Identification and Optimal Postsurgical Follow-Up of Patients with Very Low-Risk Papillary Thyroid Microcarcinomas

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Context: Most papillary thyroid microcarcinomas (PTMCs; $\leq$ 1 cm diameter) are indolent low-risk tumors, but some cases behave more aggressively. Controversies have thus arisen over the optimum postoperative surveillance of PTMC patients.

Objectives: We tested the hypothesis that clinical criteria could be used to identify PTMC patients with very low mortality/recurrence risks and attempted to define the best strategy for their management and long-term surveillance.

Design: We retrospectively analyzed data from 312 consecutively diagnosed PTMC patients with T1N0M0 stage disease, no family history of thyroid cancer, no history of head-neck irradiation, unifocal PTMC, no extracapsular involvement, and classic papillary histotypes. Additional inclusion criteria were complete follow-up data from surgery to at least 5 yr after diagnosis. All 312 had undergone (near) total thyroidectomy [with radioactive iodine (RAI) remnant ablation in 137 (44%) − RAI group] and were followed up yearly with cervical ultrasonography and serum thyroglobulin, TSH, and thyroglobulin antibody assays.

Results: During follow-up (5–23 yr, median 6.7 yr), there were no deaths due to thyroid cancer or reoperations. The first (6–12 months after surgery) and last postoperative cervical sonograms were negative in all cases. Final serum thyroglobulin levels were undetectable ($<$1 ng/ml) in all RAI patients and almost all (93%) of non-RAI patients.

Conclusion: Accurate risk stratification can allow safe follow-up of most PTMC patients with a less intensive, more cost-effective protocol. Cervical ultrasonography is the mainstay of this protocol, and negative findings at the first postoperative examination are highly predictive of positive outcomes. (***J Clin Endocrinol Metab*** **95: 4882–4888, 2010)**

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Abbreviations: ATA, American Thyroid Association; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasonography.

The increasing prevalence of papillary thyroid carcinomas less than 1 cm in diameter [*i.e.* papillary thyroid microcarcinomas (PTMCs)] is a world-wide phenomenon that poses continuous management challenges (1, 2). Many of these tumors are diagnosed incidentally after surgery for benign thyroid nodular disease; others are discovered by chance during cervical imaging studies performed for various reasons (1, 2). As noted in the recently published American Thyroid Association (ATA) guidelines for differentiated thyroid cancer (3), the optimal surveillance protocol for this group of patients has yet to be defined. On the whole, PTMCs have an excellent prognosis and carry a low risk for mortality (2). Most of these tumors display very indolent behavior, and cure rates as high as 100% have been reported, but in a minority of cases the tumor phenotype is more aggressive with lymph node and distant metastases at the time of diagnosis or during the early postoperative follow-up (4–6). For these reasons, controversies have arisen about the most effective management strategy for PTMCs (7–11).

Several risk factors have been identified that seem to be more or less strongly associated with a high-risk PTMC phenotype. The most reliable predictors include a family history of thyroid cancer, previous head and neck irradiation, multifocal tumors, extracapsular involvement, and aggressive variants of the papillary histotype (*e.g.* tall cell variant) (4–6, 12–17). Risk profiling based on these criteria could theoretically be used to tailor the postoperative management protocol to the individual patient's odds of developing recurrent/progressive disease. The absence of these characteristics should in fact be associated with a very low risk of progression and mortality, which could justify less aggressive treatment and a more relaxed follow-up protocol. This is the hypothesis addressed in the present study. We retrospectively analyzed a large cohort (n = 312) of PTMC patients whose risk for recurrence and mortality was estimated to be very low based on the absence of the risk factors listed above. All patients have been monitored for at least 5 yr (range 5–23 yr; median 6.7 yr) after primary treatment. The aims of our analysis were 2-fold: 1) to determine the actual risk of recurrence associated with this subgroup of PTMCs and 2) to define the best strategy for their management and long-term surveillance.

Subjects and Methods

Patients, management, and follow-up

Data for this retrospective study were collected from nine hospital-based referral centers for thyroid disease in Italy (including seven thyroid clinics and two nuclear medicine units). As shown in Fig. 1, 946 PTMC cases consecutively diagnosed in these centers over the last 2 decades were subjected to risk stratification. Study coordinators in each center identified a total of 710 patients (75%) who satisfied all the criteria listed in Table 1 (4–6, 12–17) and were therefore considered to be at very low risk for local recurrence or metastatic spread. The study population was drawn from this subset. It comprised the 312 patients with complete follow-up data from surgical diagnosis through the date of death or, in the absence of death, for at least 5 yr from the date of surgical diagnosis. For each case, an electronic form was filled out that provided information on the patient (including demographics, radiation exposure, family history of thyroid cancer); the tumor (including time of diagnosis and histological features); treatment (surgery, radioiodine ablation, levothyroxine therapy); and follow-up findings (including first and last cervical ultrasound findings, complete laboratory test results at the last follow-up visit, as detailed below, and case outcome). The study protocol was approved by the local ethics committee.

