Clinical outcomes after delayed thyroid surgery in patients with papillary thyroid microcarcinoma

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Abstract

Objective: Active surveillance is an option for patients with papillary thyroid microcarcinoma (PTMC). However, the long-term clinical outcomes after delayed surgery remain unclear. We compared the long-term clinical outcomes of PTMC patients according to the time interval between initial diagnosis and surgery.

Design and methods: In this individual risk factor-matched cohort study, PTMC patients were classified into three groups according to the delay period: ≤6 months, 6–12 months and >12 months. Patients were matched by age, sex, extent of surgery, initial tumor size as measured by ultrasonography (US), and by the presence of extrathyroidal extension, multifocal tumors and central cervical lymph node metastasis. We compared the dynamic risk stratification (DRS) and the development of structural persistent/recurrent disease of patients.

Results: A total of 2863 patients were assigned to three groups. Their mean age was 50 years, 81% were female and 66% underwent lobectomy. The mean tumor size at the initial US was 0.63 cm. There were no significant differences in clinicopathological characteristics between groups after individual risk factor matching. Comparison of the DRS revealed no significant difference according to the delay period ($P=0.07$). During the median 4.8 years of follow-up, there were no significant differences in the development of structural recurrent/persistent disease ($P=0.34$) and disease-free survival ($P=0.25$) between groups.

Conclusions: In PTMC patients, delayed surgery was not associated with higher risk of structural recurrent/persistent disease compared to immediate surgery. These findings support the notion that surgical treatment can be safely delayed in patients with PTMC under close monitoring.

European Journal of
Endocrinology
(2017) **177**, 25–31

Introduction

Recent studies have suggested more conservative management for small papillary thyroid carcinoma (PTC) including papillary thyroid microcarcinoma (PTMC), which is ≤1 cm in maximal tumor diameter. Generally, patients with PTMC have excellent prognosis and indolent disease course. Recently, an active surveillance approach was proposed as an alternative option for patients with PTMC, especially for those without any evidence

of invasion, metastases, or cytological or molecular aggressive features (1, 2). Low-risk PTMC patients can be closely monitored via serial neck ultrasonography (US) and physical examination with or without other imaging studies, and patients showing disease progression during follow-up or who choose to may proceed to surgery (3, 4, 5, 6). According to previous studies, active surveillance has favorable oncologic outcomes compared with immediate

surgery with up to 15% of patients proceeding to surgery from active surveillance (1, 7).

Currently, there are no data regarding the differences in long-term clinical outcomes, such as the development of structural recurrent/persistent disease after initial therapy for PTMC, between immediate and delayed surgery. Because the timing of surgery might be affected by the clinicopathological characteristics of patients such as age, sex and the size or the position of the PTMC in neck US, which are also known risk factors for recurrence in PTMC (1, 8), the analysis should match the individual risk factors and compare the long-term clinical outcomes of PTMC patients with similar clinicopathological characteristics.

In this study, we aimed to evaluate the long-term clinical outcomes of PTMC patients according to the time interval from the initial diagnosis of PTMC to thyroid surgery (delay period). We classified the patients into three groups according to the delay period: within 6 months, 6–12 months and more than 12 months. We assessed the dynamic risk stratification (DRS) categories and disease-free survivals between the groups after individual matching of various clinicopathological characteristics of patients with PTMC.

Subjects and methods

Study cohort

This retrospective cohort study initially included 9885 consecutive patients with PTMC who underwent initial

thyroid surgery between 1999 and 2013 at Asan Medical Center, Seoul, Korea. We excluded patients with incidental PTMCs, which were only identified postoperatively in thyroid specimens following thyroid surgery for presumed benign disease, and patients with lateral cervical lymph node (LN) metastases or distant metastases at initial diagnosis (clinical PTMCs) (9). We excluded patients without high-quality preoperative US images or adequate follow-up data. We also excluded patients with maximal tumor size greater than 1 cm at the initial US examination. A total of 6217 patients with PTMC were eligible for the unmatched PTMC cohort.

