Surg Today (2010) 40:199–215
DOI 10.1007/s00595-009-4034-5

SURGERY TODAY

Management of Low-Risk Papillary Thyroid Carcinoma: Unique Conventional Policy in Japan and Our Efforts to Improve the Level of Evidence

IWAO SUGITANI and YOSHIHIDE FUJIMOTO

Division of Head and Neck, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

Abstract
Papillary thyroid carcinoma (PTC) accounts for over 90% of all thyroid cancers in Japan. The majority of patients with PTC are categorized into a low-risk group according to the recent risk-group classification schemes, and they have excellent outcomes. Several management guidelines for thyroid cancers have been published in Western countries. However, the optimal therapeutic options for PTC remain controversial and high-level clinical evidence to resolve the issues is lacking. Moreover, socioeconomic differences in medical care exist; therefore, conventional policies for the treatment of PTC have been different between Japan and other countries. This report reviews the controversy in the treatment of PTC regarding the initial surgery, postoperative adjuvant therapies, and methods of surveillance. This review focuses on the unique policy in Japan preferring to treat patients with low-risk PTC by a less-than-total thyroidectomy without adjuvant therapies rather than a total thyroidectomy with radioactive iodine, in an attempt to maintain patients' quality of life. In addition, the institutional efforts to improve the level of evidence for the management of PTC are introduced, such as a randomized controlled trial for the effect of thyrotropin suppression therapy, a prospective study for selective lymph node dissection based on preoperative ultrasonography, and a prospective non-surgical observation trial for asymptomatic papillary microcarcinoma.

Key words Papillary thyroid carcinoma · Risk-group classification · Management guidelines · Controversy · Evidence level

Reprint requests to: I. Sugitani
Received: March 22, 2009 / Accepted: May 14, 2009

Introduction

Both the incidence and distribution of each histological type of thyroid carcinomas are greatly affected by iodine intake. In iodine-sufficient countries like Japan, the incidence of papillary thyroid carcinoma (PTC), with a rather favorable prognosis, is much higher than that of follicular or anaplastic (undifferentiated) carcinomas. Indeed, PTC accounts for 91.7% of all thyroid cancers according to the Japanese Society of Thyroid Surgery (JSTS) registry in 2002. In the United States, the addition of iodine to dietary salts was started in the 1920s. Using the Surveillance, Epidemiology, and End Results program and data on thyroid cancer mortality from the National Vital Statistics System, Davies and Gilbert Welch[1] reported that the incidence of thyroid cancer increased from 3.6 per 100 000 in 1973 to 8.7 per 100 000 in 2002, thus representing a 2.4-fold increase. No significant changes were seen in the incidences of the less common histological types, such as follicular, medullary, and anaplastic carcinoma. Virtually the entire increase is attributable to an increase in the incidence of PTC, which increased from 2.7 to 7.7 per 100 000; a 2.9-fold increase. Other than iodine sufficiency, these changes could partially be explained by a change in the pathological criteria for thyroid cancer. The World Health Organization (WHO) histological criteria for diagnosis of PTC were revised in 1988, and tumors showing a follicular structure with characteristics of PTC nuclei came to be diagnosed as follicular variant of PTC, not follicular carcinoma. Moreover, Davies et al. emphasized that the increasing incidence of thyroid cancer is predominantly due to the increased detection of small PTCs. This increased diagnostic scrutiny has been accomplished owing to advances in imaging and diagnostic techniques, such as ultrasonography (US) and fine-needle aspiration (FNA). Combined with the known existence of a substantial reservoir of subclinical cancers, they suggested that the increasing incidence of

thyroid cancer reflects increased detection of subclinical disease, rather than an increase in the true occurrence. Indeed, the mortality from thyroid cancer was stable between 1973 and 2002.

Several management guidelines for thyroid nodules and cancers have been recently published in Western countries. The Japan Association of Endocrine Surgeons (JAES) has now cooperated with the JSTS to establish Japanese guidelines for the management of thyroid tumors. Guidelines are essential documents in modern medicine that are systematically created to support decision-making by physicians and patients under specific clinical conditions. These documents are in accordance with evidence-based medicine and are supposed to enhance good communication between physicians and patients. However, controversy remains regarding the therapeutic options for PTC (Table 1) and we have so far barely achieved either level I or II clinical evidence according to the classification of evidence levels described by Sackett[2,3] (Table 2) based on prospective randomized controlled trials (RCTs). Approximately 10000 patients are newly diagnosed with PTC each year in Japan, and over 30000 a year are estimated to occur in the United States. The majority of these cases involve low-risk cancer with excellent survival rates exceeding 99% at 10 years after surgery. Conducting RCTs to resolve the clinical controversies associated with PTC is difficult due to the prolonged course and relative infrequency of this tumor. According to an analysis by Udelsman et al.,[4] both a very large sample size and a very long follow-up are required to determine the optimal treatment for PTC using an RCT design (Table 3). Since most information comes from studies of large patient cohorts in which therapy has not been randomly assigned, the level of evidence is generally not high and disagreements about the management of PTC continue. Moreover, social and economic differences in medical care exist between Japan and other countries (Table 4). As a result, conventional policies for the treatment of PTC have been different with regard to the initial surgery, postoperative adjuvant therapies, and methods of surveillance. The application of Western

Table 1. Controversies in therapeutic options for papillary thyroid carcinoma

Issue	Controversy
Extent of thyroidectomy	Total or near-total thyroidectomy vs thyroid-conserving surgery
Extent of lymph node dissection	Prophylactic dissection vs selective or therapeutic dissection
Postoperative adjuvant therapy	Radioactive iodine remnant ablation and life-long thyrotropin suppression therapy vs conservative follow-up
Postoperative surveillance	Stimulated thyroglobulin measurement and radioactive iodine whole body scan vs ultrasonography
Management of papillary microcarcinoma	Surgery vs observation

Table 2. Sackett's classification for level of evidence[2] modified by Heinirich[3]

Level of evidence	Type of trial	Criteria for classification
I	Large randomized trial with clear-cut results (low risk of errors)	Sample size calculation provided and fulfilled; study endpoint provided
II	Small randomized trial with uncertain results (moderate to high risk of errors)	Matched analysis; sample size calculation not given or not fulfilled; study endpoints not provided; convincing comparative studies
III	Nonrandomized; contemporaneous controls	Noncomparative; prospective
IV	Nonrandomized; historical controls	Retrospective analysis; cohort studies
V	No control; case series only; opinion of experts	Small series; review articles

Table 3. Sample size and length of follow-up required to determine optimal surgery (total thyroidectomy vs less-than-total thyroidectomy) for papillary thyroid carcinoma by randomized controlled trial: Udelsman's analysis[4]

Endpoint	Required sample size (cases)	Required length of follow-up (years)
Surgical complications	12000	—
Cancer-specific survival	3100	>20
Disease-free survival	360–800	6–10

Table 4. Differences in socio-medical environments between Western countries and Japan

Western countries	Japan
1. Many countries are in iodine-deficient areas	1. World-prominent iodine-sufficient country
2. Highly malignant thyroid cancers are prevalent	2. Low-risk thyroid cancers are prevalent
3. Prestigious endocrine surgeons are in charge of thyroid surgery	3. Thyroid surgeries are mostly performed by (young) general surgeons
4. Postoperative surveillance is performed by internists or radiologists	4. Postoperative surveillance is conducted by surgeons themselves
5. Postoperative recurrences are sometimes apt to result in a lawsuit	5. Strict legal restrictions and shortage of infrastructure for use of radioactive iodine
6. Ultrasonography is an exclusive and expensive procedure	6. Nationwide use of ultrasonography

guidelines to Japan is therefore considered less than optimal.

Several recent reports using multicenter databases have been published, which have emphasized the strength of very large numbers of samples. However, from the perspective of data accuracy, single-institution studies have the benefit of consistency and details in therapeutic policy and follow-up methods. This article reviews the present controversy in the treatment of PTC, particularly for low-risk patients, and describes the institutional efforts to improve the level of evidence for the management of PTC. The current mission is to: (1) retrospectively analyze the previous data; (2) set up appropriate policies based on these analyses; and (3) prospectively accumulate data according to these new policies. This will provide a higher level evidence from level IV to level III.

