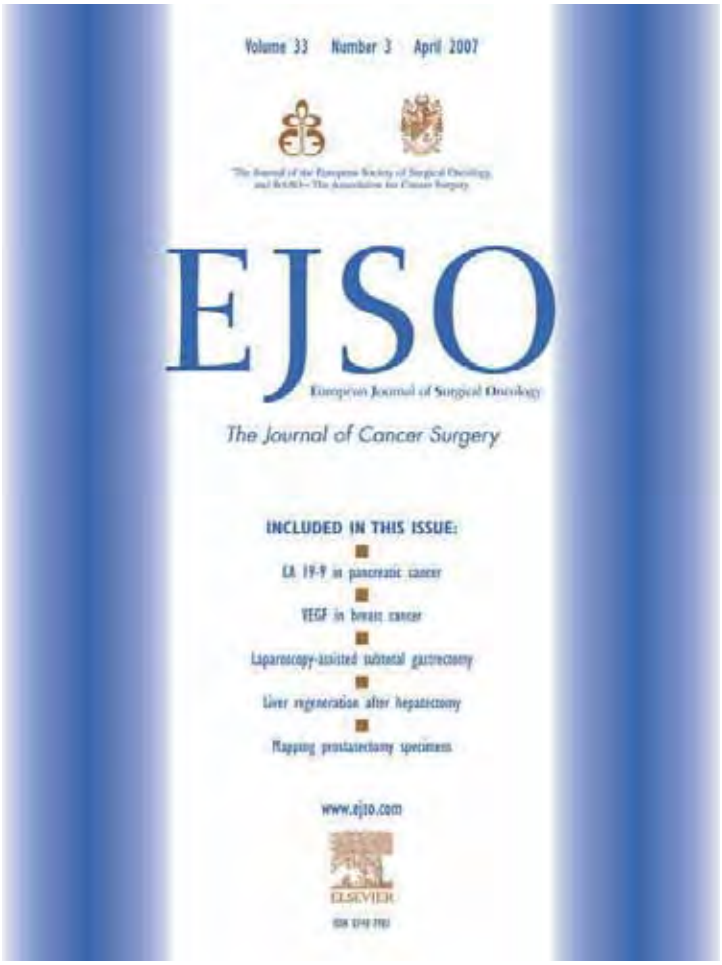

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EJSO 33 (2007) 370–375
www.ejso.com

A review of 227 cases of small papillary thyroid carcinoma

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Accepted 21 September 2006
Available online 27 October 2006

Abstract

Aims: To review differences in biological aggressiveness, clinical behaviors or selected surgical treatments between the PMC and the slightly larger PTC of $1.0 < T \leq 2.0$ cm.
Methods: Two hundred and twenty-seven cases of papillary thyroid carcinoma not larger than 2.0 cm, diagnosed and treated at the Kuma Hospital, Kobe, Japan, with a 10-year follow-up from 1992 to 2003, were reviewed.
Results: The small PTCs demonstrated excellent outcomes, and persistent/recurrent disease was identified in only nine patients (4 %). None of the patients died of the disease. A multivariate analysis revealed that massive extrathyroidal extension at presentation was the only independent prognostic factor for locoregional recurrence. Subdivision into PMCs and slightly larger tumors ($1 < T \leq 2$ cm) did not affect the excellent outcomes, but the patients in the latter subgroup received more lymph node surgery and displayed more aggressive clinicohistological features such as higher rates of extrathyroidal extension, lymph node metastasis, loss of polarity, invasive growth pattern and loss of cohesiveness.
Conclusions: Small PTC not larger than 2.0 cm could be considered as favorable a prognosis as PMC.

