Cancer Press, 2004.
5 Grebe SK, Hay ID. Follicular thyroid cancer. *Endocrinol Metab Clin North Am* 1995; **24**: 761–801.
6 Langsteger W, Koltringer P, Wolf G *et al.* The impact of geographical, clinical, dietary and radiation-induced features in epidemiology of thyroid cancer. *Eur J Cancer* 1993; **29A**: 1547–53.
7 Passler C, Scheuba C, Prager G *et al.* Prognostic factors of papillary and follicular thyroid cancer: Differences in an iodine-replete endemic goiter region. *Endocr Relat Cancer* 2004; **11**: 131–9.
8 Saikawa M, Ito K, Ohara T. The registry of malignant tumors of thyroid in Japan. In: *Abstracts of the 40th Annual Meeting of the Japanese Society of Thyroid Surgery*. Tokyo: Japanese Society of Thyroid Surgery, 2007; 121–36 (in Japanese).
9 Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S. *Cancer* 1998; **83**: 2638–48.
10 Sanders EM Jr, LiVolsi VA, Brierley J, Shin J, Randolph GW. An evidence-based review of poorly differentiated thyroid cancer. *World J Surg* 2007; **31**: 934–45.
11 Hirokawa M, Carney JA, Goellner JR *et al.* Observer variation of encapsulated follicular lesions of the thyroid gland. *Am J Surg Pathol* 2002; **26**: 1508–14.
12 Kakudo K, Katoh R, Sakamoto A *et al.* Thyroid gland: International case conference. *Endocr Pathol* 2002; **13**: 131–4.
13 LiVolsi VA, Asa SL. The demise of follicular carcinoma of the thyroid gland. *Thyroid* 1994; **4**: 233–6.
14 Lloyd RV, Erickson LA, Casey MB *et al.* Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. *Am J Surg Pathol* 2004; **28**: 1336–40.
15 Sobrinho-Simoes M. Hail to the histologic grading of papillary thyroid carcinoma? *Cancer* 2000; **88**: 1766–8.
16 Volante M, Collini P, Nikiforov YE *et al.* Poorly differentiated thyroid carcinoma: The Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *Am J Surg Pathol* 2007; **31**: 1256–64.
17 Franc B, de la Salmoniere P, Lange F *et al.* Interobserver and intraobserver reproducibility in the histopathology of follicular thyroid carcinoma. *Hum Pathol* 2003; **34**: 1092–100.
18 Bai Y, Kakudo K, Li Y *et al.* Subclassification of non-solid-type papillary thyroid carcinoma identification of high-risk group in common type. *Cancer Sci* 2008; **99**: 1908–15.
19 Kakudo K, Tang W, Ito Y, Mori I, Nakamura Y, Miyauchi A. Papillary carcinoma of the thyroid in Japan: Subclassification of common type and identification of low risk group. *J Clin Pathol* 2004; **57**: 1041–6.
20 Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; **97**: 418–28.
21 Nikiforov YE, Erickson LA, Nikiforova MN, Caudill CM, Lloyd RV. Solid variant of papillary thyroid carcinoma: Incidence, clinical-pathologic characteristics, molecular analysis, and biologic behavior. *Am J Surg Pathol* 2001; **25**: 1478–84.
22 Shaha AR, Loree TR, Shah JP. Intermediate-risk group for differentiated carcinoma of thyroid. *Surgery* 1994; **116**: 1036–40; discussion 1040–41.
23 Hay ID, Hutchinson ME, Gonzalez-Losada T *et al.* Papillary thyroid microcarcinoma: A study of 900 cases observed in a 60-year period. *Surgery* 2008; **144**: 980–87; discussion 987–8.
24 Zuo H, Tang W, Yasuoka H *et al.* A review of 227 cases of small papillary thyroid carcinoma. *Eur J Surg Oncol* 2007; **33**: 370–75.