Risk Group Classification System for Cancer-Specific Death in PTC Patients

Patients with PTC display very favorable survival rates as high as 95% at 10 years after the initial therapy. However, some cases exhibit local recurrence or extensive metastasis postoperatively, and a few patients die of the disease. According to recent large retrospective uncontrolled studies with respect to cancer-specific mortality after surgery for PTC, most authors agree on the existence of two distinctly different groups of patients: a low-risk group for which the mortality is almost identical to that predicted by actuarial curves; and a high-risk group with a high probability of cancer-specific death. The identification of low- and high-risk PTC is based on the concept that these two groups of cancer belong to biologically different categories from the time of generation, with cancers in the low-risk group generally not developing into high-risk cancers throughout the life of the patient. Various systems from several institutions have been proposed to differentiate between these two groups, including the AMES (Age, Metastasis, Extension, Size) system from the Lahey Clinic,[5] and the AGES (Age, Grade, Extension, Size)[6] and MACIS (Metastasis, Age, Completeness of resection, Invasion, Size) systems[7] from the Mayo Clinic (Table 5). All of the currently accepted systems of risk group definition classify the great majority of patients (nearly 90%) as low-risk, with a 1%–2% mortality rate. The minority of residual patients belonging to the high-risk group show a poor prognosis, with a 50%–75% mortality rate at 10 years after surgery. It would therefore appear that accurate prediction of survival and future recurrence risk for patients with PTC could be individually determined at the time of initial treatment. The use of proper risk group definitions is useful not only for tailoring selective surgical interventions and postoperative adjunctive therapies on the basis of the individual patient, but also to offer rational information to the patient and to determine the intensity of surveillance for tumor recurrence.

The most popular prognostic factors common to the various risk groups are local cancer invasion, distant metastasis, and patient age. Of note is the fact that, among the above-mentioned major classification systems, only the "completeness of resection" in the MACIS system is subject to intervention. The original biological factors are more contributive to prognosis for patients with PTC than the methods of artificial intervention. However, controversy remains regarding the relative importance of these and other prognostic factors[5–15] (Table 6). Several studies have investigated the predictive value of each classification system, and the results have generally not been satisfactory.[16,17] Inconsistencies may result from the bias of unique characteristics in patient populations, heterogeneous distribution of histological types affected by iodine intake, and differences in the therapeutic philosophy of each institution. The most accurate classification system for the individual institution might therefore be acquired using the original data from each institution.

A total of 604 patients who had undergone initial surgery for PTC (tumor diameter, >1 cm) between 1976

Table 5. Representative risk-group classification systems for differentiated thyroid carcinoma

Classification systems	Definitions	Outcomes
AMES[5] (age, metastasis, extension, size)	High-risk group: Distant metastasis Older age (male, >40 years; female, >50 years) with extrathyroidal extension and/or tumor size ≥5 cm Low-risk group: Other than the above	High-risk group: n = 33 (11%) Cause-specific mortality 46% Low-risk group: n = 277 (89%) Cause-specific mortality 1.8%
AGES[6] (age, grade, extension, size)	Score = 0.05 × age (in case of ≥40 years) +1 (in case of Grade 2) +3 (in case of Grade 3 or 4) +1 (in case of extrathyroidal extension) +3 (in case of distant metastasis) +0.2 × tumor size (cm)	High-risk group (score ≥4): n = 121 (14%) Cause-specific mortality 46% Low-risk group (score <4): n = 737 (86%) Cause-specific mortality 2%
MACIS[7] (metastasis, age, completeness of resection, invasion, size)	Score = 3.1 (in case of <40 years) or 0.08 × age (≥40 years) +0.3 × tumor size (cm) +1 (in case of incomplete resection) +1 (in case of invasion) +3 (in case of distant metastasis)	20-year survival <6.0 (n = 1492): 99% 6.0–6.9 (n = 148): 89% 7.0–7.9 (n = 59): 56% 8.0– (n = 80): 24%

and 1998 at the Cancer Institute Hospital (CIH) were retrospectively analyzed.[15] The mean duration of follow-up was 10.7 years (range, 2–25 years). A multivariate analysis for cause-specific survival (CSS) identified distant metastasis as the only significant risk factor (risk ratio = 65.1; P = 0.002) for younger patients (age, <50 years). Distant metastasis (risk ratio = 6.7, P = 0.0001), extrathyroidal invasion (risk ratio = 2.4, P = 0.03), and large nodal metastasis (≥3 cm; risk ratio = 5.3, P = 0.0009) showed relative importance for older patients (age ≥50). These results indicate that younger patients with distant metastasis and older patients with any of the three factors are defined as high-risk, while all other patients are defined as low-risk. Overall, 106 high-risk patients (17.5%) and 498 low-risk patients (82.5%) displayed 10-year CSS rates of 68.9% and 99.3%, respectively (Table 7 and Fig. 1).

Like all other sophisticated risk group definitions, this classification system has limitations, and three low-risk group patients died of the disease. These three exceptional cases should not be interpreted as the rate of malignant transformation from low-risk to high-risk cancer, but rather represent the rate of error at the initial diagnosis. Some investigators have recently recommended the TNM (tumor, nodal metastasis, distant metastasis) classification, due to the advantages of universal availability and wide acceptance for other cancer staging.[16,18] However, TNM staging is based on the concept that carcinomas usually progress from early stage to advanced stage in a time-dependent manner. This is conceptually different from a risk group definition discriminating low-risk cancer from high-risk cancer as two distinctly different disease categories. Investigations have recently been initiated to differentiate high-risk PTC from low-risk PTC using genetic markers such as BRAF mutations.[19,20] The development of new and more precise markers to distinguish the cancer-specific mortality risk is therefore eagerly anticipated.

Controversies in the Management of Low-Risk PTC and Japanese Trends

Extent of the Thyroidectomy

Considerable controversy surrounds the extent of surgery and the use of postoperative adjuvant therapies for PTC. Western guidelines usually recommend a near-total or total thyroidectomy for PTC ≥1.0–1.5 cm in diameter[13,21–23] (Table 8). Although they allow the possibility of less extensive surgeries such as a unilateral lobectomy for patients with isolated, small, intrathyroidal, node-negative tumors; the consensus guidelines suggest that tumors displaying high-risk features profit by more aggressive treatment such as a total or near-total thyroidectomy followed by radioactive iodine (RAI) ablation and life-long thyrotropin (TSH) suppression therapy. The rationale for total thyroidectomy is: (1) bilateral cancers are very common for PTC (30%–85%) and contralateral lobe recurrences are not

Table 6. Significant risk factors in respective analyses for thyroid cancer prognosis

	EORTC[8]	AMES[5]	AGES[6]	MACIS[7]	OSU[9]	MSK[10]	NTCTCS[11]	TNM[12]	NCCN[13]	Noguchi[14]	CIH[15]
Histology	All	WDTC	PTC	PTC	WDTC	WDTC	All	All	PTC	PTC	PTC
Age		S	S	S		S	S	S	S	S	S
Sex	S	S								S	
Radiation history									S		
Family history of PTC									S		
Tumor size		S	S	S	S	S	S	S	S	S	
Multiple lesions (bilaterality)					S		S		S		
Pathological differentiation			S								
Extrathyroidal extension	S	S	S	S	S	S	S		S		S
Lymph node metastasis					S		S	S	S	S	S
Distant metastasis	S	S	S	S	S	S	S	S	S		S
Completeness of resection				S							

S, significant risk factor in the analysis (the boundary of continuous variables etc. depends on each study); WDTC, well-differentiated thyroid carcinoma, including papillary and follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; EORTC, European Organization for Research and Treatment of Cancer; AMES, Age, Metastases, Extent, and Size (Lahey Clinic); AGES, Age, Grade, Extent, and Size (Mayo Clinic); MACIS, Metastases, Age, Completeness of resection, Invasion, and Size (Mayo Clinic); OSU, Ohio State University; MSK, Memorial Sloan-Kettering Cancer Center; NTCTCS, National Thyroid Cancer Treatment Cooperative Study; TNM, Tumor, Node, and Metastasis (UICC: International Union against Cancer, AJCC: American Joint Committee on Cancer); NCCN, National Comprehensive Cancer Network; CIH, Cancer Institute Hospital, Tokyo, Japan

Fig. 1. Cause-specific survival curves of low- and high-risk patients based on Cancer Institute Hospital risk-group definition for papillary thyroid carcinoma

unusual (5%–24%); (2) RAI ablation of the remaining thyroid tissue is easily performed and facilitates ^{131}I efficacy in both the diagnosis and treatment of postoperative recurrences; (3) serum thyroglobulin (Tg) measurement becomes a useful postoperative marker; and (4) the likelihood of reoperative neck surgery with increased risk of complications is minimized.

