

Active Surveillance in Papillary Thyroid Microcarcinomas is Feasible and Safe: Experience at a Single Italian Center

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Abstract

Context

The dramatic rise in the incidence of thyroid cancer over the last 30 years is largely attributable to the increasing diagnosis of papillary microcarcinomas (mPTCs). Current guidelines endorse an observational management approach in properly selected cases.

Objective

To evaluate the feasibility of active surveillance in mPTC in Italy, its impact on real life, and to identify risk factors of progression.

Design and setting

In 2014 we started a prospective–observational study of active surveillance in mPTC patients.

Patients

Included patients demonstrated a single Thy4 or Thy5 thyroid nodule, with largest diameter ≤ 1.3 cm, and no suspicious laterocervical lymph nodes by neck ultrasonography. Of 185 eligible subjects, 50.3% (93/185) enrolled in the observational management protocol while the others opted for surgery and were excluded from this analysis.

Intervention

Enrolled patients were followed with neck ultrasound at 6- to 12-month intervals. Disease progression was defined as the appearance of abnormal lymph nodes or nodule enlargement during follow-up. In these cases, patients were directed to surgery.

Results

Three patients (3/93, 3%) showed clinical progression and required surgery. Another 19 patients (19/93, 20%) decided to transition to surgical intervention even though there was no evidence of disease progression. All operated patients had excellent response to initial treatment despite the delayed surgery.

Conclusions

Within an Italian medical context, active surveillance appears to be a feasible and safe alternative to immediate surgery in healthy mPTC patients. Only 3% of mPTC demonstrated disease progression during a median follow-up of 19 months (range 6–54) and importantly demonstrated excellent outcomes after surgical intervention in a short-term follow-up.

Over the past 30 years the incidence of thyroid cancer (TC) has dramatically increased (1). Such an increase can be attributed mostly to micro (≤ 1 cm) papillary thyroid carcinoma (mPTC). Despite this impressive increased incidence, mortality from PTC has remained stable (1). It is conceivable that the widespread use of neck ultrasound (nUS), and fine needle aspiration cytology (FNAC) led to the detection of subclinical TC which would have no clinical relevance for a person's survival (2). Recently, the U S Preventive Services Task Force has given TC screening a D grade (3), recommending against screening for TC in asymptomatic people since it results in harms that outweigh the benefits. Similarly, the American Thyroid Association (ATA) guidelines (4) do not recommend FNAC for any thyroid nodule ≤ 1 cm, no matter how suspicious it appears on a nUS image.

In the past, patients with mPTC were treated as aggressively as any other PTC with potential surgical morbidity and lifelong replacement therapy. Nowadays, there is controversy over the treatment of such low-risk cancers and active surveillance was proposed in the last ATA guidelines (4) as an alternative to immediate surgical treatment especially in frail and/or older patients. It is worth noting that an active surveillance strategy has recently been demonstrated to be a viable management option for several other low-risk cancers, such as prostate cancer (5), ductal breast cancer in situ (6), and pancreatic neuroendocrine tumors (7). Previous retrospective analyses (8–10) have shown that patients with mPTC could be followed and left untreated until the evidence of tumoral growth, with no observed risk increase for mortality. However there is no consensus on how to manage patients with mPTC and how to select those who may enter an active surveillance program (11). The aim of the present observational, nonrandomized trial was to evaluate the feasibility of the active surveillance strategy in adult mPTC patients, regardless of their age and/or frailty, the impact of this strategy in real life, the progression rate of mPTC patients who entered an active surveillance strategy, and to identify possible risk factors for mPTC progression. The study hypothesis was that deferring the surgical treatment in these patients is safe, at least in a short-term follow-up.

