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Original Article

Optimization of follow-up in patients with papillary thyroid cancer who show no evidence of disease 9–12 months after treatment

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Abstract

Background: Papillary thyroid cancer (PTC) has an excellent prognosis, and recurrence is rare in patients with no evidence of disease (NED) after initial treatment. Despite this, several guidelines recommend long and costly follow-up, with limited evidence of improved patient outcomes. This study aims to examine the value of follow-up in patients with NED after treatment for PTC, by determining the rate of recurrence, recurrence-associated morbidity, and death, and whether any recurrence was diagnosed through the follow-up programme.

Methods: Patients operated for PTC at Lund University Hospital between January 2004 and December 2016 were eligible. Patients with T1a N0/NX were excluded as well as patients with any other thyroid malignancy. Data were collected retrospectively by searching the patients' medical records. NED was defined as thyroglobulin less than 1 ng/ml, thyroglobulin antibodies less than 20 kIU/l, and negative imaging. Biochemical recurrence was defined as thyroglobulin greater than 1 ng/ml, and/or thyroglobulin antibodies greater than 20 kIU/l. Structural recurrence was defined as a strong suspicion of recurrence on imaging and/or histological proof of recurrence.

Results: Out of a cohort of 187 patients, there were 90 patients with NED who were followed for a median of 6.3 years. Three patients had biochemical recurrence; none of them had symptoms, nor were they treated for their recurrence. Three had structural recurrence; all were above 75 years old and only one was diagnosed through the follow-up programme. No patient died of PTC; five patients died during the follow-up.

Conclusion: Follow-up as it is designed today cannot identify recurrences accurately and seems to be of questionable benefit in younger patients with NED after treatment for PTC.

Introduction

Papillary thyroid cancer (PTC) is the most common malignancy of the thyroid, and its incidence is rising[1]. Despite this, the mortality rate has remained low, and the prognosis is excellent[2]. PTC is treated by surgery with or without postoperative radioiodine treatment. After treatment, PTC can recur, most often in locoregional lymph nodes, but there is also a risk of distant metastasis after treatment. Previous studies have indicated that the recurrence rate for PTC is high and that it can occur a long time after initial treatment[3–5]. Recurrence rates were also shown to be higher in patients with more advanced disease at diagnosis, that is higher-stage disease[3–5]. However, more recent studies have shown that when stratifying patients according to their treatment response, the recurrence rate in patients with no evidence of disease (NED) after treatment is very low, including patients with advanced disease at diagnosis[6–11]. Despite this, most guidelines still recommend long follow-up[12–16]. Furthermore, guidelines also recommend suppression treatment with levothyroxine, resulting in iatrogenic hyperthyroidism. Suppression treatment results in low levels of thyroid-stimulating hormone, which has been shown to reduce recurrence risk[17–19], but it has also been associated with long-term adverse effects, such as an increased risk of atrial fibrillation and osteoporosis[20,21]. Thus, the present guidelines may lead to overtreatment and unnecessary follow-up of patients with NED after treatment for PTC. It also seems that previous results have not been fully implemented in clinical guidelines. Therefore, this study aimed to determine if follow-up is necessary for patients with NED after initial treatment by investigating the risk of recurrence and death. The study also aimed to identify risk factors for recurrence and to examine whether the recurrences were found inside or outside the follow-up programme.

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Methods

Study design and included patients

A single-centre retrospective observational study was performed at Skåne University Hospital Lund, Sweden. This unit is a tertiary referral centre for patients with malignancy in the thyroid. Patients who had primary surgery for PTC between 1 January 2004 and 31 December 2016 were included. Patients with a postoperative histopathological diagnosis of any other malignancy in the thyroid, such as follicular, medullary, anaplastic, poorly differentiated, or other cancers, were excluded. Patients who were lost to follow-up, that is patients who moved to another healthcare region, were excluded, as were patients with stage T1a N0/X, since the current Swedish guidelines indicate that the latter group should not be followed up due to a very low risk of recurrence[22].