Conversely, endocrine surgeons in Japan prefer a less-than-total thyroidectomy (lobectomy or subtotal thyroidectomy) for the majority of patients with PTC.[24] The extent of the thyroidectomy has been determined using preoperative US and patients have been followed without postoperative adjuvant therapies. Some foreign thyroid cancer specialists agree with this policy.[25,26] The arguments supporting this procedure are based on the facts that: (1) a total thyroidectomy will not affect survival for most patients categorized as low-risk by risk-group classification schemes; (2) small lesions in the contralateral lobe can be diagnosed by preoperative US and overlooked occult multicentricity is not clinically significant; (3) recurrences rarely occur in the thyroid bed and most neck recurrences can be cured by a reoperation; and (4) a total thyroidectomy will lead to an increased frequency of surgical complications, including recurrent nerve palsy and hypoparathyroidism. The average rates of long-term recurrent laryngeal nerve injury and hypocalcaemia are 3.0% and 2.6% after a total thyroidectomy, and 1.9% and 0.2% after a subtotal thyroidectomy.[4] These complication rates are low in experienced hands. However, when it comes to the standardization of the general policy for the management of PTC, one important consideration is that a substantial number of surgeons would perform thyroid surgery at the hospital without a higher level of oncologic specialization. Furthermore, patients undergoing more than a subtotal thyroidectomy are subject to a "lifelong imprisonment" of thyroid hormone supplementation,

Table 7. Treatment outcomes of low- and high-risk patients based on CIH risk-group definition for papillary thyroid carcinoma

Risk group	No. of patients	Cause-specific mortality	10-year cause-specific survival	Recurrences	10-year disease-free survival
Low-risk group	498 (82.5%)	3 (0.6%)	99.3%	41/498 (8.2%)	90.7%
High-risk group	106 (17.5%)	29 (27.4%)	68.9%	29/74[a] (39.2%)	63.7%

Cancer Institute Hospital (CIH) risk-group definitions:
High-risk group: patients with distant metastasis; older patients (≥50 years) with extrathyroidal invasion and/or large nodal metastasis (≥3 cm)
Low-risk group: Other than the above
[a] Patients with distant metastasis at presentation were excluded

Table 8. Extent of thyroidectomy and lymph node dissection for patients with papillary thyroid carcinoma: Recommendation according to the major Western guidelines

	AACE/AAES[21] (2001)	BTA[22] (2007)	ATA[23] (2006)	NCCN[13] (2008)
Extent of thyroidectomy				
Total or near-total thyroidectomy	High-risk cancer Ex (+) N (+) M (+) Bilateral nodularity Bilateral cancer	T >1 cm Ex (+) N (+) Multiple lesions Radiation history Family history	Age ≥45 T >1–1.5 cm N (+) M (+) Bilateral nodularity Radiation history Family history	Age <15 or >45 T >4 cm Ex (+) N (+) M (+) Bilateral nodularity Radiation history Aggressive variant
Lobectomy (+isthmusectomy)	T ≤1 cm Ex0 N0 M0	T ≤1 cm N0	Other than the above	Other than the above
Lymph node dissection				
Central compartment dissection	N (+)	T >1 cm	Always	N (+)
Lateral compartment dissection	N (+)	N (+)	N (+)	N (+)

T, tumor size; N, lymph node metastasis; M, distant metastasis; Ex, extrathyroidal extension
AACE/AAES, American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons; BTA, British Thyroid Association; ATA, American Thyroid Association; NCCN, National Comprehensive Cancer Network

and ceasing medication may lead to grave complications such as heart failure.

The guidelines advocating a total thyroidectomy for PTC are usually not based on data demonstrating any difference in survival, but rather on the possibility of recurrence and practicalities of treatment and follow-up. In 1981, Mazzaferri and Young[27] retrospectively reported the results of 576 patients with PTC who underwent surgery in multiple institutions. The median duration of follow-up was 10 years 3 months. A recurrence rate of 19.2% was demonstrated for less-than-total thyroidectomies, significantly higher than the rate for total thyroidectomies (10.9%). The death rate associated with thyroid cancer after a less-than-total thyroidectomy (1.5%) was not significantly different, but still tended to be higher than that for a total thyroidectomy (0.6%). Hay et al.[6] reported in 1987 that patients treated at the Mayo Clinic for low-risk PTC (MACIS score <4.00) also showed no improvement in survival rates after undergoing procedures more extensive than an ipsilateral lobectomy. In 1998, however, that center reported the results of a study designed to compare cancer-specific mortality and recurrence rates after a unilateral or bilateral lobectomy.[28] The study involved patients with PTC considered as low-risk by the AMES criteria. The investigators found no significant differences in the cancer-specific mortality or distant metastasis rates between the two groups, but the 20-year frequencies of local recurrence and nodal metastasis after a unilateral lobectomy were 14% and 19%, respectively, which were both significantly higher than the frequencies of 2% and 6% seen after a bilateral thyroid lobe resection. On the other hand, a report from the Memorial Sloan-Kettering Cancer Center showed the results of a matched-pair analysis in 1993 and indicated no difference in the CSS at 20 years and no significant differences in local recurrence, regional recurrence, or distant metastasis between patients who

underwent a lobectomy and those who received a total thyroidectomy.[29]

Conversely, Bilimoria et al.[30] recently demonstrated that a total thyroidectomy for PTC ≥1 cm in diameter results in lower recurrence rates and even improved survival in comparison to a lobectomy, using the National Cancer Data Base. Of the 52173 patients with PTC in the United States from 1985 to 1998, 43277 (82.9%) underwent a total thyroidectomy and 8946 (17.1%) received lobectomy. For PTC <1 cm, the extent of surgery did not impact recurrence or survival (P = 0.24, P = 0.83, respectively); however, a lobectomy resulted in a higher risk of recurrence and death (P = 0.04, P = 0.009, respectively) for tumors ≥1 cm. The data did not include important information about the pathological review, extrathyroidal extension, completeness of resection, TSH suppression therapy, RAI use, or cause of death. Moreover, a potential selection bias and uncertainty of data may exist because the data included input from over 20 years and from over 1400 hospitals. However, this study has a significant impact due to the unprecedented sample size.

At the CIH, the basic standard of primary surgery for patients with PTC has been a macroscopically complete resection of the tumor. All patients are routinely examined by preoperative US to estimate intrathyroidal spread of PTC. A lobectomy (+an isthmusectomy) of the affected side with nodal dissection of the central zone is performed when a tumor is limited to one lobe with no clinically evident lymph node metastasis. A total thyroidectomy is performed when a tumor extends to the upper part of the contralateral lobe, when nodal metastases are evident at the bilateral neck, and/or when distant metastasis is identified. Patients with clinically involved lateral cervical lymph nodes undergo a modified radical lateral neck dissection. A resection of the adjacent structures, including the trachea and/or esophagus, is administered when cancer invasion is apparent. Postoperative RAI therapy is not routinely conducted, except for patients with advanced PTC. The retrospective data from 1976 to 1998 described above shows that the recurrence rates for low-risk PTC patients after a less-than-total thyroidectomy are 1.6% in the contralateral lobe, 6.9% in the cervical lymph nodes, and 1.3% at distant sites, respectively.[15] These rates are not significantly different from patients who undergo a total thyroidectomy (Table 9).

Postoperative RAI Therapy and Surveillance of Recurrence

Radioactive iodine remnant ablation eliminates residual thyroid tissue after a total or near-total thyroidectomy. This therapy is expected to (1) decrease recurrences and cause-specific mortality, and (2) simplify follow-up methods using ^{131}I whole-body scan (WBS) and serum Tg measurement. However, no prospective studies have been performed to address the former effect. A recent systematic review and meta-analysis by Sawka et al.[31] could not demonstrate consistent results for the effect of RAI ablation in decreasing recurrence of well-differentiated thyroid cancer, particularly in the early stage. Radioactive iodine remnant ablation is associated with a significantly decreased risk of distant metastasis, but this event is relatively rare in PTC. The selective use of RAI ablation has been suggested in several clinical practice guidelines. Specifically, the use of adjuvant RAI is particularly advocated for patients considered at high-risk of mortality, and RAI remnant ablation should not be considered mandatory in patients with low-risk thyroid cancer. In Japan, the use of RAI is strictly restricted by legal regulations. Due to additional socioeconomic reasons, few institutions are able to use high-dose RAI in Japan (only 64 institutions with 158 inpatient beds as of 2007). Applying RAI therapy to all patients with PTC is impossible in Japan and selective RAI use only for high-risk patients is reasonable. Accumulating new evidence about RAI therapy in this country is therefore a difficult task.

Neck US or other imaging tools are used to detect recurrent or persistent disease for patients who have undergone a less-than-total thyroidectomy. In contrast, serum Tg measurement and WBS are useful for specifying residual disease in patients who have undergone a total thyroidectomy followed by RAI remnant ablation. These tests are more sensitive when thyroxine supplementation is stopped and TSH levels are elevated.