Patients and methods

Patients

Starting in November 2014, patients with a thyroid nodule ≤ 1.3 cm at nUS and cytological diagnosis or suspicious for PTC were asked to participate in an active surveillance program approved by our local ethics committee. Although the definition of mPTC is for nodules ≤ 1 cm, the size cut-off was set at 1.3 cm on the basis of wide echographic variability and shrinkage of paraffin-fixed tissue that usually cause an underestimation of histological measures. Inclusion criteria were patients older than 18 years; a Thy 4 or a Thy 5 thyroid nodule, according to the Italian Consensus

for thyroid cytology (12), corresponding to Bethesda V or VI classes (13); a single thyroid malignant (or suspicious) nodule. The other nodules, if present, were confirmed benign by FNAC.

Exclusion criteria were patients younger than 18 years; Thy 4 or Thy 5 thyroid nodule larger than 1.3 cm in maximal dimension or in multinodular goiter with confluent and not well measurable nodules; thyroid nodules with cytological results other than Thy 4 or Thy 5; nodules with clinical or nUS evidence of extrathyroidal extension or regional or distant metastases; thyroid dysfunction due to hyperthyroidism or the presence of concomitant antithyroid drugs; previous history of thyroid surgery.

All patients who accepted to participate in this program signed an informed consent at study entry. The appearance of metastatic lymph nodes, confirmed by cytology and thyroglobulin (Tg) measurement on the wash-out of the needle used for FNAC, or an increase in size more than 3 mm for each nUS diameter of mPTC confirmed on 2 consecutive occasions were considered indications to transition from active surveillance to surgical intervention. The withdrawal of consent for continued observation was also a criterion for interrupting the active surveillance and recommending surgical intervention. At enrollment, past medical history was assessed; a physical examination and the nUS were performed; a blood sample was collected to evaluate thyroid function and serum Tg levels. Serum calcitonin (CT) was measured to exclude medullary thyroid cancer.

After enrollment, patients performed regular evaluations in our institute every 6 months for the first 2 years and then yearly; evaluations were performed by the same 3 oncology-trained endocrinologists and consisted of nUS and blood samples. Chronic autoimmune thyroiditis was diagnosed according to standard criteria: the presence of autoantibodies and/or a hypoechoic and dishomogeneous echographic pattern (14). Levothyroxine (LT4) therapy was administered, or maintained, in hypothyroid patients to obtain a thyroid-stimulating hormone (TSH) level within the normal range. With the permission of enrolled patients, FNAC was repeated once during the observational period in order to collect samples for DNA analysis.

Methods

Neck ultrasound

nUS was performed using a real-time instrument (Esaote SPA, My Lab 50 machine with a 7.5–12 MHz linear transducer). During the follow-up, nodules and suspicious lymph nodes in neck stations were inspected. nUS was performed by the same 3 independent US-trained endocrinologists (E.M., L.P., and M.C.C.). Accurate descriptions of echogenicity, microcalcifications, integrity of halo, lengths of all diameters, location of the nodule in the thyroid lobe, and the volume of the nodule calculated using the ellipsoid formula (ie, $d1 \times d2 \times d3 \times \pi/6$) were recorded in a computerized database.

FNA and cytological diagnosis

FNAC was performed under US guidance using a 23-gauge needle attached to a 10-mL syringe. The material was air dried, stained with Papanicolaou and Giemsa, and interpreted by two experienced cytopathologists (F.B. and L.T.). The adequacy of aspirates was defined according to the guidelines of the Papanicolaou Society (15). Results of cytology were classified according to the Italian Consensus classification (12).

Histopathologic examination

Surgical samples of cases that underwent thyroidectomy were accurately described (weight, shape, color, and cut surface) and analyzed by two independent pathologists (F.B. and L.T.). The entire circumference of nodules was sampled. Samples were also made for each centimeter of extranodular parenchyma. Formalin-fixed, paraffin-embedded tissues obtained from thyroid sampling of each case were stained by hematoxylin and eosin (16). The histological diagnosis was made according to the World Health Organization guidelines (17).