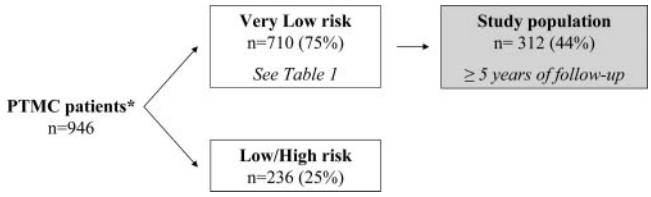

FIG. 1. Selection of the study population. *, PTMC patients in follow-up with available data for risk stratification.

All patients had undergone total or near-total thyroidectomy. In all cases, after the histological diagnosis had been made, the surgical specimen was cut into fine sections for microscopic examination to exclude the presence of other tumor foci. The decision to perform radioactive iodine (RAI) remnant ablation was left to the discretion of the team managing the case, which generally reflected institutional guidelines at the time the patient underwent surgery. In all cases, normal/suppressed TSH levels were maintained with levothyroxine (18). In all nine centers, follow-up was conducted according to the same basic protocol, which provided for an initial postoperative evaluation within 12 months after surgery and yearly visits thereafter (3, 19–22). Each visit included a physical examination and measurement of serum thyroglobulin (Tg), serum TSH, and Tg autoantibody titers, but the mainstay of the surveillance protocol was cervical ultrasonography (US), which is considered the most sensitive technique for detecting locally recurrent disease (23, 24). All examinations were performed by endocrinologists specialized in cervical US, using Color Doppler scanners with multifrequency

TABLE 1. Criteria for inclusion of PTMC patients in the very low-risk cohort

Criteria
1. No family history of thyroid cancer
2. No history of head and neck irradiation
3. Tumor staging: T1 1 cm or less, N0, M0
4. No extension beyond thyroid capsule
5. Unifocal
6. Not aggressive hystologic subtype (*e.g.* tall cell subtype)
7. Not locally invasive (angiolymphatic invasion)

TABLE 2. Characteristics of the very low-risk PTMC study population at the beginning of follow-up

Patient characteristics	Total cohort (n = 312)	Time of diagnosis			RAI remnant ablation		
		Preoperative (n = 73)	Postoperative (n = 239)	*P* value	Yes (n = 137)	No (n = 175)	*P* value
Sex, n (%)							
Male	35 (11.2)	9 (12.3)	26 (10.9)	ns	17 (12.4)	18 (10.3)	ns
Female	277 (88.8)	64 (87.7)	213 (89.1)		120 (87.6)	157 (89.7)	
Age at diagnosis (yr), median (range)	47.5 (17–81)	43 (17–68)	48 (19–81)	0.003	46 (17–71)	48 (24–81)	0.041
Time of diagnosis, n (%)							
Preoperative	73 (23.4)	73 (0)	0 (0)	N/A	47 (34.3)	26 (14.8)	<0.0001
Postoperative	239 (76.6)	0 (0)	239 (100)		90 (65.7)	149 (85.2)	
Tumor size (mm), median (range)	5 (0.5–10)	8 (2–10)[a]	5 (0.5–10)	<0.0001	6 (0.5–10)	5 (0.5–10)	0.001
Radioiodine ablation, n (%)							
Yes	137 (43.9)	47 (64.4)	90 (37.6)	<0.0001	137 (100)	0 (0)	N/A
No	175 (56.1)	26 (35.6)	149 (62.4)		0 (0)	175 (100)	

ns, Not significant; N/A, not applicable.