25 Ito Y, Uruno T, Nakano K *et al.* An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid* 2003; **13**: 381–7.
26 Williams ED. Guest editorial: Two proposals regarding the terminology of thyroid tumors. *Int J Surg Pathol* 2000; **8**: 181–3.
27 Ito Y, Hirokawa M, Fukushima M *et al.* Prevalence and prognostic significance of poor differentiation and tall cell variant in papillary carcinoma in Japan. *World J Surg* 2008; **32**: 1535–43; discussion 1544–5.
28 Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer* 1985; **55**: 805–28.
29 Chan JK. Papillary carcinoma of thyroid: Classical and variants. *Histol Histopathol* 1990; **5**: 241–57.
30 Sakamoto A. Definition of poorly differentiated carcinoma of the thyroid: The Japanese experience. *Endocr Pathol* 2004; **15**: 307–11.
31 Ito Y, Hirokawa M, Higashiyama T *et al.* Prognosis and prognostic factors of follicular carcinoma in Japan: Importance of postoperative pathological examination. *World J Surg* 2007; **31**: 1417–24.
32 van Heerden JA, Hay ID, Goellner JR *et al.* Follicular thyroid carcinoma with capsular invasion alone: A nonthreatening malignancy. *Surgery* 1992; **112**: 1130–36; discussion 1136–8.
33 Thompson LD, Wieneke JA, Paal E, Frommelt RA, Adair CF, Heffess CS. A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. *Cancer* 2001; **91**: 505–24.
34 Sobrinho-Simoes M, Nesland JM, Johannessen JV. Columnar-cell carcinoma. Another variant of poorly differentiated carcinoma of the thyroid. *Am J Clin Pathol* 1988; **89**: 264–7.
35 Sywak M, Pasieka JL, Ogilvie T. A review of thyroid cancer with intermediate differentiation. *J Surg Oncol* 2004; **86**: 44–54.
36 Carcangiu ML, Zampi G, Rosai J. Poorly differentiated ('insular') thyroid carcinoma. A reinterpretation of Langhans' 'wuchernde Struma'. *Am J Surg Pathol* 1984; **8**: 655–68.
37 Noguchi M, Mizukami Y, Michigishi T, Koyasaki N, Ohta N, Miyazaki I. Multivariate study of prognostic factors for differentiated thyroid carcinoma: The significance of histologic subtype. *Int Surg* 1993; **78**: 10–15.
38 Fonseca E, Soares P, Cardoso-Oliveira M, Sobrinho-Simoes M. Diagnostic criteria in well-differentiated thyroid carcinomas. *Endocr Pathol* 2006; **17**: 109–17.
39 Hay ID. Management of patients with low-risk papillary thyroid carcinoma. *Endocr Pract* 2007; **13**: 521–33.
40 Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: A population-based, nested case-control study. *Cancer* 2006; **106**: 524–31.
41 McConahey WM, Hay ID, Woolner LB, van Heerden JA, Taylor WF. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: Initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 1986; **61**: 978–96.
42 Shaha A. Treatment of thyroid cancer based on risk groups. *J Surg Oncol* 2006; **94**: 683–91.
43 Tubiana M, Schlumberger M, Rougier P *et al.* Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 1985; **55**: 794–804.
44 Kremser R, Obrist P, Spizzo G *et al.* Her2/neu overexpression in differentiated thyroid carcinomas predicts metastatic disease. *Virchows Arch* 2003; **442**: 322–8.
45 Tscholl-Ducommun J, Hedinger CE. Papillary thyroid carcinomas. Morphology and prognosis. *Virchows Arch A Pathol Anat Histol* 1982; **396**: 19–39.
46 Schelfhout LJ, Creutzberg CL, Hamming JF *et al.* Multivariate analysis of survival in differentiated thyroid cancer: The prognostic significance of the age factor. *Eur J Cancer Clin Oncol* 1988; **24**: 331–7.
