Papillary Thyroid Cancer: Time Course of Recurrences During Postsurgery Surveillance

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Context: The current use of life-long follow-up in patients with papillary thyroid cancer (PTC) is based largely on the study of individuals diagnosed and treated in the latter half of the 20th century when recurrence rates were approximately 20% and relapses detected up to 20–30 years after surgery. Since then, however, diagnosis, treatment, and postoperative monitoring of PTC patients have evolved significantly.

Objectives: The objective of the study was to identify times to PTC recurrence and rates by which these relapses occurred in a more recent patient cohort.

Patients and Design: We retrospectively analyzed follow-up data for 1020 PTC patients consecutively diagnosed in 1990–2008 in 8 Italian hospital centers for thyroid disease. Patients underwent thyroidectomy, with or without radioiodine ablation of residual thyroid tissue and were followed up with periodic serum thyroglobulin assays and neck sonography.

Results: At the initial posttreatment (≤12 months) examination, 948 patients had no structural/functional evidence of disease. During follow-up (5.1–20.4 years; median 10.4 years), recurrence (cervical lymph nodes, thyroid bed) was diagnosed in 13 (1.4%) of these patients. All relapses occurred 8 or fewer years after treatment (10 within the first 5 years, 6 within the first 3 years). Recurrence was unrelated to the use/omission of postoperative radioiodine ablation.

Conclusion: In PTC patients whose initial treatment produces disease remission (no structural evidence of disease), recurrent disease is rare, and it usually occurs during the early postoperative period. The picture of recurrence timing during the follow-up provides a foundation for the design of more cost-effective surveillance protocols for PTC patients. **(*J Clin Endocrinol Metab* 98: 636–642, 2013)**

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Abbreviations: ATA, American Thyroid Association; CT, computed tomography; DTC, differentiated thyroid carcinoma; dxWBS, diagnostic ^{131}I whole-body scan; EBR, external-beam radiation; FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging; PTC, papillary thyroid carcinoma; RRA, radioiodine iodine remnant ablation; Tg, thyroglobulin.

The vast majority of malignant thyroid cancers are papillary carcinomas, and the cure rate for these tumors has always been relatively high (1, 2). Nonetheless, patients with papillary thyroid carcinomas (PTCs) generally undergo life-long follow-up. This policy is largely based on landmark studies published in the mid-1990s, which looked at long-term outcomes in large cohorts of American or European thyroid cancer patients treated during the latter half of the 20th century (3, 4). In the study by Mazzaferri and Jhiang (3), for example, posttreatment recurrence rates among PTC patients were approximately 20%, and approximately 40% of the recurrences were detected more than 5 years after the initial treatment.

In the last few years, however, the cost-effectiveness of this protracted surveillance has been challenged for several reasons. Doubts have been prompted in part by ongoing increases in the incidence of PTCs, which has risen almost 3-fold since the 1970s (5, 6). This trend is largely due to increases in the incidental diagnosis of small, subclinical PTCs during neck sonography for other purposes (7), and this phenomenon is transforming the clinical profile of PTC patient populations being referred to thyroid disease clinics. For these reasons, accurate risk stratification of these patients is playing an increasingly important part in decisions regarding treatment and postoperative follow-up (8–10). Distinguishing patients with negligible risks for disease recurrence from those with higher-risk tumors that require closer and more prolonged follow-up should allow clinicians to provide increasingly cost-effective treatment and surveillance plans for both subgroups.

The past 20 years have also witnessed important changes in the methods used to detect postoperative recurrence. Various attempts have been made to identify and validate effective diagnostic tools for this purpose. Less attention has been focused on the equally important questions of when, how, and how long these tools should be used. Answers to these questions require a more complete understanding of the time course of postoperative recurrences. Thus far, this critical aspect of the disease has not been examined in ad hoc studies, and it has not been addressed in international practice guidelines (1, 2). As a result, follow-up strategies for patients with PTC are likely to reflect institutional rather than evidence-based choices.

The present study was conducted to identify times to recurrence of PTC and define the rates by which these recurrences occurred, issues that are fundamental for any attempt to improve the cost-effectiveness of postoperative surveillance in this population of patients.