[a] In one case in the presurgical diagnosis subgroup, histological examination of the surgical specimen revealed a tumor diameter of 2 mm, whereas the presurgical cervical US study indicated a nodule about 5 mm in diameter. Given the suspicious US features of the nodule, fine-needle aspiration cytology was performed, and the result was suggestive of papillary thyroid cancer.

probes (7.5–12 MHz). Cervical lymph nodes were considered suspicious if they displayed any of the following: cystic appearance, punctate hyperechogenicity, and evidence of peripheral vascularization on color Doppler (25). Secondary criteria included absence of hilar hyperechogenicity, round shapes, or a short axis greater than 5 mm (25). All suspicious nodes were subjected to fine-needle aspiration cytology, and Tg levels were measured in the needle washout fluid (26). After 1997, aspirates were also assayed for Tg/TSH mRNA (27, 28). At each follow-up visit, the outcome was classified as positive or negative for persistent/recurrent disease on the basis of US findings and unstimulated serum Tg levels (3). In the presence of negative US findings in a patient who had undergone RAI remnant ablation, serum Tg levels were considered suspicious if they were within the detectable range of the assay used. [The latter varied over time and from center to center, but final Tg levels in all cases had been obtained with immunoradiometric assays (detection limit 1 ng/ml).] If RAI ablation had not been performed, suspicion was aroused when levels increased over time (3).

Statistical analysis

The follow-up variables analyzed included the outcomes of first and last cervical US examinations (suspicious lymph nodes/no suspicious lymph nodes); final Tg levels (≤1 ng/ml *vs.* >1 ng/ml); final TSH level (≤0.1, 0.1–0.4, 0.4–1, or >1 mIU/liter); Tg autoantibody titer status (positive *vs.* negative); and case outcomes at the end of follow-up (death due to thyroid cancer *vs.* persistent or recurrent disease *vs.* complete remission, determined as described above).

For the total cohort and cohort subgroups, median values were calculated for continuous variables, and differences between medians were evaluated with the independent-samples *t* test. Differences between categorical variables were assessed with the Fisher exact test. $P < 0.05$ was used as the cutoff for statistical significance. Analyses were performed using StatView 5.0.1 software (SAS Institute Inc., NC).

Results

Characteristics of the study population at tumor diagnosis

The characteristics of the study population at the beginning of follow-up are summarized in Table 2. Roughly three quarters (239 of 312) of the PTMCs had been diagnosed incidentally after surgery for multinodular goiter. The other 73 had been diagnosed preoperatively by fine-needle aspiration cytology. These latter tumors tended to be larger than those diagnosed postoperatively, and the patients who harbored them were younger. They were also more likely to have undergone RAI remnant ablation. On the whole, this procedure was performed in 137 patients (44% of the total cohort), and the median I^{131} dose administered was 73 mCi. In all cases, whole-body scans performed after ablation revealed RAI uptake confined exclusively to the thyroid bed.

Follow-up and clinical outcome in the study population

Table 3 summarizes the end-of-follow-up findings for the total cohort and subgroups defined on the basis of time of diagnosis and treatment with RAI. The length of follow-up ranged from 5 to 23 yr (median 6.7 yr). There were no significant differences related to the time of diagnosis, but follow-ups were significantly longer in the group that received RAI remnant ablation. None of the patients died of thyroid cancer or had to undergo further surgery. The first follow-up cervical US study (6–12 months after surgery) revealed no evidence of lymph node involvement in any of the 312 patients, and these findings were consistently confirmed

TABLE 3. Characteristics of the very low-risk PTMC study population at the end of follow-up

Patient characteristics	Total cohort (n = 312)	Time of diagnosis			RAI remnant ablation		
		Preoperative (n = 73)	Postoperative (n = 239)	*P* value	Yes (n = 137)	No (n = 175)	*P* value
Length of follow-up (yr), median (range)	6.7 (5–23)	6.3 (5–21)	6.8 (5–23)	ns	7 (5–22)	6.5 (5–23)	0.028
Final TSH level, n (%)							
≤0.1 mIU/liter	81 (26.0)	22 (30.1)	59 (24.7)	ns	30 (21.9)	51 (29.1)	ns
0.1–0.4 mIU/liter	93 (29.8)	24 (32.9)	69 (28.9)		45 (32.8)	48 (27.5)	
0.4–1 mIU/liter	63 (20.2)	11 (15.1)	52 (21.7)		32 (23.4)	31 (17.7)	
>1 mIU/liter	75 (24.0)	16 (21.9)	59 (24.7)		30 (21.9)	45 (25.7)	
Final serum Tg level, n (%)							
≤1 ng/ml	300 (96.2)	71 (97.3)	229 (95.8)	ns	137 (100)	163 (93.1)	0.001
>1 ng/ml	12 (3.8)	2 (2.7)	10 (4.2)		0 (0)	12 (6.9)	
Final Tg antibodies, n (%)							
Positive	8 (2.6)	2 (2.7)	6 (2.5)	ns	2 (1.5)	6 (3.4)	ns
Negative	304 (97.4)	71 (97.3)	233 (97.5)		135 (98.5)	169 (96.6)	
First cervical US, n (%)							
Suspicious nodes	0 (0)	0 (0)	0 (0)	N/A	0 (0)	0 (0)	N/A
No suspicious nodes	312 (100)	73 (100)	239 (100)		137 (100)	175 (100)	
Final cervical US, n (%)							
Suspicious nodes	0 (0)	0 (0)	0 (0)	N/A	0 (0)	0 (0)	N/A
No suspicious nodes	312 (100)	73 (100)	239 (100)		137 (100)	175 (100)	
Disease status, n (%)							
Persistence/recurrence	0 (0)	0 (0)	0 (0)	N/A	0 (0)	0 (0)	N/A
Remission	312 (100)	73 (100)	239 (100)		137 (100)	175 (100)	