Biochemical assays

TSH was evaluated by a chemiluminescent assay, as Immulite 2000 (Siemens Healthcare, Gwynedd, UK); serum Tg was measured using a high-sensitive chemiluminescent assay, (Beckman Coulter, Fullerton, CA, USA); serum CT was assessed by a chemiluminescent assay (Immulite 2000, Siemens Healthcare, Gwynedd, UK). Serum thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were measured by a fluorescence enzyme immunoassay (AIAPack 2000; Tosoh Corporation, Tokyo, Japan).

Statistical analysis

Differences between groups were compared using either Student's t or chi-square test, as appropriate. Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median and range. Statistical significance was set at $P < .05$. The Statistical Package for the Social Sciences (IBM, SPSS Statistics, version 21) was used for analysis.

Results

From November 2014 to November 2018, 185 eligible patients were identified and 93 (50%) enrolled in the study. The number of screened and enrolled patients increased over the years, with an increasing rate of enrolled patients with respect to screened ones of 10% per year. They have been followed for a median of 19 (range 6–54) months. Of the entire cohort, 72/93 (77%) were females and 21/93 (23%) were males (F:M = 3.4:1), with a mean age of 44 years $\pm$ 15 (range 18–82 years). Previous neck irradiation for other hematologic or solid tumors was reported in 3/93 (3%) patients, whereas 10/93 (11%) patients reported a family history of TC. As required by protocol, LT4 therapy was administered, or continued, in 16/93 (17%) cases for the evidence of hypothyroidism. Thy 4 and Thy 5 cytological classes were equally distributed in our series [Thy 4: 51/93 (55%); Thy 5: 42/93 (45%)]. In 44/93 (47%) of the cases, the mPTC was localized near the thyroid capsule (ie, within 3 mm of the thyroid capsule). Microcalcifications [38/93 (41%)], hypoechogenicity [83/93 (89%)] and irregular margins [52/93 (56%)] were the most frequent nUS characteristics of mPTC. The clinical features of the patients enrolled and the nUS pattern of their mPTCs are summarized in Table 1 and in Table 2, respectively.

Despite the stability of mPTC at nUS examination and no evidence of metastatic lymph nodes, 19/93 (20%) patients withdrew their consent from the study (drop-out group) for personal reasons, after a short time of observation (median follow-up of this subgroup: 8 months, range 6–31) (Fig. 1, blue bars). When we compared the epidemiological and clinical features of patients who dropped out and those who continued the follow-up (Table 3) we observed that the thyroid volume was significantly larger in the drop-out group and the percentage of patients whose thyroid nodule was diagnosed at least 1 year before enrollment in the present study was significantly higher in the drop-out group. No difference of US features was observed between the 2 groups (Table 4) except for thyroid capsule proximity that was less frequent in the drop-out group. Nine patients of the drop-out group were operated in our hospital: in all of them the diagnosis of PTC was confirmed. The histological variants were classical in 7/9 cases, follicular in 1/9, and tall cell in 1/9. In 2 cases there was a minimal extrathyroidal extension. In 3 cases thyroid remnant ablation was performed with low activity of radioiodine (1100 MBq). At the time of this study, after a median follow-up of 22 months (range 11–34) all patients showed an excellent response to the treatment and are considered to be in clinical remission (18).

As shown in Fig. 1 (red bars), 3/93 (3%) patients in the active surveillance strategy showed mPTC progression. All of them were Thy 4 nodules. In particular, one patient (Patient A) showed the appearance of metastatic lymph nodes of laterocervical compartment 12 months after enrollment, while the other two (Patients B and C) showed an increase in nodule dimension more than 3 mm in each diameter after 13 and 23 months of follow-up, respectively. Management and clinical and histological characteristics of these three mPTCs patients are reported in Table 5. It is worth noting that patient A, who developed abnormal lymph nodes had a tall cell variant of PTC and for this

reason also required radioiodine treatment. This patient showed an excellent response to the initial treatment as did the other two, who did not require the radioiodine ablation, after a median follow-up of 18 (6–36) months.