Table 9. Comparison of outcomes between total thyroidectomy and less-than-total thyroidectomy for patients with low-risk papillary thyroid carcinoma (Cancer Institute Hospital, Tokyo, Japan)

Extent of thyroidectomy	No. of patients	Cause-specific death	10-year cause-specific survival	Recurrences	10-year disease-free survival	Recurrence in remnant thyroid	Recurrence at cervical lymph nodes	Recurrence at distant site
Less than total	451 (90.6%)	3 (0.7%)	99.2%	36 (8.0%)	95.7%	7 (1.6%)	31 (6.9%)	6 (1.3%)
Total or near-total	47 (9.4%)	0	100%	5 (10.6%)	89.2%	0	5 (10.6%)	0

However, thyroxine withdrawal affects the patient's quality of life (QOL) due to transient hypothyroidism. Recombinant human TSH (rhTSH) has recently been introduced as an alternative to thyroxine withdrawal for stimulated Tg measurement, WBS, and RAI ablation preparation. The use of rhTSH has been approved in Japan since 2009, but this approval still excludes the use for RAI remnant ablation.

The results of serum Tg measurement and WBS are sometimes inconsistent, and serum Tg is thought to offer a lower false-negative rate than WBS. Kloos and Mazzaferri[32] reported that 50% of patients with positive Tg are likely to have residual disease that can be localized immediately, and an additional 30% within the next 3–5 years. Conversely, about 2% of patients with completely undetectable Tg after stimulation show recurrence over the next 3–5 years. Another report showed that a persistent tumor could be identified on imaging studies in only one-third of a stimulated Tg-positive group.[33] Furthermore, serum Tg measurements are less sensitive in patients with small cervical metastases or a less differentiated tumor. Some guidelines have stated that serum Tg should be measured every 6–12 months, but the long-term clinical significance remains uncertain for disease only detected by minimally elevated Tg levels after stimulation. No guidelines have mentioned the optimal management for patients with persistently detectable stimulated serum Tg and how long Tg measurement should be continued to detect late recurrences. Localizing imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) are recommended for positive Tg in negative WBS patients. If imaging yields negative results, then empiric therapy with high-dose RAI might be considered to aid localization or for therapy. This approach may identify the location of persistent disease in approximately 50% of patients with a wide range of reported successes, but no study has yet demonstrated any decrease in morbidity or mortality in patients with empiric high-dose ^{131}I in this setting.[34]

Postoperative TSH Suppression Therapy

Well-differentiated thyroid carcinoma expresses the TSH receptor on the cell membrane, and responds to TSH stimulation by increasing the expression of several thyroid-specific proteins, including Tg, and by increasing the rates of cell growth. Suppression of TSH using supraphysiological doses of levothyroxine (LT4) is used in an effort to decrease the risk of thyroid cancer recurrence after surgery. In 1977, Mazzaferri et al.[35] collected multi-institutional retrospective data, and reported that the 5-year accumulated recurrence rates after initial surgery for PTC are significantly lower for patients with TSH suppression therapy in comparison to patients with no adjuvant therapy (approximately 10% vs 20%, respectively). Long-term thyroid hormone therapy aimed at suppressing serum TSH has traditionally been used in the management of well-differentiated thyroid carcinoma. However, formal validation of the effects of TSH suppression therapy through studies guaranteeing a high level of evidence is lacking. In Western countries, the optimal TSH level to be achieved in patients who have undergone a total thyroidectomy for PTC is a matter of debate. Excessive TSH suppression carries a risk of thyrotoxicosis, heart failure, and osteoporosis. Pujol et al.[36] found that constant suppression of TSH to <0.05 μU/ml is associated with a longer relapse-free survival in comparison to serum TSH levels always ≥1 μU/ml, and the degree of TSH suppression is an independent predictor of recurrence in a multivariate analysis. On the other hand, Cooper et al.[37] conducted a multicenter, prospective study using the database of the National Thyroid Cancer Cooperative Registry in 1998, analyzing 617 patients with PTC followed for a median of 4.5 years. They noted the TSH score category as an independent predictor of disease progression in high-risk patients, but the data did not support the concept that a greater degree of TSH suppression is required to prevent disease progression in low-risk patients. Jonklaas et al.[38] also reported that superior outcomes are associated with aggressive TSH suppression in high-risk patients, but are achieved with only modest suppression in stage II patients. They were unable to show any impact, positive or negative, of specific therapies in stage I patients. According to the major guidelines from Western countries, the appropriate dose of thyroid hormone for low-risk patients is the dose that decreases serum TSH concentrations to just below the lower limit of the normal range. A greater degree of TSH suppression is thus generally recommended for high-risk patients.

Lymph Node Dissection

Although PTC is associated with cervical lymph node metastasis in 30%–80% of patients, the prognostic significance of lymph node metastasis remains controversial and the optimal extent of lymph node dissection is still a matter of debate. Indeed, many endocrine surgeons have long believed that lymph node metastasis implies a higher risk of local recurrence, but has no significant influence on survival in patients with PTC. Cady[39] and others[7,40] have demonstrated that lymph node metastasis has no adverse effect on recurrence and survival. However, Mazzaferri and Jhiang[9] and others[41] have claimed that lymph node metastasis shows a significant effect on distant metastasis and survival, particularly among elderly patients. From a Japanese

institution, Ito et al.[42] reported that US-detectable lateral node metastasis significantly affects disease-free survival (DFS) in patients with PTC. As described above, large lymph node metastasis (≥3 cm) is one of the most important risk factors for CSS in elderly patients, while the number of pathological lymph node metastases affects nodal recurrence rate in younger patients.[15]

The two representative compartments to which PTC can metastasize are the central and lateral compartments. The more extensive and radical the lymph node dissection performed; the larger the number of pathological lymph node metastases that can be found. Such procedures may be able to reduce nodal recurrence rates, but the benefit to the patient is questionable. There is a slight discordance even in the indications for a central compartment node dissection in the major guidelines used in the United States for the treatment of PTC (Table 8). For example, the guidelines of the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AACE/AAES) note that nodal metastatic lesions increase the risk of subsequent nodal recurrences but have little effect on survival.[21] These guidelines and the National Comprehensive Cancer Network (NCCN) guidelines[13] recommend central compartment node dissection only if clinically positive lymph nodes are identified in this area. Conversely, the American Thyroid Association (ATA) guidelines state that as most regional metastases do not appear abnormal on inspection, central compartment node dissection may improve survival and reduce the risk of nodal recurrence.[23] Since this procedure can be achieved with low morbidity in experienced hands, they recommend the routine central node dissection for all patients with PTC. Our institution has been performing routine central compartment node dissections similar to most Japanese endocrine surgeons, because the procedure can be performed via the same incision as a thyroidectomy, and reoperation of this compartment increases the risk of complications.

Wound extension and a wide range of tissue peeling leading to postoperative discomfort in the neck and shoulder are unavoidable in the dissection of the lateral neck compartment. Routine prophylactic modified radical lateral neck dissection for patients without preoperatively positive nodes in the lateral compartment is thus not usually performed in Europe and the United States. Most Western guidelines agree on performing therapeutic dissection only when metastatic cervical lymphadenopathy is evident. However, some reports have referred to the usefulness of prophylactic lymph node dissection under specific conditions.[43] In Japan, several institutions have been performing prophylactic modified radical lateral neck dissection for all patients with PTC due to the high prevalence of pathological lymph node metastasis. As described above, Japanese endocrine surgeons have traditionally selected thyroid-conserving surgery as the initial treatment for PTC and tend to prefer performing extensive neck dissection. The argument supporting prophylactic lymph node dissection is that locoregional recurrence and even distant metastasis can be prevented. Most lymph nodal recurrences can be cured by a reoperation, and the final outcomes for patient are unaffected. Cady[44] emphasized that lymph node metastases represent indicators, not governors, of survival outcome in every major study of epithelial cancer in humans. However, "recurrence" may increase the psychological and financial burdens on the patient.