Patients were classified into three groups according to the time interval from the initial diagnosis to thyroid surgery (delay period). The time of initial diagnosis was defined as the time of initial identification of the suspicious thyroid nodules, which were finally confirmed as PTMC, by US examination. Patients who underwent immediate surgery within 6 months from the first diagnosis were classified into Group 1. Patients were classified into Group 2 when the delay period was 6–12 months and those who underwent delayed thyroid surgery after 12 months from the initial diagnosis were classified into Group 3. Group 3 had the smallest number of patients, so each group of patients was then individually matched in a 3:3:1 ratio (1227:1227:409 patients) according to their age, sex, the extent of surgery, maximum PTMC diameter at the initial neck US, the presence of extrathyroidal extension, multifocal tumors and central cervical LN metastasis at final pathology (Fig. 1). Differences within one year of age

Figure 1

Summary of patients with papillary thyroid microcarcinoma before and after individual risk factor matching. A total of 6217 patients were classified into three groups according to the time interval from initial diagnosis of papillary thyroid microcarcinoma (PTMC) to surgery. After individual matching, 2863 patients were assigned to the three groups.

and within 0.1 cm of the primary tumor size were regarded as the same during individual risk factor matching. This study was approved by the institutional review board of Asan Medical Center.

Management and follow-up protocol

The follow-up protocol was shared at our center in order to maintain consistent management across the patients as previously reported (10). Routine preoperative neck US was performed in all patients. The timing and extent of surgery were individually determined depending on the patient's preference and surgeon's decision. Patients with bilateral multifocal PTMCs or PTMCs with indeterminate nodules in the contralateral lobe were treated by total thyroidectomy, whereas the other patients were treated by lobectomy. Prophylactic ipsilateral or bilateral central neck dissection was routinely performed for patients with PTMC. Radioactive iodine (RAI) remnant ablation after total thyroidectomy was conducted for patients with risk factors for recurrence (11).

After initial therapy, all patients were regularly followed up every 6–12 months with physical examinations, as well as the measurement of thyroid function, serum thyroglobulin (Tg), serum anti-Tg antibody (TgAb) and neck US. Diagnostic RAI whole-body scan (WBS) with measurement of the serum-stimulated Tg (sTg) levels was also performed 12–24 months after the initial therapy in patients who underwent total thyroidectomy and RAI remnant ablation as previously reported (10, 11).

Definitions

The DRS according to the response to initial therapy and the development of structural persistent/recurrent disease were the primary outcomes of this study.

The DRS categories were determined using classifications described in previous studies (2, 12, 13, 14, 15) that employed serum Tg levels, serum TgAb levels and neck US with/without diagnostic WBS. Patients were classified into four groups according to their responses to initial therapy: excellent, indeterminate, biochemical incomplete and structural incomplete response.

Structural persistent/recurrent disease was defined as pathologically or cytologically proven recurrent or metastatic lesions and/or the appearance of metastatic lesions in other distant organs on imaging studies, with elevated Tg levels (10, 14). Disease-free survival (DFS) was defined as the time interval from the initial surgery to detection of structural persistent/recurrent disease.

Statistics

For individual matching, R version 3.0.1 was used. R Studio version 0.98.1091 and R libraries survival, car and gdata were used to analyze the matched data (R Foundation for Statistical Computing, <http://www.R-project.org/>). Continuous variables were presented as means with standard deviation (s.d.) or medians with interquartile range (IQR). Categorical variables were presented as numbers with percentages. Chi-square or Fisher's exact tests were used to compare categorical variables, and one-way analysis of variance (ANOVA) was used to compare continuous variables.

DFS curves in the matched data set were constructed using the Kaplan–Meier method by GraphPad Prism version 5.01 (GraphPad Software). Log-rank tests were also performed to evaluate differences in the DFSs between groups. A Cox proportional hazard model was also used to evaluate the risk factors of structural recurrent/persistent disease. For the Cox proportional hazard model analysis, age and primary tumor size were categorized. An age of 45 years and a primary tumor size of 0.5 cm were the cut-off points for categorization (16). All *P* values were two-sided, and *P* < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients with PTMC before individual risk factor matching

The clinicopathological characteristics of 6217 patients before individual risk factor matching are shown in Table 1 (left panel). Mean age of the patients was 48.9 years, and 5142 (83%) were female. The mean tumor size as measured by neck US at the diagnosis of PTMC was 0.65 cm. Approximately half of the patients underwent lobectomy, and the others underwent total thyroidectomy. The mean primary tumor size at the final pathology was 0.60 cm, and 1908 patients (31%) had central cervical LN metastases. During a median of 4.8 years of follow-up (IQR: 3.6–6.5 years), 88 patients (1.4%) were determined to have structural persistent/recurrent disease.