Data collection

Patients were identified by cross-linking data from two clinical registers: the Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery (SQRTPA) and INCA, the Swedish national register for thyroid cancer[23,24]. SQRTPA has registered patients since 2004 and INCA since 2015 in Skåne. Registration in SQRTPA is carried out after written informed consent is given by patients. After identification of patients, data for the present study was further added by searching patients' electronic hospital records and entered into a specific database for the study. This study was approved by the regional ethics committee (DNR 2019–02060) as well as the committee for matters regarding quality registers, medical databases and preparation in Skåne Region (case number 130–139), both of which waived the need for further patient consent.

The variables collected from hospital records, SQRTPA and INCA were: age at diagnosis, sex, date of surgery, TNM stage, multifocality, the extent of primary treatment, disease status including unstimulated thyroglobulin (Tg) levels, thyroglobulin antibodies (TgAb) levels, imaging at the follow-up visit 9–12 months after treatment and at all other follow-up visits afterwards, type and treatment of, and status after, recurrence if any, disease status after treatment of recurrence, whether the recurrence was found through the follow-up programme or not, and cause of death in patients who died during follow-up.

Swedish national guidelines for papillary thyroid cancer

The patients included in this study were treated and followed up according to the Swedish national guidelines for PTC. The first national guidelines for PTC in Sweden were published in 2012. They were based on the guidelines published by ETA in 2006[25]. According to the Swedish guidelines from 2012, all tumours except T1a were recommended for total thyroidectomy followed by radioiodine suppression therapy. The patients were then recommended a 1-year follow-up visit with neck ultrasonography and Tg and TgAb tests. Low-risk patients (pT1b, T2, pN0-X, M0-X) were recommended annual follow-up with Tg and TgAb tests, and if these showed undetectable levels after 2 years they could be referred for continued follow-up by their family doctor. High-risk patients (pT3, T4, pN1a, pN1b, M0-X) were recommended every other year follow-up visits with Tg and TgAb tests at a specialist centre for a minimum of 10 years before referral to their family doctor[22].

Classification of no evidence of disease, endpoints and risk groups

Response to treatment was classified at the scheduled follow-up visit 9–12 months after treatment, that is thyroid surgery with or without postoperative radioiodine remnant ablation (RRA). Patients were classified as having NED if they had unstimulated Tg levels less than 1 ng/ml, and TgAb levels less than 20 kIE/l, as well as no signs of disease on imaging. Imaging was performed according to hospital protocols and included cervical ultrasonography.

Recurrence was classified as: biochemical recurrence only with Tg greater than 1 ng/ml and/or TgAb greater than 20 kIE/l without imaging or clinical suspicion of recurrence; or structural recurrence with imaging strongly suspected for and/or biopsy-verified recurrence or metastasis with or without biochemical evidence of recurrence.

Patients were followed from the date of their primary surgery until the last scheduled follow-up visit in the follow-up programme. Every patient's medical record was searched for signs of recurrence at any visit to Skåne University Hospital until and including the end date of 1 December 2020. Time to recurrence was calculated by using the date of primary surgery as the starting date, and the first record of the recurrence as the end date. Death was ascertained either through patients' medical records or through INCA. Death was defined as overall or disease-specific, using information available either from death certificates or patients' hospital records.

Patients were stratified into groups of a low, intermediate or high risk of recurrence by American Thyroid Association (ATA) 2015[12] based on the patients' pathological TNM (pTNM) stage at diagnosis, using the TNM 7th edition[26].

Statistical analysis

Statistical analysis was performed using STATA/MP, version 16.1 for Mac (StataCorp, College Station, Texas, USA). Medians and interquartile ranges were reported for continuous variables; numbers and percentages for discrete variables. Characteristics among patients with and without recurrence were compared using Pearson's chi-squared or Fisher's exact test, where appropriate. All tests were two-sided, and a difference with a $P < 0.050$ was considered significant.

Results

Characteristics of patients and clinical outcomes

The inclusions and exclusions of patients in this study are illustrated in *Fig. 1*. There were 295 patients treated with thyroid surgery and with PTC as the only malignant thyroid diagnosis during the study period; nine were lost to follow-up, and a further 108 had T1aN0/X. Of the remaining 178 patients, 88 had either biochemical or structural persistent disease. Thus, 90 patients remained who had NED after treatment, and who constituted the study cohort of the present report.