Efforts to Improve the Level of Evidence for Management of PTC

Dual Policy for the Extent of Thyroidectomy and Informed Decisions by Patients

"Medical professionalism in the new millennium: a physicians' charter," published in *The Lancet* in 2002, declared that patient autonomy is one of the three fundamental principles for definitive professional responsibilities.[45] This charter says that "Physicians must have respect for patients' autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care." Many controversial issues remain regarding the treatment options for low-risk PTC, and high-level evidence is lacking. A conventional style of "informed consent" where doctors present a single policy and obtain agreement from patients does not seem appropriate. NCCN guidelines also claim that decisions surrounding the extent of thyroidectomy should be individualized and undertaken in consultation with the patient.[13] Since 2005 the CIH has explained the two policies for treatment to patients with low-risk PTC, namely: (1) a total thyroidectomy followed by RAI remnant ablation and TSH suppression therapy; and (2) a conservative thyroidectomy without any adjuvant therapies. The patients are then required to make an "informed decision" about which policy they choose. The explanation format includes: (1) the risk group definition for PTC and retrospective outcomes; (2) the pros and cons of the two policies and expected outcomes; and (3) the postoperative adjuvant therapies and methods of surveillance. As of 2007, there were 167 patients diagnosed with low-risk PTC, excluding 41 patients for whom a total thyroidectomy was considered to be unavoidable. Among these

167 patients, seven (4%) elected to receive a total thyroidectomy with adjuvant therapy and 140 (84%) chose conservative surgery. The remaining 20 patients (12%) could not decide by themselves and left the matter up to the doctor.

On the other hand, a total thyroidectomy has not always been selected even for patients with high-risk PTC as of late, as long as the patient does not have clinically evident distant metastasis. Instead, aggressive radical surgery was conducted including the resection and reconstruction of the invaded adjacent organs, and extended lymph node dissection to the mediastinum and/or retropharyngeal space. As a result, locally curative surgery was conducted for all but one patient between 1976 and 1998, and the 10-year CSS for high-risk PTC was almost identical to those in Western reports.[15] However, since 2005 a total thyroidectomy and RAI ablation has been recommended in addition to locally aggressive surgery for every patient with high-risk PTC. Accumulation of these prospective outcomes and comparison with historical controls are an area of high priority.

RCT for the Effects of TSH Suppression Therapy

A meta-analysis studying the effect of TSH suppression therapy was performed by McGriff et al.[46] in 2002. Although a total of 28 clinical trials published between 1934 and 2001 were identified, only 10 (36%) were amenable to the meta-analysis. Out of 4174 patients with well-differentiated thyroid carcinoma (WDTC), 2880 (69%) were reported as being on TSH suppression therapy, and patients who received TSH suppression therapy had a decreased risk of major adverse clinical events (risk ratio = 0.73, 95% confidence interval = 0.60–0.88, $P < 0.05$). However, the authors concluded that future research will better define the effects of TSH suppression on clinical outcomes for well-differentiated thyroid carcinoma, because most primary studies were imperfect.

In January 1996, a single-center, open-label, prospective RCT on the effectiveness of TSH suppression therapy was initiated. The ethics committee of the CIH approved the study. The primary endpoint was clinical recurrence. The trial was designed as a noninferiority study to demonstrate that the DFS for patients without TSH suppression therapy was not worse than that for patients with the therapy. The 5-year DFS for patients with TSH suppression was assumed to be 90% and the inferiority margin was set as 10%. The planned sample size of 204 patients for each group provided 80% power to declare inferiority. Patients who had been diagnosed with PTC by FNA and had provided written informed consent were randomly assigned to undergo postoperative TSH suppression therapy or not, using a permuted blocked design. Patients were stratified according to the AMES risk-group classification before assignment. Patients with microcarcinoma, age ≥80 years, distant metastasis, Basedow's disease, heart failure, or severe osteoporosis were excluded. Patients who showed a final pathological diagnosis other than PTC (benign nodule or poorly differentiated carcinoma) were also excluded after assignment. For patients assigned to Group A, LT4 was administered from postoperative day 1, controlling serum TSH levels to <0.01 μU/ml according to a third-generation TSH assay. In contrast, the TSH level was adjusted within the normal range (0.4–5.0 μU/ml) for patients assigned to Group B. Patients were evaluated for hormonal balance and tumor recurrence every 6 months by blood testing, physical examination, neck US, chest radiography, or lung CT. Confirmation of recurrence required a pathological evaluation or imaging. Patients in Group A showing symptoms of thyrotoxicosis, angina, arrhythmia, or progressive osteoporosis were censored to undergo TSH suppression. The planned number of patients was accumulated by February 2005. The interim results were reported in 2006, with a median follow-up period of 4.0 years. Among 218 patients in Group A, 12 (6%) developed recurrence (11 lymph nodes, 5 distant sites). Conversely, 18 of 216 patients (8%) in Group B showed recurrence (1 remnant thyroid, 16 lymph nodes, and 7 distant sites). The standard of the hazard ratio was 2.1 to demonstrate noninferior recurrence rates in patients without TSH suppression therapy in comparison to patients with the therapy. A nonparametric examination showed that the 95% confidence interval for the hazard ratio was 0.31–1.3 with the intent-to-treat approach. This was not beyond the standard and even less than 1.5 for <5% inferiority. Moreover, TSH suppression therapy was suspended in Group A for 12 patients with thyrotoxicosis, 2 with angina, and 6 with progressive osteoporosis. The required duration of follow-up will be completed soon and the final report will then be published.

Prospective Outcomes of Selective Lymph Node Dissection Based on Preoperative US

The Western guidelines recommend therapeutic lateral neck dissection for patients with clinically evident metastasis in the lateral neck (Table 8). However, several authors have recommended a prophylactic lateral neck dissection based on specific risk factors. Simon et al.[47] recommended prophylactic lateral neck dissections in patients with central node metastasis. Machens et al.[48] claimed that patients with tumors >1 cm represent candidates for prophylactic lateral neck dissection. Marchesi et al.[49] found that patients evaluated as high-risk according to the AMES classification should

undergo prophylactic lateral neck dissection. Noguchi et al.[50] reported that patients with extracapsular invasion and women >60 years old show a benefit from prophylactic modified radical lateral neck dissection. Ito et al.[51] recently described a retrospective study of outcomes for 1231 patients who underwent a prophylactic MND, and identified male sex, age ≥55 years, maximum diameter >3 cm, and massive extrathyroidal extension as the main risk factors for nodal recurrence in patients with PTC. They recommended a prophylactic lateral neck dissection for patients displaying two or more of these factors. All these recommendations have been derived from retrospective studies.

A cervical lymph node dissection has been conducted based on a preoperative suspicion of lymph node metastasis by US since 1993. A prospective analysis was conducted for 361 consecutive patients with PTC who received the initial surgery between 1993 and 2001.[52] The mean duration of follow-up was 8.1 years. A central compartment node dissection was performed for patients with lymph node metastasis in the central zone only and for patients with no nodal metastasis detected by US (D1 group). A modified radical lateral neck dissection combined with a central node dissection was performed for patients diagnosed with lateral neck lymph node metastasis (D2 group). Pathological lymph node metastasis was found in 136 of 231 D1 group patients (59%). Nodal recurrences, all occurring in the lateral cervical region associated with 1 case in the contralateral paratracheal region, were seen in 18 patients (8%) and 10-year nodal DFS was 91%. A univariate analysis revealed true-positive diagnosis by US, large primary tumor (≥4 cm), primary tumor located in the upper part of the thyroid lobe, presence of distant metastasis, extrathyroidal invasion of the primary tumor, and a poorly differentiated component of primary tumor as significant risk factors for nodal recurrence. A multivariate analysis showed that among the risk factors that could be diagnosed preoperatively, distant metastasis (risk ratio = 46.0, $P = 0.01$) and large primary tumor (risk ratio = 3.6, $P = 0.03$) were the most important factors (Fig. 2). Of the other 130 patients in D2 group, only 3 patients had no pathological lymph node metastasis. Twenty-six patients (20%) developed nodal recurrence, with a 10-year nodal DFS of 76%. Age ≥50 years, large nodal metastasis ≥3 cm, extrathyroidal invasion, and higher serum thyroglobulin level ≥320 ng/ml represented significant factors for nodal recurrence. These prospective data for selective lymph node dissection indicate that when preoperative US shows no lymph node metastasis or indicates only metastasis in the central compartment, dissection of the central compartment alone offers a sufficient alternative to routine prophylactic lateral neck dissection. However, patients with PTC demonstrating large