47 Akslen LA. Prognostic importance of histologic grading in papillary thyroid carcinoma. *Cancer* 1993; **72**: 2680–85.
48 Akslen LA, LiVolsi VA. Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. *Cancer* 2000; **88**: 1902–8.
49 D'Avanzo A, Treseler P, Ituarte PH *et al.* Follicular thyroid carcinoma: Histology and prognosis. *Cancer* 2004; **100**: 1123–9.
50 Kakudo K, Miyauchi A, Katayama S, Watanabe K. Ultrastructural study of poorly differentiated medullary carcinoma of the thyroid. *Virchows Arch A Pathol Anat Histopathol* 1987; **410**: 455–60.
51 Hiltzik D, Carlson DL, Tuttle RM *et al.* Poorly differentiated thyroid carcinomas defined on the basis of mitosis and necrosis: A clinicopathologic study of 58 patients. *Cancer* 2006; **106**: 1286–95.
52 Albores-Saavedra J, Carrick K. Where to set the threshold between well differentiated and poorly differentiated follicular carcinomas of the thyroid. *Endocr Pathol* 2004; **15**: 297–305.
53 Ortiz S, Rodriguez JM, Parrilla P *et al.* Recurrent papillary thyroid cancer: Analysis of prognostic factors including the histological variant. *Eur J Surg* 2001; **167**: 406–12.
54 Fadda G, LiVolsi VA. Histology and fine-needle aspiration cytology of malignant thyroid neoplasms. *Rays* 2000; **25**: 139–50.
55 Tang W, Nakamura Y, Zuo H *et al.* Differentiation, proliferation and retinoid receptor status of papillary carcinoma of the thyroid. *Pathol Int* 2003; **53**: 204–13.
56 Baloch ZW, Livolsi VA. Follicular-patterned lesions of the thyroid: The bane of the pathologist. *Am J Clin Pathol* 2002; **117**: 143–50.
57 Nishiyama RH. Overview of surgical pathology of the thyroid gland. *World J Surg* 2000; **24**: 898–906.
58 Vasko V, Espinosa AV, Scouten W *et al.* Gene expression and functional evidence of epithelial-to-mesenchymal transition in papillary thyroid carcinoma invasion. *Proc Natl Acad Sci USA* 2007; **104**: 2803–8.
59 Hunt J. Understanding the genotype of follicular thyroid tumors. *Endocr Pathol* 2005; **16**: 311–21.
60 Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: Implications for diagnosis, treatment and prognosis. *Expert Rev Mol Diagn* 2008; **8**: 83–95.
61 Franssila KO. Is the differentiation between papillary and follicular thyroid carcinoma valid? *Cancer* 1973; **32**: 853–64.
62 Donohue JH, Goldfien SD, Miller TR, Abele JS, Clark OH. Do the prognoses of papillary and follicular thyroid carcinomas differ? *Am J Surg* 1984; **148**: 168–73.
63 Pellegriti G, Giuffrida D, Scollo C *et al.* Long-term outcome of patients with insular carcinoma of the thyroid: The insular histotype is an independent predictor of poor prognosis. *Cancer* 2002; **95**: 2076–85.
64 Chow SM, Law SC, Au SK *et al.* Differentiated thyroid carcinoma: Comparison between papillary and follicular carcinoma in a single institute. *Head Neck* 2002; **24**: 670–77.
65 Lin JD, Huang MJ, Juang JH *et al.* Factors related to the survival of papillary and follicular thyroid carcinoma patients with distant metastases. *Thyroid* 1999; **9**: 1227–35.
66 Sanders LE, Cady B. Differentiated thyroid cancer: Reexamination of risk groups and outcome of treatment. *Arch Surg* 1998; **133**: 419–25.
67 Lind P, Langsteger W, Molnar M, Gallowitsch HJ, Mikosch P, Gomez I. Epidemiology of thyroid diseases in iodine sufficiency. *Thyroid* 1998; **8**: 1179–83.