Subjects and Methods

Patients and study design

We conducted a retrospective analysis of data collected prospectively in 8 hospital-based referral centers for thyroid disease in Italy. Since 1990, all 8 centers have been using a common postoperative follow-up protocol for PTC patients, which is described in detail below. The cohort examined in this study consisted of individuals consecutively diagnosed with PTC since January 1, 1990. The only inclusion criteria applied were negative thyroglobulin (Tg) antibody levels at the time of diagnosis and 3 or more years of follow-up before study data lock (January 31, 2012).

Treatment and follow-up

All patients had had total/near-total thyroidectomies. Decisions regarding cervical lymph node dissection and postoperative radioiodine iodine remnant ablation (RRA) were made on the basis of institutional guidelines at the time the patient underwent surgery.

Table 1. Characteristics of the Study Population at Baseline

	Study Population (n = 1020)
Gender, n, %	
Male	207 (20.3)
Female	813 (79.7)
Age at diagnosis, y, median (range)	44 (13–78)
Tumor size, mm, median (range)	15 (0.3–90)
Tumor foci, n, %	
Unifocal	656 (64.3)
Multifocal	364 (35.7)
Unilateral	765 (75)
Bilateral	255 (25)
Extrathyroidal extension, n, %	
No	776 (76)
Yes	244 (24)
Lymph node metastases, n, %	
Nx	93 (9)
N0	673 (66)
N1	254 (25)
Distant metastases, n, %	
No	987 (96.8)[a]
Yes	33 (3.2)
AJCC stage, n, %	
I	753 (73.8)
II	82 (8)
III	117 (11.4)
IVa	41 (4)
IVb	0 (0)
IVc	15 (1.4)
Unknown[b]	12 (1.2)
ATA risk level, n, %	
Low	625 (61.3)
Intermediate	362 (35.5)
High	33 (3.2)
Radioiodine remnant ablation, n, %	
Yes	902 (88.4)
No	118 (11.6)
Follow-up duration, y, median (range)	8.5 (2.7–21.4)

Abbreviation: AJCC, American Joint Committee on Cancer.

[a] Includes the 118 patients who did not undergo radioiodine remnant ablation. Imaging studies to exclude distant metastases were not done, but all 118 were classified as low risk and none had any clinical signs suggestive of extracervical tumor spread.

[b] Primary tumor size was not specified. All patients in this class were older than 45 years of age and had no evidence of extrathyroidal invasion.

The basic follow-up protocol used in all 8 centers since 1990 called for an initial assessment 12 or fewer months after the initial treatment and yearly visits thereafter. Each visit included neck ultrasound (US) and assessment of stimulated and/or basal serum Tg levels. In some centers, diagnostic ^{131}I whole-body scans (dxWBS) were also performed routinely at the initial postoperative visit. In all centers, additional imaging studies [eg, dxWBS, computed tomography (CT), magnetic resonance imaging (MRI)] were performed, as needed, whenever clinical findings raised the suspicion of recurrent disease.

Serum Tg levels were measured with various immunoradiometric assays; all had functional sensitivities of approximately 1 ng/mL. Basal levels were measured in all patients; stimulated levels were assessed only in those who had undergone RRA. Serum Tg assays were considered negative if they were 1 ng/mL or less under basal condition and 2 ng/mL or less after TSH stimulation. Both conditions were required when patients had undergone RRA. Sonographic examinations of the neck were performed by endocrinologists specialized in cervical US using color Doppler scanners with multifrequency probes (7.5–12 MHz). All suspicious lymph nodes (11) were subjected to fine-needle aspiration cytology (FNAC), and Tg levels were measured in the needle washout fluid. Starting in 1997, aspirates were also assayed for Tg/TSH mRNA (12).

Patients were classified as having persistent structural disease if residual tumor tissue was demonstrated at the first follow-up assessment (6–12 months after the initial treatment) by neck US (confirmed by FNAC), CT, MRI, or dxWBS. These individuals were referred for additional treatment [surgery, radioiodine, external-beam radiation (EBR), depending on the site of involvement].