At present, 71/93 (76%) of enrolled patients are still in follow-up [median 24 (6–54) months]. With only 3 cases demonstrating disease progression, statistical comparison with the stable cohort ($n = 71$) was not informative. Nevertheless, while not statistically significant, a review of the epidemiological, clinical, and pathological features of the 3 progressing cases (Table 5) showed that the 2 that progressed in size had the largest tumor volume, both at enrollment and at last follow-up.

We also evaluated the change in mPTC volume during follow-up, since there is evidence to suggest that serial volume determinations can also be used to assess tumor growth over time. In our series 15/93 (16%) cases showed an increasing volume varying from 50% to 251% but only 2 of these cases (2.1%) (Patients B and C) showed a consistent increase of 3 mm in all dimensions in 2 consecutive controls. The remaining 13 cases demonstrating a significant increase in tumor volume are still under observation.

Discussion

An active surveillance strategy has been recently proposed for patients diagnosed with mPTC (8, 9, 19), particularly for older and/or frail subjects. In the largest study on active surveillance conducted in Japan, 55% of patients with mPTC accepted an active surveillance strategy (20). Consistent with the Japanese experience, our data also demonstrates that 50% of our eligible mPTC patients agree to participation in an active surveillance monitoring prospective protocol. Moreover, we observed that the number of patients who accepted to participate in the study has been increasing over the years, thus demonstrating that active surveillance is becoming an appealing management option of these low-risk PTC patients in our country too.

The Japanese studies (8, 9, 19) have consistently shown that patients demonstrating disease progression during active surveillance had an excellent outcome with no impact on survival as a result of delayed surgical intervention, with 10-year lymph node recurrence-free survival rate, distant recurrence-free survival rate, and cause-specific survival rate of 99%, 100%, and 100%, respectively (21). In our study the number of patients who progressed is rather small and no definitive conclusions can be drawn. Our results are consistent with the low incidence of disease progression during early follow-up in previous reports on active surveillance.

Currently, strong resistance to adopt an observational management strategy is still present among some physicians, particularly among surgeons. One study surveying thyroid surgeons found that 100% recommended surgery for mPTC on initial patient consultation, and 99% continued to recommend surgery after active surveillance was introduced as an option (22). Our study confirms that delayed surgery is not associated with a worse response to the initial treatment, at least in a short-term follow-up. Thus, the study supports the concept that active surveillance can be considered a viable alternative to immediate surgical treatment and may be the only strategy to avoid complications from unnecessary surgery (23). Results from a longer period of observation of both our and other patients enrolled in similar studies (24) are needed to verify these important initial observations.

In our series, after a mean follow-up of 19 months (range 6–54) of active surveillance, only 1 patient out of 93 (1.1%) developed lymph node metastases. This prevalence is consistent with that reported by Sugitani et al. (19), who showed metastases to cervical lymph nodes in 1.40% and 3.45% after 5- and 10-year follow-ups, respectively. The patient who developed metastatic lymph nodes had an aggressive variant (ie, tall cell variant) at histology, but delayed surgery and radioiodine treatment did not have any impact on the short-term outcome since the response to the initial treatment had been excellent. The group of patients that decided to transition to surgical intervention despite the stability of the nodule also showed excellent outcomes, at least in a short-

term follow-up, reinforcing the concept that delaying surgery, varying in this group from 6 to 31 months, did not affect prognosis.

On the basis of previous experience (8, 9, 19) recommendations for surgical intervention was given when tumor diameter increased by 3 mm, consistent with an arbitrary cut-off based on the most available data in the field (8, 9, 19). According to this criterion we had only 2 patients who progressed and were submitted to surgery. However, we observed a larger group of patients (n = 15) with a significant increase as determined by changes in tumor volume (including Patients B and C). These results are in keeping with those reported by Tuttle et al. (25), who also found a higher number of cases with a 50% volume increase but only a few with an increase of >3 mm in diameter. The question of whether it is better to consider the increasing diameters or the increasing volume is still to be answered and only the follow-up of the cases with the increasing volume >50% will tell us if and when they will reach the 3-mm threshold in 2 consecutive controls and if this criterion should be used to guide recommendations for transition to surgical intervention.