Keywords: Small papillary thyroid carcinoma; Prognostic factors; PMC; Extrathyroidal extension; TNM staging

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for 80 % of cases.[1] In countries like Japan, where a high iodine intake is common, the incidence of PTC exceeds 85 % of all thyroid cancer.[2] Patients with PTC usually have a very good prognosis and a mortality rate of less than 10 % at 10 years after surgery. Furthermore papillary microcarcinoma (PMC) originally proposed by Harzard and later defined by the World Health Organization (WHO) as a tumor of 1.0 cm or less in diameter,[3] exhibits more favorable outcomes than larger tumors in a number of studies[4–6] despite the fact that some PMCs also might develop locoregional recurrences, distant metastases and cause death of the patients.[7,8]

With improved preoperative diagnostic techniques, including fine-needle aspiration cytology and high-resolution ultrasonography, PMC can be diagnosed before definitive surgery and thyroid cancer also tends to be diagnosed at an early stage.[7,9,10] However, determination of prognostic factors in small PTC still remains uncertain.

The newly adopted TNM (AJCC/UICC) classification of thyroid tumors has changed the size threshold of T1 from 1.0 cm to 2.0 cm, which raises the question of whether PTC larger than 1.0 cm, but still small (not larger than 2.0 cm), has a similar favorable outcome as PMC.

Our previous studies have identified histological parameters, such as invasive growth pattern and two cellular characteristics—loss of cellular polarity and loss of cellular cohesiveness—as significant indicators of the risk of recurrence in the well-differentiated type of PTC in a cohort of patients.[11]

Therefore, we reviewed 227 patients with PTC $\leq$ 2.0 cm treated at one institute and tried to identify the prognostic factors and optimal treatment strategy for this group of

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doi:10.1016/j.ejso.2006.09.024

patients, and to determine whether there is any biological difference between cancers measuring $1.0 < T \leq 2.0$ cm and those of $T \leq 1.0$ cm (PMC).

Patients and methods

We reviewed 227 patients with tumors not larger than 2 cm, who were diagnosed and operated on for PTC at Kuma Hospital, Kobe, Japan between February 1992 and June 1993, and were followed postoperatively till 2003. The average follow-up period for the patients was 86.98 ± 37.605 months. All cases were diagnosed as differentiated PTC; other histological types of thyroid carcinoma such as follicular carcinoma, medullary (C-cell) carcinoma, anaplastic carcinoma, or malignant lymphomas were excluded from the study. The clinical information for the cases is summarized in Table 1.

Because isotope ablation has not been comprehensively adopted in Japan, thyroidectomy with modified radical neck dissection (MND) is adopted as a standard surgical procedure for PTC, as described elsewhere.[12] In brief, the patients underwent either total thyroidectomy (including subtotal thyroidectomy) or lobectomy (with or without isthmusectomy), depending on the routine preoperative estimate of intrathyroidal spread of PTC by ultrasonography and fine needle aspiration biopsy: when a tumor was limited to one lobe, lobectomy with or without isthmusectomy of the affected side was performed; when a tumor involved both lobes, or nodal metastases at the bilateral neck or distant metastasis were evident, total or subtotal thyroidectomy was the choice. In principle, nodal dissection of the central compartment was routinely performed. We performed MND for either therapeutic or prophylactic purpose on patients when lateral cervical lymph nodes larger than 1 cm in diameter were detected by sonography. Postoperative radioiodine ablation was carried out only on the patients with distant metastases. In cases of incidental malignancy lymph node dissection was not performed.

Extrathyroidal extension of the tumor was categorized as: no extension (Ex0, also as T1 according to the definition of the sixth edition of TNM), minimal extension (e.g. extension to the sternothyroid muscle and/or perithyroid soft tissues; Ex1, also defined as T3 in the sixth edition of TNM) or massive extension (e.g. invasion to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; Ex2, also defined as T4a in the sixth edition of TNM), based on both pathological and intra-operative surgical findings. Multifocality was regarded as two or more lesions occurring separately within the ipsilateral or/and contralateral lobe. Postoperative patients were continuously followed up by ultrasonography, computer tomography, radioiodine scintigraphy and routine chest radiography to identify recurrence in lymph nodes, remnant thyroid or distant organs. Recurrence in residual thyroid and/or lymph nodes was diagnosed by performing ultrasonography-guided fine needle aspiration biopsy of suspicious lesions. Tumors were staged according to both the fifth and sixth editions of TNM staging.