Baseline clinicopathological characteristics of the included patients are shown in *Table 1*. The median age was 48 (i.q.r. 40–64) years. There were 74 women and 16 men, who were followed for a median of 6.3 years; a median period of 4.7 years was in the scheduled follow-up programme. Their clinical outcomes are presented in *Table 2*. Eighty-four patients (93.3 per cent) remained free of tumour during follow-up, while three (3.3 per cent) patients developed exclusively biochemical signs of recurrence, and additionally three (3.3 per cent) developed a confirmed

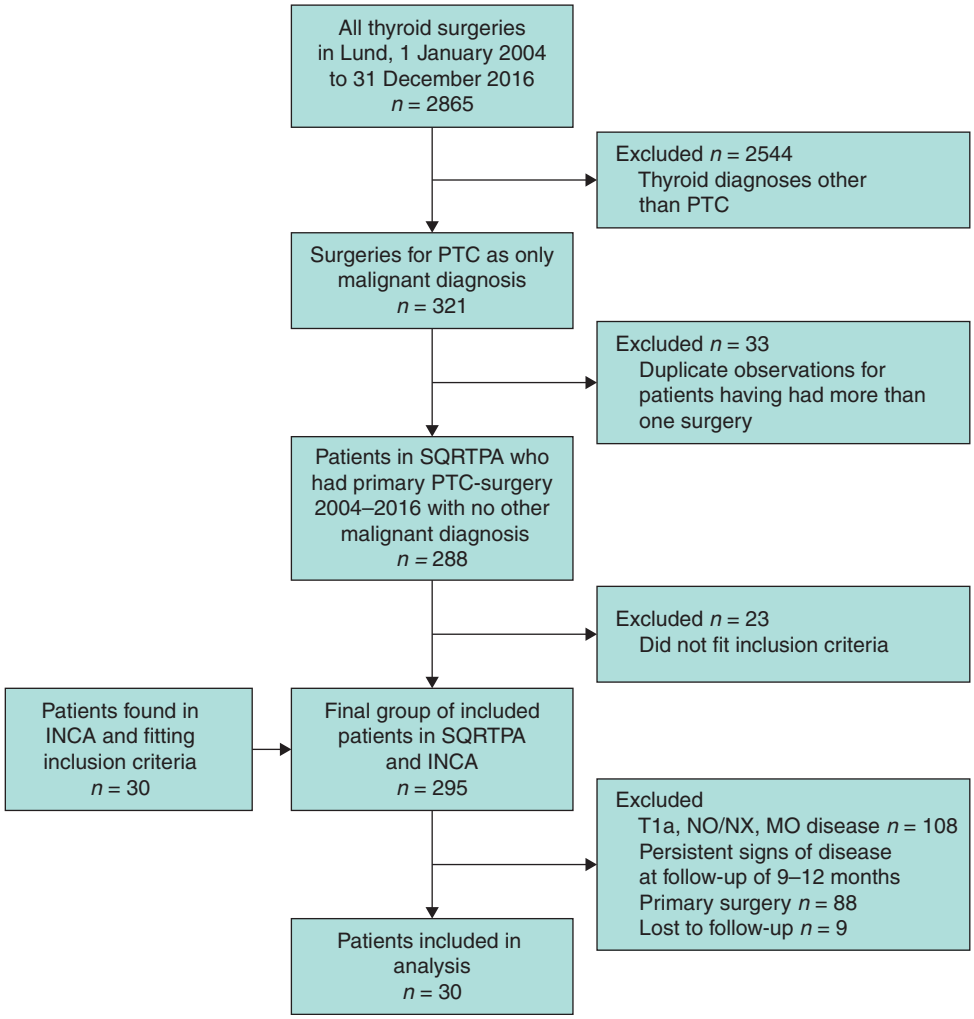

Fig. 1 Flow chart of included and excluded patients

PTC, papillary thyroid cancer; SQRTPA, Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery; INCA, Swedish national quality register for thyroid cancer.

structural recurrence. Five patients (5.6 per cent) died during follow-up. They were all above 75 years of age at the time of death. According to medical records and death certificates, all died of causes other than PTC.