Regarding the volume of the nodules, we observed that the two cases that progressed for increasing diameters had greater volume both at baseline and at time of surgery with respect to the mean volume of the stable nodules. We are conscious that the number of progressing cases in our series is too small to draw any conclusion but, according to this observation, the volume of the nodules at enrolment in observational studies might play a prognostic role. Larger studies examining more progressing cases and longer follow-up are needed to clarify its potential predictive role for progression.

As expected, the clinical value of Tg as a progression marker is null in this setting due to the presence of thyroid in site, and should not be assessed in future similar studies (26, 27). Unfortunately, no other biomarker of disease progression is available to date. With the aim of finding some significant marker we are now collecting data on the genetic profile of these mPTC that will be correlated with the progression of the disease.

While 50% of screened patients opted to enroll in our surveillance program, 20% of them dropped out after a median follow-up of 8 months (range 6–31). We did not find relevant differences in the epidemiological and clinical features of these patients with respect to those who continued surveillance, with the exception of a higher prevalence of thyroid nodular disease with a diagnosis performed at least 1 year before and a bigger thyroid volume that could at least in part justify the surgical option. These patients decided for personal reasons, family pressures, or other physicians' advice to opt for surgical treatment. The evidence that the majority of them abandoned surveillance after a few months from enrolment suggests that a strong motivation is needed to continue observation. Moreover, the protocol should not be too stressful for patients; to avoid a stressful program, we decided to submit our patients to the FNA only once and to nUS every 6 months for 2 years and then yearly. These time points could even be delayed up to once a year, if the long-term follow-up confirms the safety of this strategy. We also hope that this study, particularly when sufficient long-term follow-up of these patients is reached, will reassure the scientific community about the indolent behavior of mPTC and discourage continued routine FNAC evaluation of suspicious thyroid nodules ≤1 cm as already suggested by the ATA guidelines (4) but, at present, disregarded by most community centers (28).

Some limitations have to be acknowledged in the present study. First, the study was conducted in a tertiary referral center for TC in Italy and does not reflect everyday life of clinical management of these patients. Quality of life of a patient unable to sustain the burden of cancer diagnosis can be very poor and a quality-of-life questionnaire should be given to all eligible patients in order to analyze in detail reasons for their potential discomfort and understand reasons for dropping out. Unfortunately a quality-of-life questionnaire was not envisioned in the original protocol, but, from these results, the new enrolled patients will undergo a thyroid cancer-specific quality-of-life questionnaire (29) and, likely, a psychological evaluation. Nevertheless, patients considering active surveillance can be informed that, although it is expected to experience a certain degree of anxiety at first, there is a rapid adjustment that can revert anxiety to low levels within 2 years, as well demonstrated in 413 men with low-grade localized prostate cancer who were enrolled in an active surveillance program (30). One year after beginning the surveillance, the prevalence of prostate

cancer-specific anxiety was 29%; it dropped to about 20% at 5 years and to 15% for patients followed for as long as 7 years. Recently, similar results were observed in a large sample of thyroid cancer patients in Japan. These authors show that the level of worry decreases over time, and that patient-specific support helps in managing anxiety (31).

Another limit of the study is that it is not randomized and the control group is formed by those patients who immediately refused the active surveillance program and were surgically treated. We are conscious of this limitation but our ethics committee did not allow a blinded randomized study to be performed. This should be possible in the future if the active surveillance program is officially recognized as a comparable strategy of cure in clinical practice. Finally, it may appear that the sample size is relatively small. However, TC is a rare neoplasm, mPTC represents 40% of the thyroid cancer cases, and active surveillance is a novel approach to cancer management. When considering that only 50% of mPTC accepted active surveillance, our sample, collected at a single center, can be considered remarkable.