In addition, histological invasive growth pattern is defined as growth of neoplastic cells that infiltrates into surrounding thyroid parenchyma with ill-defined margin and usually lacking a fibrous capsule. In contrast, an expansive growth pattern is usually manifested as a fully or partially encapsulated lesion with well-circumscribed margin. Loss of cellular polarity is characterized by elevated nuclei in the middle or on top of the cytoplasm in cancer epithelium, which gives a hobnail appearance. Loss of cellular cohesion is characterized by loosely or individually arranged cancer cells that are usually seen in the invasive front of the tumors.[13]

Statistical analysis

Time-independent, categorical and continuous data were evaluated using the chi-square test, Student's *T*-test or Fisher's exact test as appropriate. The disease-free survival period (DFS) was calculated from the time of primary surgery to the final contact day or the day that recurrence was identified. DFS analysis was performed using Kaplan–Meier plots and log rank tests were used to determine prognostic factors. Univariate analysis was performed on the following parameters: age, sex, multifocality, tumor size, extrathyroidal extension, type of operation, nodal metastasis, and histological characteristics such as invasive growth pattern, cellular polarity and cellular dissociation. All factors found to be significant by univariate analysis were subjected to multivariate analysis using Cox proportional hazards regression model. The differences were considered statistically significant when a p value was less than 0.05. Data analysis was performed using Stat View-J, version 5.0 statistical software (SAS Institute Inc, Cary, NC, USA).

Results

As shown in Table 1, of 227 patients with small tumors—which dominated in females (95 %)—80 cases (35 %) were found with multifocal lesions and 96 cases (42 %) with extrathyroidal extension. Among 96 cases of PTC with extrathyroidal extension, 90 patients had minimal extrathyroidal extension (Ex1, T3) spreading beyond the capsule of the thyroid and involving the adjacent fat or muscle, and the remaining six cases had massive extrathyroidal extension (Ex2, T4a) that invaded to surrounding structures, among which four cases invaded the recurrent nerve, one case invaded the trachea and one case invaded both the recurrent nerve and the trachea. All of the T4a cases underwent total/subtotal thyroidectomy and MND.

Among 189 patients (83 % of 227 patients) who underwent lymph node (LN) dissection, 123 patients (65 %) were identified with LN metastases, and metastasis to lateral cervical LN (N1b) was found in up to 39 % of those 189 patients. The remaining 38 patients (17 % of 227 patients)

Table 1
Clinical information for the 227 cases of small PTC and comparison of clinical characteristics and outcomes after subdivision into $T \leq 1.0$ cm and $1.0 < T \leq 2.0$ cm groups

	$T \leq 2.0$ cm	$T \leq 1.0$ cm	$1.0 < T \leq 2.0$ cm	p
Number of cases	227	90	137	–
Patient age, average and range or ±SD (year)	49.72 (19–84)	49.333 ± 11.942	49.971 ± 13.445	0.7155
≥45	149	57	93	0.5540
<45	78	33	45	
Female/male (% female)	215/12 (95)	85/5 (94)	130/7 (95)	0.8835
Total thyroidectomy/lobectomy (% total thyroidectomy)	121/106 (53)	53/37 (59)	68/69 (50)	0.1716
Multifocal lesions (%)	80 (35)	34 (38)	46 (34)	0.5176
Extrathyroidal invasion (%)[a]	96 (42)			
Ex0	131 (58)	65 (72)	66(48)	
Ex1	90 (40)	24 (27)	66(48)	0.0014
Ex2	6 (3)	1 (1)	5 (4)	
Lymph node surgery				
Not performed (%)	38 (17)	28 (31)	10 (7)	
Central dissection (%)	37 (16)	21 (23)	16 (12)	<0.0001
Modified neck dissection (%)	152 (67)	41 (46)	111 (81)	
Lymph node metastases (%)	123 (65)			
N0	66 (35)	30	36	
N1a	49 (26)	17	32	0.0063
N1b	74 (39)	15	59	
Positive nodes	2.9 ± 4.3	1.7 ± 2.4	3.4 ± 4.8	0.0069
Loss of polarity (%)	76 (33)	19 (21)	57 (42)	0.0014
Invasive growth pattern (%)	59 (26)	17 (19)	42 (31)	0.0480
Loss of cohesiveness (%)	54 (24)	12 (13)	42 (31)	0.0027
Local recurrence (%)	9 (4)	2 (2)	7 (5)	0.2574
Distant metastases (%)	1 (0.44)	0	1	0.4166
Ten-year survival (%)				
Cause-specific survival	100	–	–	–
Locoregional failure-free survival rate	93.3	95.3	91.8	0.2627[b]
Distant metastasis failure-free survival	99.5	–	–	–