ns, Not significant; N/A, not applicable.

in all cases by the results of subsequent annual follow-up visits and the final US examination. The negative predictive value of the initial US study was thus 100%.

Tg levels at the end of the follow-up period

Tg levels showed no correlation with TSH levels in either the RAI or non-RAI subgroup. At the end of follow-up, all 137 patients in the former group had undetectable serum Tg levels, which confirmed the disease-free status indicated by their cervical US findings. Interestingly enough, final Tg levels were also less than 1 ng/ml in most of the patients (163 of 175; 93%) who had not undergone RAI ablation (Table 3). The characteristics of the other 12 patients in this group are shown in Table 4. Their final serum Tg levels ranged from 1.3 to 6.0 ng/ml. In all 12 cases, the level had remained stable or decreased progressively during follow-up. The presence of residual thyroid tissue was clearly documented by cervical US, but none of the final scans showed any sign of lymph node involvement. Patient 12, whose final Tg level was particularly high (6.0 ng/ml), has been extensively investigated to rule out the presence of recurrent disease. After administration of

TABLE 4. Patients with detectable Tg levels at the last follow-up visit[a]

n	Sex	Age at diagnosis (yr)	Time of diagnosis	Tumor size (mm)	Final Tg (ng/ml)[b]	Final TSH (mIU/liter)	Follow-up (yr)
1	F	64	Postsurgical	2	1.3	0.03	8.3
2	F	41	Presurgical	9	1.4	1.78	6.3
3	F	56	Postsurgical	6	1.51	1.07	5.2
4	F	58	Postsurgical	8	1.8	1.3	5.8
5	F	49	Postsurgical	3	2.3	0.04	14
6	F	41	Presurgical	10	2.78	0.70	5.8
7	F	53	Postsurgical	10	2.8	2.1	19.9
8	F	65	Postsurgical	8	3.1	0.1	14.3
9	F	46	Postsurgical	3	3.3	0.11	8.4
10	F	51	Postsurgical	7	3.84	0.37	8.9
11	F	34	Postsurgical	8	3.97	5.1	20.4
12	F	47	Postsurgical	8	6	0.1	5.9

F, Female.

[a] None of these patients had undergone RAI remnant ablation.

[b] Serum Tg antibody titers were negative in all cases.

recombinant human TSH, his Tg level rose to 10 ng/ml, and the whole-body scan revealed uptake only in the thyroid bed (I^{131} uptake 2.5%). These findings, together with the absence of suspicious lymph nodes on cervical US, are very unlikely to be expression of persistent disease.

Discussion

For several years, the optimal management of PTMC has been a subject of debate (7–11). Extent of surgery, use of postoperative RAI remnant ablation and TSH suppression, frequency of follow-up, and methods used for surveillance all have obvious relevance for cost-effective health care management, but they also have important implications for the quality of the patient's life. Consequently, defining an optimal surveillance protocol for PTMC patients is becoming an increasingly high priority. Some experts have underlined the extremely indolent behavior of the majority of these small tumors, which argues for a more relaxed follow-up compared with that reserved for larger papillary thyroid cancers (PTCs) (8, 9). Others maintain that PTMCs should be managed exactly like classical PTCs because the two groups of tumors are basically no different in terms of rates of recurrence, extrathyroid extension, or case outcomes (10, 11). Although the prognostic significance of tumor size in general is widely recognized, it is becoming increasingly clear that this cannot be used as the only criterion for the risk stratification of PTC patients. It is inaccurate and misleading to regard all PTMC patients as having the same level of risk.