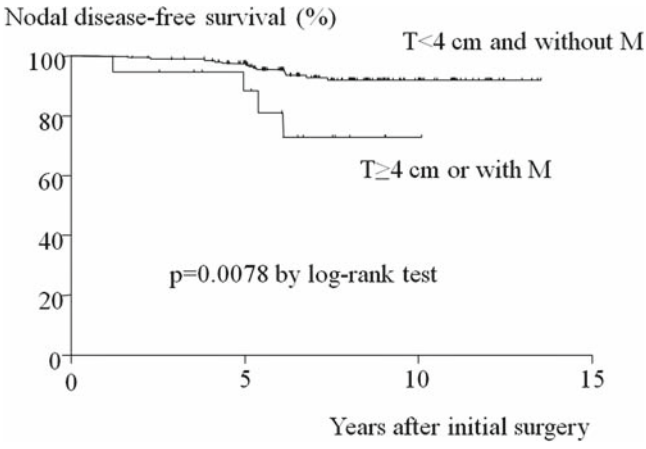

Fig. 2. Risk factors for nodal recurrences in patients who underwent dissection of the central compartment only. *T*, primary tumor size; *M*, distant metastasis

primary tumor and/or distant metastasis are at high risk of recurrence in the lateral cervical compartment. Therefore, prophylactic lateral neck dissection could reduce the rate of lateral neck recurrence for those patients. According to the risk-group classification, 217 of 231 patients (94%) in the D1 group belonged to the low-risk group. Consequently all patients in the D1 group, including patients who experienced nodal recurrence, are still alive. Further study is necessary to determine whether prophylactic lateral neck dissection is beneficial in terms of CSS, QOL, and medical costs. Conversely, of the 130 patients in the D2 group, 39 patients (30%) were in the high-risk group. In this group, the 10-year nodal DFS was only 44%. Recurrence within the formerly dissected area and repeated nodal recurrence were frequent. Aggressive extended neck dissection cannot save these patients. As a result, 11 of 130 patients (8%) who underwent a modified radical lateral neck dissection died, mainly due to distant metastases.

Management of Papillary Microcarcinoma

Papillary microcarcinoma (PMC) is defined as PTC with a diameter of ≤1.0 cm according to the WHO histologic classification published in 1988. Papillary microcarcinomas are usually discovered on autopsy or in the pathological examination of thyroid specimens surgically resected due to benign diseases. However, the widespread use of US (and even PET) with US-guided FNA in recent years have greatly facilitated the diagnosis of such subclinical cancers. In 1969, Takahashi[53] reported an unexpectedly high detection rate of 13.8% for PMC in 320 autopsy cases. Since then, many worldwide autopsy series have also shown a surprisingly high prevalence of PMC, ranging from 8% to 36% of patients dying from diseases other than thyroid cancer.[54–57] Simi-

larly, the prevalence of "incidental" PMCs, which go undetected on preoperative imaging studies but are identifiable in the pathological examination of surgical specimens resected for benign thyroid diseases, ranges from 13% to 24%.[58] In comparison, the incidence of clinically evident thyroid cancer is known to be only about 0.1%–0.05% in the general population. These minute cancers are usually thought to remain harmless and asymptomatic throughout the life of the patient. In fact, many authors have reported excellent surgical outcomes for PMC, even if the cancers were associated with small regional metastasis.[59,60] Moreover, incidental PMC is also associated with good prognosis, and further surgery, such as completion of a total thyroidectomy or lymph node dissection immediately after the pathological diagnosis of incidental PMC, is thought to be unnecessary. Rosai et al.[61] claimed that the term "carcinoma" might result in overtreatment and represent a source of psychological anxiety for patients with PMC. They proposed renaming PMC as "papillary microtumor." A more deliberate diagnostic approach is needed for screening tests for the purpose of preventing cancer deaths. The American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi (AACE/AME) guidelines clearly declared that US should not be performed as a screening test in the general population, except for patients with some risk of thyroid cancer (history of familial thyroid cancer or external irradiation) and for patients with palpable thyroid nodules or adenopathy suggestive of a malignant lesion.[62] "Overdiagnosis" is a cause for concern, since this act as an impediment to identifying which patients need treatment. Currently, however, patients once diagnosed with PMC routinely receive surgical treatment according to the guidelines.

Every patient with PMC at the CIH initially underwent surgery. The outcomes for 178 patients with PMC between 1976 and 1993 were retrospectively reviewed to determine the prognostic factors for mortality of the disease.[63] The most significant risk factors were the presence of clinically apparent lymph node metastasis and hoarseness due to recurrent nerve palsy at the time of diagnosis. All four cases of distant metastasis and four cases of cancer-specific death occurred in 30 patients with symptomatic PMC who had either cervical lymphadenopathy >1.0 cm, recurrent nerve invasion, or both. On the other hand, neither distant metastasis nor cause-specific death was seen in the remaining 148 patients without those symptoms (Table 10).

Following these results, prospective clinical trials of nonsurgical follow-up for asymptomatic PMC were initiated in 1995.[64] Patients with PMC diagnosed by US-guided FNA are evaluated with regard to the presence of distant metastasis, clinically apparent lymphadenopathy (>1 cm), or extrathyroidal invasion. Written informed consent is obtained after explaining: (1) the varieties of thyroid cancer and the prognosis of PTC; (2) the incidence of PMC based on an autopsy series or US screening tests in comparison to the clinical prevalence; and (3) the pros and cons of both nonsurgical follow-up and surgery. In cases of nonsurgical follow-up, the tumor is surveyed by palpation, US, chest radiography, or CT, with serum Tg measurement every 6 or 12 months. Surgery is recommended during follow-up if the patient meets the following criteria: (1) change in patient preferences; (2) tumor has grown backward in the thyroid, near the adjacent structures such as the recurrent laryngeal nerves, trachea, and esophagus; (3) development of clinically evident lymph node metastasis or distant metastasis; or (4) increased tumor size. As of 2007, 190 of 202 patients (94%) with asymptomatic PMC have elected to receive nonsurgical follow-up. After the mean follow-up of 4.5 years (range, 1–15 years), 26 of 219 lesions (12%) have increased in size. However, 178 lesions (81%) have shown no change and 15 lesions (7%) have decreased in size. No patients have developed extrathyroidal invasion or distant metastasis. Three patients who developed apparent nodal metastasis and 7 patients whose tumor increased in size eventually underwent surgery after 1–9 years of follow-up. The postoperative courses were favorable.

A similar trial was undertaken at Kuma Hospital in Japan.[65] In 2003, the investigators reported the results of an observation trial performed on 162 patients from among 732 candidates (22%). The follow-up period ranged from 18 to 113 months and more than 70% of patients showed no change in size. They also did not encounter cases showing distant metastasis or extrathyroidal invasion, although 1.2% of patients developed lymph node metastasis and subsequently underwent

Table 10. Outcomes for patients with papillary microcarcinoma (PMC) who underwent surgery (1976–1993 at Cancer Institute Hospital, Tokyo, Japan)

Type of PMC	No. of patients	Recurrence		Cause-specific mortality	10-year cause-specific survival
		Local	Distant		
Asymptomatic PMC	148 (83.1%)	4 (2.7%)	0	0	100%
Symptomatic PMC	30 (16.9%)	9 (30.0%)	4 (13.3%)	4 (13.3%)	74.1%

Symptoms at presentation: clinically evident nodal metastasis ≥1 cm ($n = 29$) and/or palsy of the recurrent laryngeal nerve ($n = 5$)

Table 11. Hazard ratio of risk factors for 57 patients with symptomatic papillary microcarcinoma (1976–2006 at Cancer Institute Hospital, Tokyo, Japan)

Endpoint	Cause-specific mortality	Recurrence	Distant metastasis
Risk factors			
Female	0.68	0.86	1.08
Age ≥50	1.11	1.54	0.70
T ≥5 mm	1.27	0.86	0.54
Multiple lesions	0.73	1.73	1.54
Ex	***6.59***	***2.04***	***3.64***
Poorly differentiated component	***2.90***	***2.82***	***4.67***
Size of N ≥2 cm	***2.89***	1.73	0.96
No. of pN ≥5	0.64	0.50	1.04

Symptoms included 1 cm or larger clinically evident nodal metastasis ($n = 57$) and/or palsy of the recurrent laryngeal nerve ($n = 8$). One patient with distant metastasis at presentation was excluded
T, primary tumor size; Ex, extrathyroidal invasion by primary tumor or metastatic node; N, clinical node metastasis; pN, pathological node metastasis
Bold, italic data show significance

surgery. Conservative follow-up is feasible and seems to be an attractive alternative to surgery, as long as the PMC is asymptomatic.

Conversely, patients with PMC occasionally present with bulky lymphadenopathy or with distant metastasis, and experience an unfavorable course.[66] The 10-year CSS of 57 patients with symptomatic PMC (excluding 1 patient with distant metastasis at diagnosis) treated at the CIH between 1976 and 2006 was 78%. A multivariate analysis showed that extrathyroidal invasion, large lymph node metastasis (≥2 cm), and a poorly differentiated component were significantly related to adverse outcomes (Table 11). These symptomatic PMCs definitely fall within the high-risk group of PTC, despite the small size of the primary tumor. Patients with such lesions might benefit from aggressive treatment such as a total thyroidectomy and RAI treatment.