The other patients were presumed to be disease free and enrolled in the ongoing surveillance program. During the follow-up, patients were considered to have recurrent disease if either or both of the following were observed: 1) positive imaging findings (neck US + FNAC, CT, MRI, or dxWBS); 2) significant increases (ie, ≥50%) in stimulated and/or basal serum Tg levels with respect to the previous visit(s) (13).

Data collection

Charts were reviewed, and the following data were recorded for each case at baseline (ie, immediately after the initial surgical procedure): patient demographics; tumor characteristics (including date of diagnosis and histological features); and treatment (surgery, RRA, other interventions). Using the prospectively collected data, we also retrospectively calculated the baseline tumor stage and the baseline risk for persistent/recurrent disease [as defined, in both cases, by the 2009 American Thyroid Association (ATA) Management Guidelines for Differentiated Thyroid Cancer (1)]. We reviewed the results of each follow-up visit (cervical US, laboratory tests, and the results of any functional or cross-sectional imaging studies), and for each case of persistent or recurrent disease, we recorded the site/extension of involvement, time and method of detection, time and type of treatment, and the results of the final follow-up visit.

Statistical analysis

Patient characteristics are reported as median values and ranges (continuous variables) or absolute numbers and percentages (categorical variables). The intergroup differences involving these variables were assessed with the independent-samples *t* test or the Fisher exact test, respectively. Differences with a $P < .05$ were considered statistically significant. All analyses were performed with StatView 5.0.1 software (SAS Institute Inc, Cary, North Carolina).

Results

Characteristics of the study population

Table 1 shows the characteristics of the 1020 patients in the study cohort at baseline (ie, immediately after the initial treatment, which consisted in total or near total thyroidectomy, with or without RRA). The case spectrum is representative of patients with PTC seen over the past 2 decades in hospital-based centers for the management of thyroid disease (as opposed to cancer referral centers). Most patients had asymptomatic thyroid cancers that met the ATA criteria (1) for a low risk of recurrence (61.3%). The vast majority of the tumors were unifocal (64.3%) stage I (73.8%) PTCs confined to 1 lobe of the gland (75%). In 3 of 4 cases, there was no evidence of extrathyroidal extension (76%) at baseline.

Persistent disease

As shown in Table 2, 72 of the 1020 patients (7.2%) presented persistent structural disease after the initial

Table 2. Clinical Findings at the First Postoperative Follow-Up Visit

	RRA (+) (n = 902)	RRA (−) (n = 118)	Total (n = 1020)
Disease free, n, %	832 (92.2)	116 (98.3)	948 (92.9)
Imaging findings negative, serum Tg assay negative[a]	665 (73.7)	98 (83)	763 (74.8)
Imaging findings negative, serum Tg assay positive[b]	167 (18.5)	18 (15.2)	185 (18.1)
Persistent disease, n, %	70 (7.8)	2 (1.8)	72 (7.1)
Imaging findings positive, serum Tg assay negative[a]	14 (20)	1 (50)	15 (21)
Imaging findings positive, serum Tg assay positive[b]	56 (80)	1 (50)	57 (79)

Abbreviations: RRA (−), no radioactive iodine remnant ablation; RRA (+), radioactive iodine remnant ablation.

[a] Basal serum Tg was 1 ng/mL or less and stimulated serum Tg was 2 ng/mL or less for patients who did undergo RRA; basal serum Tg was 1 ng/mL or less for those who did not.

[b] Basal serum Tg was greater than 1 ng/mL or stimulated serum Tg was greater than 2 ng/mL for patients who did undergo RRA; basal serum Tg was greater than 1 ng/mL for those who did not.