[a] Ex0, tumor limited to the thyroid; Ex1, tumor with minimal extrathyroidal extension, involving the adjacent fat or muscle; Ex2, tumor with massive extrathyroidal extension, invading to surrounding structures like the recurrent nerve, trachea, larynx, esophagus or subcutaneous soft tissues.
[b] Using the log rank test.

did not undergo LN dissection because of incidental PTC. The average number of positive lymph nodes for each case was 2.9. Also, one patient (0.44 %) presented with distant metastasis to the lung at presentation. Furthermore, locoregional recurrence occurred in nine patients (4 %), including the LN in seven patients, in the residual thyroid bed in one patient and in the skin of the surgical wound in one patient. During the follow-up one patient who had recurrence in lymph nodes also developed lung metastasis at 22 months after the primary operation. No patient in this cohort died from the disease.

Univariate analysis of preoperative prognostic factors for relapsing disease

In Table 2, clinical and pathological parameters at the initial surgery and the results of univariate analysis of these variables are summarized. In the Cox univariate analysis, male sex, extrathyroidal extension, five or more lymph node metastases, presence of histological characteristics, such as invasive growth pattern and loss of polarity were significant prognostic factors for locoregional recurrence. When using LN recurrence as end point, in addition to the prognostic factors for locoregional recurrence, the histopathological characteristic of cellular dissociation was identified as a predictor for LN recurrence. However the following characteristics were not significant prognostic factors in the Cox univariate analysis: age, the percentages of patients older or younger than 60 years, multifocality or ratio of patient undergoing total thyroidectomy-to-lobectomy (data not shown).

Multivariate analysis of preoperative prognostic factors

A multivariate analysis was carried out for the preoperative prognostic factors shown as significant by univariate analysis. Results revealed that the presence of massive

Table 2
Univariate analysis of clinical and histopathological parameters in patients with small PTC, using locoregional recurrence or lymph node recurrence as end point by log rank tests

Parameters	Univariate analysis ($T \leq 2$ cm)			
	Locoregional recurrence		LN recurrence	
	No.	p value	No.	p value
Gender				
Female	7/215	0.0006	5/215	0.0002
Male	2/12		2/12	
Diameter of lesion				
$1 < T \leq 2$	7/137	0.2627	6/137	0.1580
$T \leq 1$	2/90		1/90	
Extrathyroidal extension				
Ex0	5/131	<0.0001	3/131	<0.0001
Ex1	2/90		2/90	
Ex2	2/6		2/6	
Positive LN >5				
No	5/184	0.0444	3/183	0.0074
Yes	4/43		4/43	
Pathological LN	9/189		7/189	
N0	2/66	0.6031	1/66	0.4892
N1a	2/49		2/49	
N1b	5/74		4/74	
Type of LN dissection				
No performed	0/38	–		–
Central compartmental dissection	2/37	0.7841	3/37	0.5054
Modified neck dissection	7/152		5/152	
Growth pattern				
Expansive	4/168	0.0304	3/168	0.0465
Invasive	5/59		4/59	
Cellular polarity				
Maintenance	3/151	0.0331	2/151	0.0336
Loss	6/76		5/76	
Cellular dissociation				
Absent	5/173	0.1530	3/173	0.0374
Present	4/54		4/54	

extrathyroidal extension (T4a) was the only independent factor predicting both locoregional and LN recurrences (data not shown).