In conclusion, our data show that an active surveillance strategy is safe and feasible in a large set of patients with mPTC not restricted just to patients who may be at increased surgical risk because of their age and health frailty. To our knowledge this is the first reported experience on this specific topic, after the Japanese studies, showing that a conservative approach, accepted only in Japan to date, is also feasible in our country and with no major risks for our patients. Only 3% of mPTC patients demonstrated disease progression and delayed surgery did not impact on the excellent results of the treatment, even when radioiodine treatment was required. Additional studies are needed to address the impact of an active surveillance for a malignant disease on quality of life of patients with mPTC. Moreover, more work is needed from the scientific community to provide additional quality data to reassure not only patients, but also their physicians, on the safety of this approach (32).

Abbreviations

ATA: American Thyroid Association

CT: calcitonin

FNAC: fine needle aspiration cytology

LT4: levothyroxine

mPTC: papillary microcarcinoma

nUS: neck ultrasound

TC: thyroid cancer

Tg: thyroglobulin

TSH: thyroid-stimulating hormone.

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Table 1. Epidemiological and clinical features of enrolled patients at baseline.

Gender	Female: 72/93 (77%) Male: 21/93 (23%) F/M: 3.4/1
Age (mean $\pm$ SD)	44 $\pm$ 15 years
<40 years, n (%)	37/93 (42)
Previous neck radiotherapy, n (%)	3/93 (3)
Family history of thyroid cancer, n (%)	10/93 (11)
Chronic autoimmune thyroiditis, n (%)	19/93 (20)
Levothyroxine therapy, n (%)	16/93 (17)
TSH (mean $\pm$ SD)	1.4 $\pm$ 0.8 mU/L
Thyroglobulin (mean $\pm$ SD)	11 $\pm$ 10 μ g/L
Thyroid volume (mean $\pm$ SD)	11.3 $\pm$ 4.7 mL
Patients with detectable TgAb, n (%)	19/93 (20)
Diagnosis of thyroid nodule at least 1 year before enrollment, n (%)	50/93 (54)
Time elapsing (years) from first diagnosis and enrollment (mean $\pm$ SD)	3.3 $\pm$ 2.9 years
Follow-up (median, range)	19 (6–54) months

Table 2. US features of Thy4 and Thy5 nodules of enrolled patients at baseline.

Mean $\pm$ SD diameter at baseline	9.4 $\pm$ 2.5 mm
Mean $\pm$ SD diameter at last follow-up	9.8 $\pm$ 3.3 mm
Mean $\pm$ SD volume at baseline	0.33 $\pm$ 0.24 mL
Mean $\pm$ SD volume at last follow-up	0.39 $\pm$ 0.3 mL
Thyroid capsular proximity ^a , n (%)	44/93 (47)
Microcalcifications, n (%)	38/93 (41)
Hypoechogenicity, n (%)	83/93 (89)
Irregular margins, n (%)	52/93 (56)
Multinodular, n (%)	31/93 (33)
Cytological results, n (%)	Thy4: 51/93 (55) Thy5: 42/93 (45)

^aThyroid capsular proximity is defined as a lesion located near the thyroid capsule, within 3 mm abutting the capsule.

Table 3. Epidemiological and clinical features of patients who spontaneously dropped out and those who continued the follow-up

	Drop out group (n=19)	Follow-up group (n=74)	P
Gender (n,%)	Female: 14/19 (74%) Male: 5/19 (26%) F/M: 2.8/1	Female: 58/74 (78%) Male: 16/74 (22%) F/M: 3.6/1	.66
Age (mean $\pm$ SD)	44 $\pm$ 19 years	44 $\pm$ 15 years	.96
<40 years, n (%)	8/19 (42%)	29/74 (39%)	.81
Previous neck radiotherapy, n (%)	0	3/74 (4)	.37
Family history of thyroid cancer, n (%)	2/19 (11)	8/74 (11)	.97
Chronic autoimmune thyroiditis, n (%)	2/19 (11)	17/74 (23)	.23
LT4 therapy, n (%)	1/19 (5)	15/74 (20)	.12
TSH (mean $\pm$ SD)	1.2 $\pm$ 0.8 mU/L	1.4 $\pm$ 0.8 mU/L	.29
Thyroglobulin (mean $\pm$ SD)	11 $\pm$ 7 μ g/L	11 $\pm$ 10 μ g/L	.98
Thyroid volume (mean $\pm$ SD)	13 $\pm$ 5 mL	11 $\pm$ 5 mL	.04
Patients with detectable TgAb, n (%)	3/19 (16)	16/74 (22)	.3
Diagnosis of thyroid nodule at least 1 year before enrollment, n (%)	16/19 (84)	34/74 (46)	.003
Time elapsing (years) from first diagnosis and enrollment (mean $\pm$ SD)	4 $\pm$ 2.9 years	3 $\pm$ 2.8 years	0.23