Patients were classified into three groups according to the delay period until the thyroid surgery. About 68% of patients underwent thyroid surgery within 6 months (Group 1), and 25% underwent surgery between 6 and 12 months (Group 2). The delay period for thyroid surgery was longer than 12 months in 448 patients (7%, Group 3). The median interval from initial diagnosis to surgery was

Table 1 Clinicopathological characteristics of patients with PTMC before and after individual risk factor matching. Continuous variables are presented as mean $\pm$ S.D. Categorical variables are presented as numbers with percentages.

	Before individual risk factor matching				After individual risk factor matching			
	Total (n=6217)	Group 1 (n=4209)	Group 2 (n=1560)	Group 3 (n=448)	P-value	Group 1 (n=1227)	Group 2 (n=1227)	Group 3 (n=409)
Age (years)	48.9 $\pm$ 10.3	48.2 $\pm$ 10.3	48.9 $\pm$ 10.3	50.1 $\pm$ 10.5	<0.001	49.1 $\pm$ 9.7	49.9 $\pm$ 9.9	50.0 $\pm$ 10.3
Sex (female)	5142 (83)	3529 (84)	1256 (81)	357 (80)	0.003	996 (81)	1002 (82)	332 (81)
Maximal nodule size at the initial US (cm)	0.65 $\pm$ 0.19	0.66 $\pm$ 0.19	0.64 $\pm$ 0.19	0.62 $\pm$ 0.19	<0.001	0.60 $\pm$ 0.18	0.60 $\pm$ 0.18	0.60 $\pm$ 0.19
Initial operation					<0.001			
Lobectomy	3106 (50)	1825 (43)	998 (64)	283 (63)		804 (66)	816 (67)	268 (66)
Total thyroidectomy	3111 (50)	2384 (57)	562 (36)	165 (37)		423 (34)	411 (34)	141 (34)
Pathologic findings								
Primary tumor size (cm)	0.60 $\pm$ 0.21	0.61 $\pm$ 0.21	0.59 $\pm$ 0.21	0.58 $\pm$ 0.21	<0.001	0.60 $\pm$ 0.21	0.60 $\pm$ 0.21	0.60 $\pm$ 0.21
Minimal extrathyroidal extension (Y)	2864 (46)	1944 (46)	748 (48)	172 (38)	0.002	507 (41)	510 (52)	169 (41)
Multifocality (Y)	1670 (29)	1145 (27)	405 (26)	120 (27)	0.64	314 (26)	297 (24)	106 (26)
Central cervical LN metastasis (Y)	1908 (31)	1324 (31)	459 (29)	125 (28)	0.25	327 (27)	330 (27)	109 (27)

Group 1, patients who underwent surgery within 6 months after initial diagnosis of papillary thyroid microcarcinoma (PTMC); Group 2, patients who underwent surgery between 6 and 12 months after initial diagnosis of PTMC; Group 3, patients who underwent surgery more than 12 months after initial diagnosis of PTMC; LN, lymph node; US, ultrasonography.

3 months (IQR: 1.6–4.4 months) in Group 1, 8 months (IQR: 6.7–9.4 months) in Group 2 and 17 months (IQR: 13.6–23.9 months) in Group 3. Patients who underwent delayed surgery tended to be older, male and have undergone lobectomy ($P<0.001$, $P=0.003$ and $P<0.001$, respectively). Furthermore, the size of the PTMC at their initial US and at final pathology tended to be smaller with the delay of surgery ($P<0.001$, and $P<0.001$, respectively) (Table 1).