The criteria we used for risk stratification of our PTMC cohort are based on information that is readily available in all cases, *i.e.* tumor node metastasis staging, patient and family histories, and surgical histology (Table 1), and some of them have been incorporated into the ATA guidelines (3). The first major objective of our study was to assess the actual risk of the patient subgroup identified with these criteria, and our findings confirmed that PTMC patients who meet all of the prerequisites listed in Table 1 can be reliably considered to have a very low probability of disease recurrence. This conclusion is based on long-term follow-up of 312 patients for periods ranging from 5 to 23 yr, during which time there were no deaths due to thyroid cancer, and all of the patients met the ATA criteria for disease-free status (3). The decision to limit our analysis to cases with at least 5 yr of follow-up was based on the fact that most recurrences in PTMC patients are detected within the first 3 yr after surgery, and almost all relapses are diagnosed within the first 5 yr (29). We cannot exclude that occult tumor foci may require a longer follow-up period before becoming clinically detectable. However, about a quarter of our patients (24.3%) have been followed up for more than 10 yr, which represent a reliable period to detect recurrences.

The second objective of our study was to identify an optimal follow-up protocol for these very low-risk patients. One of the strong points of the present study is that all patients in the cohort underwent yearly cervical US examinations beginning 6–12 months after surgery. In the mid-1980s, our group pioneered the use of cervical US in the follow-up of all patients with neoplastic thyroid disease, and it was the mainstay of our surveillance protocol in the present study. Ultrasonography is widely available, rapid, and noninvasive, and its sensitivity and specificity in the detection of suspicious cervical lymph nodes are excellent (near 100% in most available studies) (24, 30–34). Furthermore, the aggressive behavior of PTMCs seems to be predominantly local: with the exception of a few anecdotal reports, distant metastases have rarely been reported in the absence of locoregional lymph node involvement, even after prolonged surveillance. Cervical US is particularly important in a cohort like the one described here, in which less than half of the patients had undergone RAI ablation. In these cases, detectable serum levels of Tg may be produced exclusively by the small amount of completely normal thyroid tissue left after surgery. Therefore, absolute Tg levels are unreliable markers of recurrent or residual disease if less than total thyroidectomy is done. This situation is becoming more and more common because RAI adjunct therapy is being used less frequently. (As shown by the fact that in Table 3, follow-ups for the RAI subgroup were significantly longer because this type of therapy was more common among the older cases in our cohort.) It is important to note, however, that even when RAI remnant ablation has been performed, a thorough sonographic examination of the neck can sometimes detect local recurrence before the serum Tg reaches detectable levels (24).

In our cohort of very low-risk PTMC patients, the yearly US examinations were consistently negative, even in the 76 cases (24.3%) that were followed up for more than 10 yr. This experience indicates that in the vast majority (about 75%) of all PTMC cases, effective postoperative surveillance can be based exclusively on cervical US. In addition, the initial postoperative studies displayed a negative predictive value of 100% for persistent/recurrent disease (for postsurgery intervals of up to 23 yr). This suggests that yearly US examinations are probably unnecessary in these patients, at least after the first 5 yr of follow-up, *i.e.* the interval during which most recurrences occur (29). The Tg levels observed in our cohort at the end of the study challenge the conventional justification for the use of adjuvant postoperative RAI

treatment, *i.e.* that it allows Tg levels to be monitored as a marker of recurrence. Indeed, final Tg levels were below the detection limit in all patients who had undergone remnant ablation, which confirms the validity of negative sonographic findings, but the same result was also observed in the vast majority of patients who had not received postoperative ablation. This finding is consistent with previous reports, which indicate that Tg levels in PTC patients decrease progressively over the first 2–3 yr after thyroidectomy (24, 21, 35), even when RAI remnant ablation is not used. The temporal characteristics of this decline probably depend on the amount of thyroid tissue left after surgery.

It is important to stress that the findings reported here are based on retrospective analyses. Ideally, they need to be confirmed in a randomized prospective study.

In conclusion, this long-term follow-up (median 6.7 yr) of more than 300 consecutive patients shows that, with a simple set of clinical criteria, we can reliably identify those patients with PTMC who are most likely to experience complete cures with total or near-total thyroidectomy. In these patients, who appear to represent approximately 75% of all PTMC cases, postoperative RAI remnant ablation and TSH suppression are not necessary, and the single most important component of the postsurgery surveillance protocol is cervical US performed by an experienced operator. Negative findings at the first postoperative scan are highly predictive of a favorable outcome, so yearly examinations at least after 5 yr are probably not required. Therefore, with effective risk stratification, the majority of PTMC patients can be safely followed with a protocol that is less intensive and more cost effective.

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