What Is the Best Way to Treat Patients with Low-Risk PTC?

The treatment policies for patients with low-risk PTC and efforts to elevate the level of evidence are described in Table 12. Some readers might think it strange that these perspectives differ so markedly to those in Western countries.

Favorable Prognosis for Low-Risk PTC. Is it Due to Early Detection? Or Is the Cancer a Different Disease from the High-Risk One?

Radical treatment should therefore be recommended as early as possible if the majority of PTCs are detected in an early stage but inevitably progress to the advanced stage sooner or later. On the other hand, the hypothesis that low-risk PTC belongs to an independent disease category and is never related to cancer-specific mortality is accepted; minimally invasive treatment should be advocated.

It is a fact that PTC, the most common endocrine malignancy in humans, displays a peculiar characteristic in which some biological discrepancies exist between the clinical and subclinical cancers. For example, although the prevalence of microcarcinoma in autopsy series is as high as 36% among the general population, the clinical prevalence of PTC is 0.1% at the most. Pathological examinations have shown that intrathyroidal multiple lesions of PTC are seen in as many as 80% of patients, but the recurrence rate from the remnant thyroid when the contralateral lobe is preserved is only 1.6%.[15] Similarly, PTC is pathologically associated with lymph node metastases in 30%–80% of patients, while nodal recurrence in patients not receiving prophylactic dissection is reportedly around 10%. In addition, Fujimoto and Sugitani[67] performed a long-term (35–45 years) follow-up study on patients with intrathyroidal PTC, in an attempt to reveal the natural history of the disease. Among 49 patients who underwent insufficient surgery, only one definitely died of thyroid cancer. As for PTC, "cancer" is sometimes present which has no deleterious effect on the individual throughout their life.

However, a few exceptional cancer-specific deaths are seen among patients classified into the low-risk group. It is unclear whether these patients were essentially high-risk but were categorized into the low-risk group by mistake due to the limitations of the adopted risk group definition, or whether some patients belong to an intermediate-risk group in which cancer progresses in a time-dependent manner. In addition, it is necessary to be very specific about what outcomes are predicted with these risk-stratification schemes. When the outcomes are converted from CSS to DFS, the range of the "high-risk" group is necessarily extended.[68]

Table 12. Our efforts to elevate the level of evidence in management of low-risk papillary thyroid carcinoma

Controversies	Level of evidence		
	Level IV	Level III	Level I–II
	Retrospective analysis	Prospective study	Randomized controlled trial (RCT)
Extent of thyroidectomy	1976–1998 Risk-group classification system based on age, distant metastasis, extrathyroidal invasion and size of nodal metastasis	2005– Patient's informed decision regarding dual policy	–
Extent of lymph node dissection		1993–2001 Risk factor analysis for nodal recurrence after selective lymph node dissection based on preoperative ultrasonography	?– Prophylactic lateral neck dissection for selected patients?
Postoperative adjuvant therapy		–	1996–2004 RCT for effects of TSH suppression therapy
Management of papillary microcarcinoma	1976–1993 Categorization by symptoms	1995– Nonsurgical observation trial for asymptomatic papillary microcarcinoma	

Refer to Table 2 for the level of evidence

How Should We Consider "Recurrence" in Patients with PTC?

More than 30% of patients with PTC experience tumor recurrences or are likely to have residual disease based on persistent measurable stimulated Tg. A small percentage of recurrences must be regarded as the first sign of a potentially lethal outcome. We have previously reported recurrence at any site within 3 years after the initial surgery to be a significant life-threatening factor among patients with high-risk PTC.[15] However, the majority of recurrences are curable, particularly in patients with low-risk PTC. Indeed, occasional minor persistent cancerous lesions in the remnant thyroid, cervical lymph nodes, and even the lung stay harmless throughout the life of the patient. This discrepancy between cancer-related mortality and frequency of tumor recurrence probably accounts for most of the profound disparity of opinion among clinicians concerning optimal treatment for patients with PTC. In a situation where most patients do not succumb to cancer, many investigators might naturally have placed stronger emphasis on potential morbidity than on mortality.

The Western guidelines tend to set the range of "low-risk" PTC significantly narrower than in Japan, with much more emphasis on the risk of recurrence than on mortality. For example, the ATA guidelines allow for a conservative thyroidectomy in patients with small (<1–1.5 cm), isolated, intrathyroidal PTC in the absence of cervical lymph node metastasis. A history of radiotherapy to the head and neck, first-degree family history of differentiated thyroid carcinoma, or age >45 years may also be criteria for recommending a near-total or total thyroidectomy due to higher recurrence rates.[23] Considering the burden of the term "recurrence" on both patients and physicians is important. In addition, increasing the risk of surgical complications and medical costs for reoperations cannot be considered a negligible issue. However, aggressive treatment of all persistent or recurrent disease that never leads to mortality is not always beneficial for patients. Cady,[69] one of the first proponents of risk-group definitions for differentiated thyroid carcinoma, has often claimed that the "punishment has to fit the crime" and has cautioned against overtreatment for low-risk PTC.

Whether meticulous surveillance by stimulated Tg and WBS once annually after a total thyroidectomy and RAI remnant ablation improves patient outcomes is also uncertain. Both the positive predictive value for persistently detectable stimulated Tg and the negative predictive value for negative Tg are far from 100%. Many patients only experience mental anguish from Tg-positive, WBS-negative results. In such cases, an expensive PET scan might indicate the existence of distant lesions, but effective treatment methods are usually lacking. Moreover, nobody knows how long sur-

veillance should be continued for patients with undetectable stimulated Tg. The most important task is to develop the ability to more precisely predict those patients who are likely to be harmed by their disease and those who will live unaffected by their disease. Novel techniques such as molecular markers that can identify small cervical metastases with the potential to progress to clinically significant metastases or to metastasize to distant sites are desired.

Why Has a Total Thyroidectomy Not Been Prevalent in Japan for Patients with Low-Risk PTC?

Most patients diagnosed with thyroid cancer in Western countries now undergo a total thyroidectomy. This is the case even if the cancer is papillary and very small. A total thyroidectomy carries a small but significant risk of surgical complications. In addition, these policies commit the patient to a lifetime sentence of thyroid hormone replacement therapy and punishment due to long-term surveillance by stimulated Tg measurement and WBS. Hoftijzer et al.[70] recently assessed the QOL in 153 cured differentiated thyroid carcinoma patients treated by a near-total thyroidectomy, and followed by postoperative RAI ablation. They reported that patients display an evident decrease in QOL that may be restored only after years (approximately 12–20 years) of follow-up, despite achieving a cure and excellent prognosis.

Given that one of the contemporary trends in cancer treatment has been limiting surgical intervention, the aggressive treatment policy for low-risk PTC seems out of date. This may be due to the fact that an effective systemic treatment for thyroid cancer other than RAI leading inevitably to a total thyroidectomy is still lacking. However, the effectiveness of RAI remnant ablation for patients with low-risk PTC is not justified by a high level of evidence. Furthermore, neither RAI treatment nor TSH suppression therapy offer sufficient efficacy for patients with high-risk cancers that are poorly differentiated and progress rapidly.[71] As described at the beginning of this article, Davies and Gilbert Welch[1] found that an increase in the apparent incidence of thyroid cancer over the last three decades was regrettably not connected to any clinical impact on mortality or decrease in anaplastic thyroid carcinoma, which has a dismal prognosis. Anaplastic carcinoma is not thought to originate from common PMC, and novel therapeutic measures are necessary to achieve a cure of high-risk thyroid carcinoma.

Proponents of total or near-total thyroidectomies have pointed out that patients from older age groups, minority ethnic groups, and the lower socioeconomic strata dominate the set of patients undergoing a hemithyroidectomy.[72] Moreover, patients at low-volume and community hospitals are less likely to undergo a total thyroidectomy. These investigators determined that these practice patterns likely reflect disparities in access to health care, medication, and comprehensive cancer centers. Regarding the reason behind a total thyroidectomy and RAI treatment not being the first-choice treatment among patients with low-risk PTC in Japan, Japanese investigators tend to humble themselves and attribute this to sociomedical circumstances with strict legal regulations and a shortage of institutions performing RAI. However, the fact that Japanese pioneers have understood the biological characteristics of low-risk PTC and have avoided overtreatment for those patients while regarding their QOL is remarkable. It is therefore necessary to analyze these precious data precisely and thereby provide an important message from Japan to the whole world.