Risk factors for recurrence

Due to the low number of included patients and the low number of events, no multivariable analysis to identify risk factors for recurrence was possible. Patients with structural recurrence were more often aged 75 years or older at treatment ($P = 0.004$), they had a higher risk group (stage) at diagnosis ($P = 0.04$), and more often had a multifocal primary tumour ($P = 0.04$), *Table 2*.

Recurrences

The details of the patients who had recurrence are summarized in *Table 3*. The biochemical recurrences were detected 3.1, 5.1 and 15.0 years after initial diagnosis. These patients were 32, 39 and 72 years old at diagnosis of the primary disease. The structural recurrences were detected 2.3, 2.7 and 6.9 years after the initial diagnosis. Patients with structural recurrence were 76, 85 and 86 years old at diagnosis of their primary disease.

Biochemical recurrences

Out of the three patients with biochemical recurrence, two presented exclusively with elevated concentrations of TgAb; the third had elevated levels of Tg. None of them presented with any symptoms of recurrence during their follow-up and none of them were treated further. All of them were recommended to have continued follow-up, and during this study none of them had any structural evidence of disease and none of them died.

Structural recurrences

All patients with structural recurrence of disease were female and 75 years or older at the time of diagnosis and all of them were 80 years or older at the time of recurrence. One structural recurrence was detected at a scheduled follow-up visit; the other two were detected due to symptoms leading the patient to seek care outside the follow-up programme. All three patients with structural recurrence were scheduled for or had undergone treatment for their recurrence. None of these patients remained disease-free at the end of follow-up, and two of the patients with structural recurrence died. One died from a heart attack while the other had several potential causes of death stated in the medical records (renal failure, infection and possibly stroke), none related to PTC.

Table 1 Baseline clinicopathological characteristics of included patients

Characteristics	Patients ($n = 90$)
Gender	
Female	74 (82.2)
Male	16 (17.8)
Age at diagnosis (years)*	48 (40–64)
Multifocality	
Yes	42 (46.7)
No	48 (53.3)
T-stage	
T1a	2 (2.2)
T1b	31 (34.4)
T2	18 (20.0)
T3	34 (37.8)
T4	5 (5.6)
Lymph node metastasis	
N1a (treated with central dissection)	29 (32.2)
N1b (treated with lateral dissection)	2 (2.2)
N0 or Nx	59 (65.6)
Initial risk-group of recurrence	
Low risk	43 (47.8)
Intermediate risk	42 (46.7)
High risk	5 (5.6)
Radioiodine remnant ablation	
Yes	86 (95.6)
No	4 (4.4)
Total follow-up time (years)*	6.3 (5.0–9.7)
Follow-up time in scheduled programme (years)*	4.7 (3.2–5.8)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.).

Discussion

The present study found that of 90 patients with NED after treatment for PTC, only three developed a structural recurrence. Out of these three patients with structural recurrence, the follow-up programme detected only one; the other two patients had symptomatic recurrences and sought medical care between follow-up visits. A further three patients had elevated levels of Tg or TgAb, which were classified as biochemical recurrences.

The rate of structural recurrence of 3.3 per cent in the present study is in line with rates reported in previous studies[6–11]. The finding that only one out of three recurrences was detected through the follow-up programme has not been published previously.

The definition of biochemical recurrence varies. Some authors have suggested a suppressed Tg greater than 1.0 ng/ml[6]; others also include raised TgAb, above 60[7] or 100 kIU/l[8]. Two out of three patients with biochemical recurrence in this study had levels of TgAb between 20 and 60 kIU/l, which would not have been classified as recurrences in previous studies[6–8]. None of the patients with biochemical recurrence in this study had symptoms or received treatment but continue to be followed up. Their risk of any future structural recurrence is unclear. In the study by Han and colleagues[8], out of ten patients converting from TgAb levels less than 100 kIU/l after treatment to levels above 100 kIU/l during follow-up, none developed structural recurrence. Rising Tg seems to impart a higher risk of later structural recurrence. Thus, in the same study, five out of 37 (13.5 per cent) patients with rising Tg later developed structural recurrence. Scheffel and co-workers[27] found six structural recurrences in 90 patients with NED and rising levels of Tg, resulting in a rate of 6.7 per cent. These results suggest that the risk of structural recurrence after biochemical signs of recurrence may not be very high.