Table 4. Ultrasound features of Thy4 and Thy5 nodules of patients who spontaneously dropped out and those who continued the follow-up.

	Drop out group (n=19)	Follow-up group (n=74)	P
Mean $\pm$ SD diameter at baseline (mm)	10 $\pm$ 2.3	9.2 $\pm$ 2.5	.15
Mean $\pm$ SD diameter at last follow-up (mm)	10.5 $\pm$ 2.8	9.6 $\pm$ 3.4	.31
Mean $\pm$ SD volume at baseline (mL)	0.41 $\pm$ 0.26	0.31 $\pm$ 0.23	.13
Mean $\pm$ SD volume at last follow-up (mL)	0.44 $\pm$ 0.35	0.38 $\pm$ 0.37	.54
Thyroid capsular proximity ^a n (%)	4/19 (21)	40/74 (54)	.01
Microcalcifications, n (%)	9/19 (47)	29/74 (39)	.52
Hypoechoogenicity, n (%)	17/19 (89)	66/74 (89)	.97
Irregular margins, n (%)	10/19 (52)	42/74 (56)	.74
Multinodular, n (%)	6/19 (31)	25/74 (33)	.85
Cytological results, n (%)	Thy4: 10/19 (53) Thy5: 9/19 (47)	Thy4: 41/74 (55) Thy5: 33/74 (45)	.83

^aThyroid capsular proximity is defined as a lesion located near the thyroid capsule, within 3 mm abutting the capsule.

Table 5. Epidemiological, clinical, and pathological features of patients with disease progression.

	Patient A	Patient B	Patient C
Age at diagnosis, years	51	36	33
Gender	F	F	F
Thyroglobulin, µg/L	10	21	2
TgAb	Undetectable	Undetectable	Undetectable
Thyroid volume, mL	10	10	15
Maximum diameter at baseline, mm	9	13	13
Maximum diameter at last follow-up, mm	8	18	18
Nodule volume at baseline, mL	0.22	1.1	0.8
Nodule volume at last follow-up, mL	0.26	2.1	1.6
Nodule's echography pattern	Hypoechoic, irregular margins	Hypoechoic, irregular margins, microcalcification	Hypoechoic, microcalcification
Thyroid subcapsular proximity ^a	Yes	yes	yes
Cytology	TIR4	TIR4	TIR4
Follow-up under active surveillance, months	12	13	23
Surgery	Total thyroidectomy and lymphadenectomy of laterocervical compartment	Total thyroidectomy	Total thyroidectomy
TMN (8° edition)	T1b(m)N1bM0	T1bNXMX	T1bNXMX
Histological variant of PTC	Tall cell	Classic	Classic
Maximum diameter histology (mm)	13	17	17 m
Remnant radioablation	Yes (activity 1100 MBq)	No	No
Follow-up after surgery, months	36	12	6
Outcome	Excellent response	Excellent response	Excellent response

^aThyroid capsular proximity is defined as a lesion located near the thyroid capsule, within 3 mm abutting the capsule.

Figure 1. Waterfall graph showing the story of each patient enrolled in the study. The different colors distinguish patients who continued active surveillance program (green bars), from those with a disease progression (red bars) and patients who opted for thyroid surgery despite the clinical stability (blue bars). The length of the bars represents the duration of follow-up.