Acknowledgment. This work was supported in part by the Foundation for the Promotion of Cancer Research, Japan.

References

1. Davies L, Gilbert Welch H. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006;295:2164–67.
2. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95:2S–4S.
3. Heinrich S, Schäfer M, Rousson V, Clavien PA. Evidence-based treatment of acute pancreatitis: a look at established paradigms. Ann Surg 2006;243:154–68.
4. Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. World J Surg 1996;20:88–93.
5. Cady B, Rossi R. An expanded view of risk group definition in differentiated thyroid carcinoma. Surgery 1988;104:947–53.
6. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102:1088–95.
7. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050–8.
8. Byar DP, Green SB, Dor P, Williams ED, Colon J, van Gilse HA, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. thyroid cancer cooperative group. Eur J Cancer 1979; 15:1033–41.
9. Mazzaferri EL, Jhiang S. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418–28.
10. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 1996;3:534–8.
11. Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, et al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83:1012–21.
12. UICC TNM classification of malignant tumours, 6th ed. New York: Wiley-Liss; 2002. p. 52–6.
13. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Thyroid carcinoma. Version 1. 2008. http://www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf. Accessed 15 May 2009.

14. Noguchi S, Murakami N, Kawamoto H. Classification of papillary cancer of the thyroid based on prognosis. World J Surg 1994; 18:552–8.
15. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery 2004;135:139–48.
16. Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer 1997;79:2414–23.
17. Lang BH, Lo CY, Chan WF, Lam KY, Wan KY. Staging systems for papillary thyroid carcinoma: a review and comparison. Ann Surg 2007;245:366–78.
18. Loh KH, Greenspan FS, Gee L, Miller TR, Yeo PPB. Pathological Tumor-Node Metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997;82:3553–62.
19. Kim TY, Kim WB, Rhee YS, Song JY, Kim JM, Gong G, et al. 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.
20. Elisei R, Ugolini C, Viola D, Lupi C, Biagini A, Giannini R, et al. BRAF (V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15\year median follow-up study. J Clin Endocrinol Metab 2008;93:3493–9.
21. Cobin RH, Gharib H, Bergman DA, Clark OH, Cooper DS, Daniels GH, et al. AACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. American Association of Clinical Endocrinologists. American College of Endocrinology. Endocr Pract 2001;7:202–20.
22. British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer. 2nd ed. 2007. http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf. Accessed 15 May 2009.
23. The American Thyroid Association Guideline Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109–42.
24. Shigematsu N, Takami H, Ito N, Kubo A. Nationwide survey on the treatment policy for well-differentiated thyroid cancer: results of a questionnaire distributed at the 37th meeting of the Japanese Society of Thyroid Surgery. Endocr J 2005;52:479–91.
25. Cady B. Our AMES is true: how an old concept still hits the mark, or risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. Am J Surg 1997;174: 462–8.
26. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope 2004;114:393–402.
27. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981;70:511–8.
28. Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998;124:958–64.
29. Shah JP, Loree TR, Dharker D, Strong EW. Lobectomy versus total thyroidectomy for differentiated thyroid carcinoma of the thyroid: a matched-pair analysis. Am J Surg 1993;166:331–5.
30. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375–84.
31. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC. A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3668–76.
32. Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 2005;90:5047–57.
33. Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, et al. Author's response: a consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88:4508–10.
34. Pacini F, Agate L, Elisei R, Capezzone M, Ceccarelli C, Lippi F, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic 131-I whole body scan: comparison of patients treated with high 131-I activities versus untreated patients. J Clin Endocrinol Metab 2001;86:4092–7.
35. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine 1977;56:171–96.
36. Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 1996;81: 4318–23.
37. Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998;8:737–44.
38. Jonklaas J, Sarlis NJ, Litofsly D, Ain KB, Bigos T, Brierley JD, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16:1229–42.
39. Cady B. Staging in thyroid carcinoma. Cancer 1998;83:844–7.
40. Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery. 1995;118: 1131–8.
41. Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998;82:375–88.
42. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Ultrasonographically and anatomopathologically detectable node metastasis in the lateral compartment as indicators of worse relapse-free survival in patients with papillary carcinoma. World J Surg 2005;29:917–20.
43. Bae JS, Park WC, Song BJ, Jung SS, Kim JS. Endoscopic thyroidectomy and sentinel lymph node biopsy via an anterior chest approach for papillary thyroid cancer. Surgery Today 2009;39: 178–81.
44. Cady B. Regional lymph node metastases, a singular manifestation of the process of clinical metastases in cancer: contemporary animal research and clinical reports suggest unifying concepts. Ann Surg Oncol 2007;14:1790–800.
45. Medical Professionalism Project. Medical Professionalism in the new millennium: a physician's charter. Lancet 2002;359:520–2.
46. McGriff NJ, Csako G, Gourgiotis L, Guthrie LC, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. Ann Med 2002;34: 554–64.
47. Simon D, Goretzki PE, Witte J, Röher HD. Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. World J Surg 1996;20:860–6.
48. Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002;26:22–8.
49. Marchesi M, Biffoni M, Biancari F, Berni A, Campana FP. Predictors of outcome for patients with differentiated and aggressive thyroid carcinoma. Eur J Surg Suppl 2003;588:46–50.
50. Noguchi S, Murakami N. Yamashita H, Toda M, Kawamoto H. Papillary thyroid carcinoma: modified radical neck dissection improves prognosis. Arch Surg 1998;133:276–80.
51. Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, et al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively

detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg 2007;31:2085–91.
52. Sugitani I, Fujimoto Y, Yamada K, Yamamoto N. Prospective outcomes of selective lymph node dissection for papillary thyroid carcinoma based on preoperative ultrasonography. World J Surg 2008;32:2494–502.
53. Takahashi S. Clinicopathological studies of latent carcinoma of the thyroid (in Japanese). Nippon Naibunpi Gakkai Zasshi (Folia Endocrinol Japon) 1969;45:65–79.
54. Sampson RJ, Key CR, Buncher CR, Oka H, Iijima S. Papillary carcinoma of the thyroid gland: sizes of 525 tumors found at autopsy in Hiroshima and Nagasaki. Cancer 1970;25:1391–3.
55. Sampson RJ, Woolner LB, Bahn RC, Kurland LT. Occult thyroid carcinoma in Olmsted country, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. Cancer 1974;34:2072–6.
56. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. Cancer 1975;36:1095–9.
57. Bondeson L, Ljungberg O. Occult thyroid carcinoma at autopsy in Malmö, Sweden. Cancer 1981;47:319–23.
58. Nasir A, Chaudhry AZ, Gillespie J, Kaiser HE. Papillary microcarcinoma of the thyroid: a clinico-pathologic and prognostic review. In Vivo 2000;14:367–76.
59. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. World J Surg 2008;32:747–53.
60. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 2008;144:980–8.
61. Rosai J, LiVolsi VA, Sobrinho-Simoes M, Williams ED. Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal. Int J Surg Pathol 2003;11:249–51.
62. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006;12:63–102.
63. Sugitani I, Fujimoto Y. Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective analysis of surgical outcome and prognostic factors. Endocr J 1999;46:209–16.
64. Sugitani I, Fujimoto Y, Yamada K. Treatment strategy for patients with papillary microcarcinoma (in Japanese with English abstract). Nippon Rinsho (Jpn J Clin Med) 2007;65:2045–8.
65. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381–7.
66. Sugitani I, Yanagisawa A, Shimizu A, Kato M, Fujimoto Y. Clinicopathologic and immunohistochemical studies of papillary thyroid microcarcinoma presenting with cervical lymphadenopathy. World J Surg 1998;22:731–7.
67. Fujimoto Y, Sugitani I. Postoperative prognosis of intrathyroidal papillary thyroid carcinoma: long-term (35–45 year) follow-up study. Endocr J 1998;45:475–84.
68. Tuttle RM. Risk-adopted management of thyroid cancer. Endocr Pract 2008;14:764–74.
69. Cady B. Presidential address: beyond risk groups- a new look at differentiated thyroid cancer. Surgery 1998;124:947–57.
70. Hoftijzer HC, Heemstra KA, Corssmit EPM, van der Klaauw AA, Romijn JA, Smit JWA. Quality of life in cured patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:200–3.
71. Sugitani I, Fujimoto Y, Yamamoto N. Papillary thyroid carcinoma with distant metastases: survival predictors and the importance of local control. Surgery 2008;143:35–42.
72. Bilimoria KY, Zanocco K, Sturgeon C. Impact of surgical treatment on outcomes for papillary thyroid cancer. Adv Surg 2008;42:1–12.