The third patient in this study with biochemical recurrence demonstrated an elevated Tg to 4.6 ng/ml. This patient did not undergo RRA at baseline, indicating that the rising levels of Tg might have been due to regrowth of benign thyroid remnants, and not recurrence of malignant disease.

In contrast to Tuttle and colleagues[6] who found that structural recurrences occur 4 to 11 years after primary treatment,

Table 2 Clinical endpoints

	No recurrence	Biochemical recurrence	Structural recurrence	P†
Total*	84 (93.3)	3 (3)	3 (3)	
Sex				0.70
Female	69 (82.1)	2	3	
Male	15 (17.9)	1	0	
Age				0.004
>75 years	9 (10.7)	0	3	
<75 years	75 (89.3)	3	0	
Risk group				0.036
Low	43 (51.2)	0	0	
Intermediate	37 (44.1)	3	2	
High	4 (4.8)	0	1	
Multifocality				0.040
Yes	39 (46.4)	0	3	
No	45 (53.6)	3	0	
T-stage				0.15
T1a	2 (2.4)	0	0	
T1b	31 (36.9)	0	0	
T2	18 (21.4)	0	0	
T3	29 (34.5)	3	2	
T4	4 (4.8)	0	1	
Lymph node metastasis				0.55
Yes	28 (33.3)	1	2	
No	56 (66.7)	2	1	
RRA at primary treatment				
Yes	81 (96.4)	2	3	0.25
No	3 (3.6)	1	0	

Values in parentheses are percentages, presented as columnar percentage, except *presented as row percentage. Biochemical recurrence, thyroglobulin >1 ng/ml and/or thyroglobulin antibodies >20 kIE/l without imaging or clinical suspicion of recurrence; structural recurrence, biopsy- or surgically verified recurrence/metastasis or imaging strongly suggesting recurrence/metastasis. †Fisher's exact test. RRA, radioiodine remnant ablation.

Table 3 Details of patients with recurrence

Number	1	2	3	4	5	6
Age at initial surgery (years), sex	39, male	72, female	32, female	86, female	85, female	76, female
Type of recurrence	Biochemical	Biochemical	Biochemical	Structural	Structural	Structural
Stage	T3N0	T3N1a	T3N0	T3N1a	T3N1b	T4N0
Risk group	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	High
Site of recurrence	Laboratory	Laboratory	Laboratory	Lymph gland neck	Lymph gland neck	Metastasis os ilium dx
Time to recurrence (years)	5.1	3.1	15.0	2.7	2.3	6.9
Positive findings for detection	44 TgAb	34 TgAb	4.6 Tg	7.7 Tg, positive FNA and US	Positive FNA and US	18 120 Tg and positive PET
Place for detection of recurrence	Scheduled visit	Scheduled visit	Scheduled visit	Scheduled visit	Medical care for other reasons	Patient sought care due to pain in the groin
Treatment of recurrence	None	None	None	Recommended for radiation therapy	Surgery	Radioiodine treatment
Final outcome	44 TgAb, negative US	50 TgAb, negative US	4.0 Tg, negative US	532 Tg, positive US	1.6 Tg, negative US	1895 Tg, positive PET
Final follow-up time (years)	5.1	3.7	15.6	5.8	5.8	8.5
RRA at primary treatment	Yes	Yes	No	Yes	Yes	Yes
Deceased	No	No	No	Yes, of other cause (before treatment of recurrence)	Yes, of other cause	No

TgAb, thyroglobulin antibodies (kIU/l); Tg, thyroglobulin (ng/ml); US, ultrasonography; FNA, fine needle aspiration; RRA, radioiodine remnant ablation; PET, positron emission tomography.

two of the three structural recurrences in the present study were detected after 2.3 and 2.7 years. Due to this relatively short recurrence time, it is possible these were not true recurrences but instead persistent disease. Both recurrences were metastatic lymph nodes in the neck. Both of the patients with these recurrences were initially diagnosed with lymph node involvement at primary diagnosis, one in the central neck (N1a) and the other in the lateral neck (N1b). A study by Llamas-Olier and colleagues[28] in 2018 showed that N1b at diagnosis is a risk factor for early recurrence or persistent disease.