Comparison of clinical and histopathological characteristics and outcomes between patients with tumors of $T \leq 1.0$ cm and $1.0 < T \leq 2.0$ cm

The subdivision of tumors according to size ($T \leq 1.0$ cm vs. $1.0 < T \leq 2.0$ cm) did not have a significant impact on patient outcomes with regard to the locoregional/LN recurrence (Table 2), or 10-year locoregional failure-free survival rate (Table 1), as determined by log rank tests. As shown in Table 1, there were 90 patients with PMCs: they had lower rates of extrathyroidal extension and lymph node metastases at presentation. A smaller number of positive lymph nodes per case (1.7 vs. 3.4) were also detected. About 30 % of patients with PMC did not undergo lymph node dissection because of incidental malignancy; that occurred only in 7 % of patients with slightly larger tumors. Also, a lower percentage of PMC patients underwent MND (46 % vs. 81 %). In addition, three histological parameters, namely invasive growth pattern, loss of polarity and loss of cohesiveness, characterized PMCs with much more benign biological properties than the slightly larger tumors ($1.0 < T \leq 2.0$ cm). No difference was identified between these two subgroups in the following characteristics: age, the percentages of patients older or younger than 45 years, gender, multifocality or ratio of patient undergoing total thyroidectomy-to-lobectomy.

Comparison of TNM staging of small PTC according to the 5 th and the 6 th edition

In the recently revised AJCC/UICC TNM classification of thyroid tumors, the cutoff size for primary tumors of T1, limited to the thyroid, has been changed from 1 cm to 2 cm, but on the other hand the massive extrathyroidal extension of the primary tumor (T4a) and lateral cervical lymph node metastasis (N1b) are specified and emphasized as the prognostic factors for poor outcomes. As shown in Table 3, which compares the new edition to the old TNM classification, in the patients older than 45 years, 12 cases previously classified as Stage II were now classified as stage I. The outcome of these 12 patients was excellent without relapse. However, 44 cases that previously would be classified as Stage III were now classified as Stage IVA. Among them, 40 patients were classified as stage IVA solely because of N1b and among them there were two relapses; of the remaining four patients, one was classified as IVA solely because of T4a and the other three patients were both T4a and N1b; among them, there was one relapse. Among patients less than 45 years old, two were

Table 3
Fifth and sixth editions of TNM staging for 124 patients (age ≥45 years)[a] with PTC less than 2 cm in size

6th edition	5th edition				Total
	I	II	III	IV	
I	20	12			32
II					0
III			47		47
IVA			44		44
IVB					0
IVC				1	1
Total	20	12	91	1	124

[a] Patients under 45 years of age ($n = 78$) are not listed because T and N states have no impact on staging and no difference between the new and the previous editions exists. Among 149 patients ≥45 years, 25 patients did not receive lymph node surgery because of incidental carcinomas and their N states could not be properly classified. Therefore, only 124 patients were included in this table.

with T4a and one relapsed. Therefore, there were a total of two relapses in six patients with T4a.

Discussion

In this series excellent outcomes were confirmed for patients with small PTC measuring ≤2.0 cm; none of the 227 patients died of the disease, and the local recurrence rate was only 4 %.