Clinicopathological characteristics of patients after individual risk factor matching

After individual matching of age, sex, the size of PTMC measured at the initial US, the extent of surgery, the presence of extrathyroidal extension, multifocal tumors and cervical central LN metastasis at final pathology, 1227 patients each was assigned to Groups 1 and 2, and 409 patients were assigned to Group 3. In the matched data set, the mean age of patients was 50.0 years, and 81% of patients were female. The mean size of PTMCs measured in the initial US was 0.63 cm, and about 66% of patients underwent lobectomy (Table 1, right panel). All preoperative and postoperative characteristics of patients with PTMCs were not significantly different between groups after individual matching.

The clinicopathological characteristics of patients with PTMC who were excluded after individual risk factor matching are shown in Supplementary Table 1 (see section on supplementary data given at the end of this article).

Clinical outcomes of patients according to the thyroid surgery delay period

We evaluated the DRS after initial therapy in patients with PTMC and observed no significant differences in the DRS categories between the groups ($P=0.07$). Excellent responses were confirmed in 942 (77%) patients in Group 1, 953 patients (78%) in Group 2 and 303 patients (74%) in Group 3 (Table 2). Only 20 patients (2%) in Group 1, 7 patients (0.6%) in Group 2 and two patients (0.5%) in Group 3 presented with structural incomplete responses.

During follow-up, structural persistent/recurrent disease was detected in 19 patients (1.6%) in Group 1, 13 patients (1.1%) in Group 2 and three patients (0.7%) in Group 3. The median duration from initial surgery to the detection of structural persistent/recurrent disease was 3.3 years (IQR: 1.3–5.0 years). There was no significant difference in the incidence of structural

Table 2 Clinical outcomes of patients with PTMC after individual risk factor matching. Data are presented as *n* (%).

	Group 1 (<i>n</i> = 1227)	Group 2 (<i>n</i> = 1227)	Group 3 (<i>n</i> = 409)	<i>P</i> -value
Dynamic risk stratification				0.07
Excellent	942 (77)	953 (78)	303 (74)	
Indeterminate	192 (16)	189 (15)	78 (19)	
Biochemical incomplete	73 (6)	78 (6)	26 (7)	
Structural incomplete	20 (2)	7 (0.6)	2 (0.5)	
Structural persistent/recurrent disease	19 (1.6)	13 (1.1)	3 (0.7)	0.34
Contralateral lobe	5 (26)	5 (38)	1 (33)	0.38
Postoperative bed/central cervical LN	1 (5)	2 (15)	1 (33)	
Lateral cervical LN	13 (68)	6 (46)	1 (33)	

LN, lymph node.

persistent/recurrent disease between the three groups ($P=0.34$). The DFS curves also did not differ significantly between the groups (Fig. 2, $P=0.25$). When we sub-classified the structural persistent/recurrent disease by the recurrence sites, there was no significant difference in the site of persistent/recurrent disease according to group ($P=0.38$, Table 2).

Analysis of the risk factors for structural persistent/recurrent disease of PTMC patients in the matched dataset revealed that male gender (hazard ratio (HR)=2.43, 95% confidence interval (CI): 1.21–4.91, $P=0.013$) and multifocal tumors (HR=2.45, 95% CI: 1.24–4.83, $P=0.010$) were independent risk factors (Table 3). The thyroid

surgery delay period was not associated with the risk of structural persistent/recurrent disease in PTMC patients.

Discussion

In this study, we evaluated the impacts of delayed thyroid surgery on the long-term clinical outcomes of patients with PTMC. We used a matched data set by individually matching patient age, sex, extent of surgery, size of PTMC measured at the initial US, the presence of extrathyroidal extension, multifocal tumors and cervical central LN metastasis at final pathology in order to minimize other confounding factors associated with long-term clinical outcomes of PTMC. The thyroid surgery delay period was classified into three groups: within 6 months, between 6 and 12 months and more than 12 months. There were no significant differences in the DRS categories and the development of structural recurrent/persistent disease in PTMC patients between the groups. These findings suggest that delayed surgery may not affect the long-term clinical outcomes of low-risk patients with PTMC.