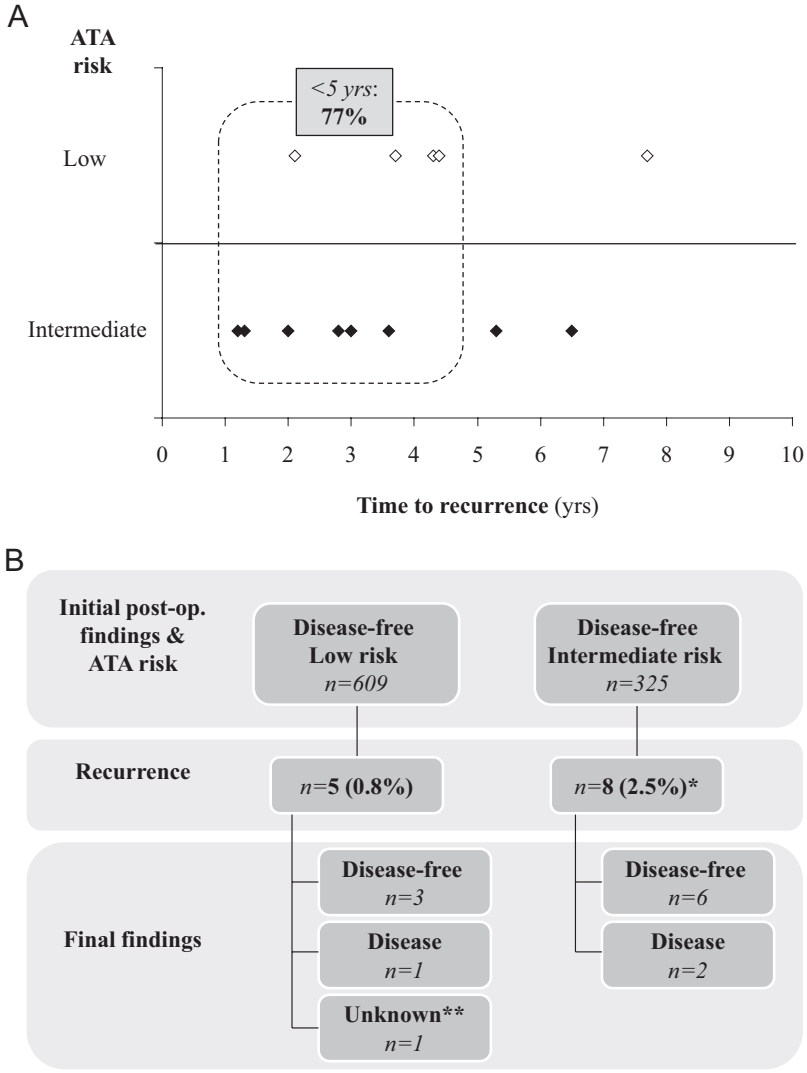

Figure 1. Timing of recurrences and final outcome of patients without structural evidence of disease at the first postoperative follow-up according to ATA risk score. A, Time to detection of recurrence in subgroups classified as disease free on the basis of findings at the initial postoperative follow-up visit. Risk for recurrence was estimated according to the 2009 American Thyroid Association risk stratification system: low (white diamonds) and intermediate (black diamonds). B, End-of-follow-up findings for the patients who experienced recurrent disease. *Recurrence was significantly more common in the intermediate-risk group than in the low-risk group ($P = .02$); **the time of the final visit is the date of treatment. No further follow-up data were available at the time of study data lock.

treatment. This subgroup comprised 16 (2.5%) of the 625 with low risk, 41 (11.3%) of the 362 intermediate-risk patients, and 23 (69.7%) of the 33 whose risk was classified as high. The latter finding explains why persistence was more common in the RRA (+) subgroup (Table 2) because ablation was more likely to be used in patients with higher risk tumors. All 72 patients were promptly retreated (surgery, RRA, or EBR, depending on the site of involvement) and subsequently reinserted in the surveillance program. At the end of follow-up (median 10.4 years after the initial treatment; range 5.1–20.4 years), 14 of the 72 (19.5%) still had imaging-documented disease. The other 58 (80.5%) were considered disease free.

Recurrent disease

The 948 patients considered disease-free on the basis of the initial postoperative imaging studies (92.9%) included 763 who also had negative serum Tg assays (≤1 ng/mL under basal condition, ≤2 ng/mL after TSH stimulation) and 185 whose Tg assays were positive (Table 2). All 948 patients remained under surveillance, as planned, and most [935 patients (98.6%)] remained without structural evidence of disease for the duration of the follow-up.