The slightly larger PTC ($1.0 < T \leq 2.0$ cm) shows more aggressive biological behaviors than PMC ($T \leq 1.0$ cm)

Recently, AJCC/UICC revised the TNM classification for thyroid carcinoma and in the new edition the higher cut-off point of 2 cm for T1 is used, which raises a concern about whether 1.0 cm tumor size should still be considered as a threshold for risk evaluation. According to our results, slightly larger tumors could be assimilated with PMC into one larger group in terms of clinical outcomes. However, a closer look shows that the slightly larger tumors ($1.0 < T \leq 2.0$ cm) demonstrated obviously more aggressive biological behaviors than did PMCs at presentation: for instance, more often they extended beyond the thyroidal capsule and invaded the surrounding structures, and they spread more frequently to local lymph nodes. The progressions in malignancy revealed in the slightly larger tumors were also clearly demonstrated by all three histological indexes: loss of cellular polarity, loss of cellular cohesiveness and invasive growth pattern. These histological characteristics were first described by Tang et al. (2003)[13] as being associated with cell growth in PTC and were then applied by Kakudo et al. (2004)[11] in 213 patients with PTCs larger than 1 cm, in whom they were identified as useful parameters for predicting patient outcome in terms of recurrence and cancer-related deaths. In this report we have demonstrated that in small tumors ($T \leq 2$ cm) these cytological features were also useful prognostic factors in predicting disease recurrence.

Hence most patients with slightly larger tumors ($1 < T \leq 2$ cm) underwent more lymph node surgery: 81 % underwent MND versus only 46 % in the PMC group; more patients in the latter group did not undergo the LN surgery because of incidental malignancy, and more underwent only central compartment dissection. It was interesting to note that none of 38 cases of incidental cancer relapsed in this cohort of small PTCs, which supports the notion that incidental cancers have more favorable prognosis as reported also by Barbaro et al.[14] On the contrary, the increase in the tumor sizes did not lead to corresponding aggressiveness in thyroidectomy: almost equal proportions of patients in these two subgroups underwent total/subtotal thyroidectomy. The reason for that was that the same high rate of multifocality (over 30 %) existed among them.

Massive extrathyroidal extension is the only significant prognostic factor for unfavorable outcomes for small PTC

We investigated the potential variables that might be potential predictors of unfavorable outcomes for small PTC. A multivariate analysis suggested that massive extrathyroidal extension to surrounding structures (T4a) at presentation would be the only significant prognostic factor for both local and LN relapses. Recently a retrospective analysis by Ito et al. (2006)[15] on 1067 PTC patients who were treated at the same hospital as those in the present study showed that it was massive extrathyroidal extension rather than minimal ones that affected the relapse-free survival, consistent with our findings. However extrathyroidal extension revealed no adverse influence on prognosis in some series of small PTCs ($T \leq 1.5$ cm)[16] and PMCs ($T \leq 1.0$ cm).[7] Nevertheless, the extrathyroidal extensions in those studies were not stratified into massive and minimal ones for statistical analyses, which probably blurred their impacts on prognosis. In addition, the different therapeutic approaches adopted in each institution might also influence the relative importance of the prognostic factors identified in different studies.

The new TNM classification distinguishes the tumors with minimal extrathyroidal extension (Ex1, T3) from tumors that invade to subcutaneous soft tissue or organs and structures surrounding the thyroid (Ex2, T4a), such as larynx, trachea, esophagus or recurrent nerve, which were all staged as T4 in the previous edition. From our results, T4a seemed to be the single decisive factor for determining unfavorable outcomes because there were two relapses in six patients of T4a. In the present study, we relied on MND to control locoregional lymphatic spread, and postoperative iodine ablation and TSH suppression therapies were only performed in the patients with distant metastases. Hence, we suggest that patients with massive extrathyroidal extension be considered for adjuvant therapy after surgery which would reduce locoregional recurrence;[17] close follow-up would be required. Also the new classification accentuates a more unfavorable prognosis for tumors with cervical or superior mediastinal lymph node involvement (N1b) than for those with pretracheal, paratracheal, and prelaryngeal/Delphian lymph node involvement (N1a). In this cohort of small PTCs, a total of 44 cases were upgraded to Stage IVA in the new version from Stage III in the previous version of the TNM stage system; of those, 40 cases were upgraded solely because of N1b. However our data did not demonstrate any adverse influence of N1b on the long-term prognoses, even by univariate analysis, probably due to the aggressive lymphadenectomy policy adopted in this study and the indolent nature of the small PTCs.