Active surveillance is a conservative observational approach and gained attention when it was first reported in PTMC (1, 17). However, this approach was only validated in Japan in retrospective observational studies, and there are concerns of disease progression during active surveillance, especially in young patients (1, 18). Previous studies from Japan reported that disease progression during active surveillance could be treated successfully with thyroid surgery (7), but the long-term disease outcome was not elucidated. In the present study, delayed surgery (median 17 months after initial diagnosis) was not associated with an increased risk for structural recurrent/persistent disease compared to immediate surgery. There were also no differences in the DRS categories after initial therapy according to the delay period from diagnosis

Figure 2

Disease-free survival curves of patients in three groups according to the thyroid surgery delay period after individual risk factor matching. Group 1, patients who underwent surgery within 6 months after initial diagnosis of papillary thyroid microcarcinoma (PTMC); Group 2, patients who underwent surgery 6–12 months after initial diagnosis of PTMC; Group 3, patients who underwent surgery more than 12 months after initial diagnosis of PTMC. *P*-value was determined by the log-rank test.

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Table 3 Univariate and multivariate analyses of risk factors for structural recurrent/persistent disease of PTMC.

	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥ 45 years)	0.84	0.42–1.70	0.63			
Sex (male)	2.54	1.26–5.11	<0.001	2.43	1.21–4.91	0.013
Extent of operation (TT)	1.12	0.57–2.22	0.74			
Primary tumor size (>0.5 cm)	2.24	1.08–4.67	0.031	1.76	0.83–3.75	0.14
Minimal extrathyroidal extension (Y)	1.59	0.82–3.09	0.17			
Multifocality (Y)	3.01	1.55–5.85	0.001	2.45	1.24–4.83	0.010
Cervical central LN metastasis (Y)	2.18	1.12–4.23	0.022	1.77	0.90–3.49	0.10
Delayed period to surgery						
Group 1	Ref.					
Group 2	0.76	0.37–1.54	0.44			
Group 3	0.59	0.17–2.00	0.40			

CI, confidence interval; HR, hazard ratio; Ref, reference; TT, total thyroidectomy; Y, yes.

to thyroid surgery. Even though the patients who had delayed surgery in this study were not those who showed disease progression during active surveillance, our findings suggest that delayed surgery 1–2 years after the initial diagnosis might not be unfavorable and provides indirect evidence for the safe application of active surveillance for low-risk PTMCs.

Before individual risk factor matching, patients in Group 3, who underwent surgery 12 months after initial diagnosis, were likely to be older, male and have smaller tumors compared to those in Groups 1 and 2. These are well-known factors associated with the recurrence of PTMCs (8, 11, 16) and can affect a surgeon's decision to perform surgery. Therefore, we evaluated the clinical outcomes after individual matching of patient age, sex, primary tumor size as well as the extent of surgery. Furthermore, the number or position of suspicious nodules at initial US might affect the decision to perform surgery; therefore, we matched all other pathological variables such as the presence of extrathyroidal extension, multifocal tumors and central cervical LN metastasis at final pathology in this study. In these matched datasets, only male gender and multifocal tumors were independent risk factors of the structural persistent/recurrent disease in patients with PTMC, and delay period was not associated with the risk of structural persistent/recurrent disease in PTMC patients.

This study has limitations due to its retrospective design that included patients from a single tertiary referral center. We could not evaluate the exact reasons for delayed or immediate surgery based on our review of the medical records. We also could not evaluate how many patients in the Group 3 had delayed surgery due to disease progression during observation. Thus, the result of this study could not give adequate information about the role of active surveillance in PTMC. However, our study has several advantages, including its long-term evaluation of

the clinical outcomes of patients who underwent delayed thyroid surgery compared with balanced control groups in low-risk patients with PTMC.

In conclusion, after individual risk factor matching, delayed surgery for patients with PTMC was not associated with increased risk for structural recurrent/persistent disease compared to immediate surgery. These findings support that the surgical treatment can be safely delayed in patients with PTMC under close monitoring.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-17-0160>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This study was supported by a grant from the Korean Health Technology R&D project, Ministry of Health & Welfare, Republic of Korea (HC15C3372), and a grant (No. 2017-582) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.

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Received 24 February 2017

Revised version received 12 April 2017

Accepted 21 April 2017