The other 13 (1.4%), who developed recurrent disease (Figure 1 and Table 3), included 12 of the 763 patients (1.6%) who had been imaging and Tg negative and 1 of the 185 (0.5%) who had been imaging negative and Tg positive. In all 13 cases, the recurrence was confined to the cervical lymph nodes or thyroid bed (n = 3). All but 2 of the lesions (both confined to the thyroid bed) were detected with neck US. In 7 cases, the positive US findings were accompanied by Tg assay positivity. The group with recurrences included 8 of the 325 intermediate-risk patients (2.52%) and 5 of the 609 with low-risk tumors (0.8%).

As shown in Figure 1A, approximately 3 of 4 recurrences were discovered within the first 5 years of follow-up, and more than half were identified within the first 3 years. The recurrence rate appears to be related to the baseline ATA risk level, being 0.8% in low-risk patients and 2.5% in those carrying an intermediate risk ($P = .02$) (Figure 1B). Most recurrences were treated with surgery and/or radioiodine administration, and at the end of the follow-up period, 3 of the 13 patients still had persistent structural disease (Table 3).

Discussion

Can we consider PTC patients cured if, 1 year after the initial treatment, total or near-total thyroidectomy, with or without RRA, they have undetectable serum Tg levels and negative neck US (both of which have high negative predictive value NPV) (8, 14, 15)? If the answer is yes, do these patients still require active, life-long surveillance? Or should all follow-up cease? Or should it continue but at a more relaxed pace? And if so, how relaxed? Current practice guidelines offer no clear recommendations in this area,

Table 3. Patients With Recurrences

Number	ATA Risk	pTNM	Age at Diagnosis, y	AJCC Stage	Extent of LND at Initial Surgery	Time to Recurrence, y	Site of Recurrence	Positive Findings at Detection	Treatment	End of Follow-Up Findings	Time of Final Visit, y
1	Low	T1a Nx M0[a]	≥45	I	No LND	3.6	Central neck	Neck US, Tg	RAI, surgery	NA[b]	7
2	Low	T1b N0 M0	≥45	I	Central	3.7	Lateral neck	Neck US	Surgery	Disease free	5.7
3	Low	T1b N0 M0	<45	I	Central	2.0	Central neck	Tg, WBS	RAI	Disease free	10.5
4	Low	T1b N0 M0	<45	I	Central	6.5	Lateral neck	Neck US	Surgery	Disease free	8.5
5	Low	T1b N0 M0	<45	I	Central	7.7	Lateral neck	Neck US, Tg	Surgery	Persistent disease[c]	15.6
6	Intermediate	T3 N1b M0	<45	I	Central, lateral	2.1	Central neck	Tg, WBS	RAI	Disease free	10.1
7	Intermediate	T3 N0 M0	<45	I	Central	2.8	Lateral neck	Neck US	RAI, surgery	Disease free	20
8	Intermediate	T3 N1a M0	<45	I	Central	3.0	Central neck	Neck US	None	Persistent disease[c]	5.3
9	Intermediate	T3 N0 M0	<45	I	Central	4.4	Lateral neck	Neck US, Tg	RAI, surgery	Disease free	6.2
10	Intermediate	T3 Nx M0[a]	≥45	III	No LND	1.3	Lateral neck	Neck US, Tg	Surgery	Disease free	10.3
11	Intermediate	T3m N0 M0	≥45	III	Central	4.3	Lateral neck	Neck US, Tg	RAI, surgery, EBR	Persistent disease[c]	8.6
12	Intermediate	T3 N1a M0	≥45	III	Central	5.3	Lateral neck	Neck US	RAI, surgery	Disease free	7
13	Intermediate	T3 N1b M0	≥45	IVa	Central, lateral	1.2	Lateral neck	Neck US, Tg	RAI, surgery	Disease free	5.7

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; Central, central neck compartments; Lateral, lateral neck compartment; LND, lymph node dissection; NA, not available; pTNM, pathological tumor node metastasis; RAI, radioactive iodine; Tg, serum thyroglobulin (significant increase relative to previous findings); WBS, whole-body scan.

[a] Nx with normal postoperative neck US (cN0).

[b] The most recent data on this patient refer to the date of the neck surgery. No further follow-up visit was available at the time of study data lock.