Another study, from Memorial Sloan Kettering Center in 2015, of 3664 patients with differentiated thyroid cancer illustrated that the risk of recurrence increases with age, regardless of stage[29]. Thus, they found a 37-fold increase in the risk of recurrence in patients above 70 years of age compared with patients below the age of 40. This aligns with the results in the current study, where patients with structural recurrences were 76, 85 and 86 years old at the time of diagnosis, compared with the median age of 48 years in the cohort.

Some studies have investigated whether molecular markers can be used to determine prognosis in thyroid cancer[30]. The most studied marker is mutation of the *BRAF* gene. A study from 2013 published by Xing and co-workers[31] showed that the risk of metastasis, death and old age at diagnosis are all higher in PTC containing a specific *BRAF* mutation. Thus, it is plausible that PTC is not a single disease but consists of several different molecular types of cancer, and that prognosis is determined by early genetic events. Unfortunately, data on *BRAF* mutations were not available in the present study.

The results of the present study contrast with earlier studies which found high rates of recurrence after treatment for PTC. For instance, Mazzaferi and Kloos[5] in 2001 found a PTC-recurrence rate of 23.5 per cent, and a study from the Mayo Clinic of 800 patients who had PTC surgery between 1946 and 1970 found a recurrence rate of 18 per cent[3]. Early studies such as these are often cited to support the value of extensive follow-up of PTC. However, their results are in stark contrast to the 1 to 4 per cent recurrence rate presented in more recent studies of patients with NED after treatment[6–11]. Reasons for the lower contemporary recurrence rate might be improved surgical treatment. Today, surgeons perform more compartment-oriented lymph node dissection instead of so-called 'berry picking', where only suspicious-looking lymph nodes are excised[32]. Other reasons include improved RRA[33]. Most importantly, the evaluation of disease status after surgical treatment with Tg, TgAb and imaging, makes prediction of recurrence much more precise than previously[34,35]. In this regard, it is important to note that out of 295 patients with PTC in this study, 88 did not have NED after primary treatment, but showed signs of persistent disease. Thus, the very low risk of recurrence only relates to patients with NED after treatment.

A strength of the present study is its single-centre design, which minimizes confounding factors regarding differences in treatment and follow-up between different clinics. This study is the first northern European study on how to follow patients with PTC and NED optimally after treatment.

Some limitations of the present study need to be mentioned. First, the Tg assay has changed over time. Before 2016, Skåne University Hospital Lund used an assay with a sensitivity of 1.0 ng/ml. From 2016, a more sensitive assay of 0.1 ng/ml was introduced. Thus, patients who were considered biochemically free of disease before 2016 could theoretically still have had levels of

Tg between 0.1 and 1.0 ng/ml. ATA 2015[12] recommend a suppressed Tg level of less than 0.2 ng/ml as the definition of NED, the sensitivity of the Tg assay used in the period 2004–2016 of 1.0 ng/ml at Skåne University hospital Lund, which was also used in the present study, made the inclusion criteria of less than 0.2 ng/ml impossible; therefore Tg less than 1.0 ng/ml was used to define NED.

In 2009, all thyroid cancer treatment was centralized to Lund. Due to this centralization of healthcare, the number of patients included in this study who had surgery after 2009 is much greater than before 2009. The detection of more indolent PTC in later years could also have affected the results.

Other limitations of this study include its retrospective design and the low number of recurrences, which decrease the statistical power and make it impossible to perform multiple regression analysis to identify risk factors. However, age above 75 years was clearly a significant risk factor for recurrence, since no patient below 75 years of age with NED had a structural recurrence.

A further limitation is the lack of molecular analysis in the present paper. It can only be speculated that old age of patients with structural recurrence is a confounder for a specific molecular type of cancer associated with higher recurrence risk. Further studies are needed to explore this.

Only three out of 90 patients who had NED after primary treatment experienced structural recurrence, none of them was below 75 years of age and the follow-up programme accurately identified only one of them. Thus, follow-up, as it is designed today, seems to be of questionable benefit in younger patients with PTC and NED 9 to 12 months after treatment.

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