In summary, in this series the small tumors ($T \leq 2$ cm) of PTCs had excellent outcomes. Further dividing the group of small tumors into PMC ($T \leq 1$ cm) and slightly larger

tumor ($1 < T \leq 2$ cm) did not reveal any difference in long-term prognoses. Our data—evaluated by multivariate analysis—showed that massive extrathyroidal extension at presentation was the sole predictor of persisting/relapsing disease for small tumors, which suggested that the new TNM classification seems to perform better than the previous version, due to its renewed emphasis on extrathyroidal invasion, which allows a distinction between a massive extrathyroidal extension and a minimal one. Furthermore the presence of massive extrathyroidal extension in patients necessitates postoperative adjuvant treatment and close follow-up.

Acknowledgements

This work was supported in part by grants from Wakayama Foundation for the Promotion of Medicine to Hui Zuo.

References

1. Rosai J, Zampi G, Carcangiu ML. Papillary carcinoma of the thyroid, a discussion of its several morphologic expressions, with particular emphasis on the follicular variant. *Am J Surg Pathol* 1983;**7**:809–17.
2. Ezaki H, Ebihara S, Fujimoto Y, et al. Analysis of thyroid carcinoma based on material registered in Japan during 1977–1986 with special reference to predominance of papillary type. *Cancer* 1992;**70**:808–14.
3. Hedinger C, Williams ED, Sobin LH. Histological typing of thyroid tumours. *WHO international histological classification of tumours*. 2nd ed. Berlin: Springer; 1988. p. 9–11.
4. Hay ID, Grant CS, van Heerden JA, et al. Papillary thyroid microcacinoma: a study of 535 cases observed in a 50-year period. *Surgery* 1992;**112**:1139–47.
5. Baudin E, Travagli JP, Ropers J, et al. Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;**83**: 553–9.
6. Furlan JC, Bedard Y, Rosen IB. Biological basis for the treatment of microscopic, occult well-differentiated thyroid cancer. *Surgery* 2001; **130**:1050–4.
7. Chow SM, Law S, Chan J, et al. Papillary microcarcinoma of the thyroid-prognostic significance of lymph node metastasis and multifocality. *Cancer* 2003;**98**:31–40.
8. Salvadori B, Del Bo R, Pilotti S, et al. 'Occult' papillary carcinoma of the thyroid: a questionable entity. *Eur J Cancer* 1993;**29A**:1817–20.
9. Noguchi S. Differentiated thyroid carcinomas in Japan: our own experience and review of the literature. *Thyroidol Clin Exp* 1998; **10**:41–51.
10. Renshaw A. Papillary carcinoma of the thyroid $\leq$1.0 cm. Rarely incidental or occult any more. *Cancer* 2005;**105**:217–9.
11. Kakudo K, Tang W, Ito Y, et al. Papillary carcinoma of the thyroid in Japan: subclassification of common type and identification of low risk group. *J Clin Pathol* 2004;**57**:1041–6.
12. Ito Y, Tomoda C, Uruno T, et al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg* 2005;**29**:917–20.
13. 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.
14. Barbaro D, Simi U, Meucci G, et al. Thyroid papillary cancers: microcarcinoma and carcinoma, incidental cancers and non-incidental cancers – are they different diseases? *Clin Endocrinol (Oxf)* 2005;**63**: 577–81.
15. Ito Y, Tomoda C, Uruno T, Takamura Y, et al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World J Surg* 2006;**30**:780–6.
16. Pellegriti G, Scollo C, Lumera G, et al. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. *J Clin Endocrinol Metab* 2004;**89**:3713–20.
17. Shaha AR. Prognostic factors in papillary thyroid carcinoma and implication of large nodal metastasis. *Surgery* 2004;**135**:237–9.