[c] Persistent structural disease.

and the prospective data needed to answer these questions are simply not available (1, 2). And yet a more rational, cost-effective approach to the postoperative surveillance of these patients is clearly needed.

Defining the natural history of PTC recurrences is, however, an essential step toward this goal, and it was the main objective of our study. We found that, within the first year after initial treatment, unequivocal evidence of persistent disease develops in a small but by no means negligible subset of patients (n = 72; 7.1%). This group included almost 70% (23 of 33) of the patients whose baseline assessment revealed a high risk for persistent/recurrent disease. The other 948 (92.9%) were considered disease free at the first postoperative assessment, although 185 had detectable serum Tg levels (including almost 20% of those who had undergone RRA) (Table 2). Interestingly, the rates of complete clinical responses were almost identical in the RRA and no-RRA patient subgroups (Table 2), which tends to support current recommendations for more selective use of RRA (1).

Later, recurrent disease was documented in 13 patients (1.4%) (Figure 1 and Table 3). Half of the recurrences were detected within the first 3 years of follow-up, and more than 75% were identified within the first 5 years. These data are at variance with those reported in the mid-1990s (3, 4). In the PTC patients in the study by Mazzaferri and Jhiang (3), the recurrence rate exceeded 20% (241 of 1077; 22.3%). Moreover, 43.3% of the recurrences were identified after more than 5 years of follow-up, and 19.3% were detected more than 10 years after the original treatment. Findings of this type are cited to support the practice of life-long surveillance for all PTC patients, and our experience also shows that recurrences can occur several years after the initial treatment. However, in our cohort, such events were much less common: only 3 of the recurrences (23%) were discovered more than 5 years after surgery (5.3, 6.5, and 7.7 years), and none were identified after several years from the initial treatment.

The differences between the findings of these 2 studies are largely a reflection of the changing demography of the differentiated thyroid carcinoma (DTC) patients seen in general thyroid disease practices. Today's PTCs are much more likely to be diagnosed at a subclinical stage than those treated in 1960s to the 1990s. Indeed, 46% of the PTC patients studied by Mazzaferri and Jhiang (3) had detectable regional lymph node metastases at the time of initial therapy, almost twice the rate observed in our cohort (25%). Furthermore, although the staging criteria applied in the 2 studies are somewhat different, the percentage of stage I tumors in our cohort (73.3%) was approximately 5 times higher than that reported in 1994 (3).

The postoperative follow-up of DTC patients has also evolved, with a clear decline in the use of ^{131}I WBS and increasingly widespread reliance on high-resolution neck ultrasonography and sensitive serum Tg assays. Neck ultrasound has proved to be more accurate than ^{131}I WBSs for detecting residual/recurrent disease in low-risk DTC populations (16–18). As for serum Tg assays, detection limits have markedly improved in the years (19), but the enhanced sensitivity is also associated with a high rate of false-positive results. In our

cohort, recurrence was ultimately diagnosed in only 1 of the 185 patients who had detectable Tg levels but no structural evidence of disease at the initial postoperative assessment. This experience, along with previous reports, confirms the low positive predictive value of Tg assays in the early stages of surveillance (13, 20, 21).

It should be emphasized that the time course of recurrences described in this study refers specifically to patients at low to intermediate risk of recurrence (by the ATA staging system) that subsequently had no structural or functional evidence of disease at the 1-year follow-up. Similar results may or may not be seen with higher-risk patients. In 2 recent studies, the rate of recurrence in ATA high-risk patients that achieved initial remission ranged from about 5 to 14% (9, 10).

With improved knowledge of the timing of PTC recurrences, we can begin to define more cost-effective surveillance protocols for PTC patients. Our data will hopefully serve as a springboard for prospective studies aimed at redefining the frequency of check-ups, the duration of surveillance, and the diagnostic tools that should be used in each phase. These questions, which involve the vast majority of thyroid cancer patients, have major implications for more rational distribution of health care spending. Using the right tools in the right patients at the right times, we will hopefully be able to offer more vigilant surveillance for the small (but by no means negligible) subset of thyroid cancer patients with substantial risks for recurrence and simpler but equally effective follow-ups for lower-risk patients.

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