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Original Article

Active surveillance for young patients with insular thyroid cancer: an initial and novel finding

Zeming Liu[1*], Wen Zeng[2*], Ling Zhou[1], Wei Zhou[1], Danyang Chen[1], Haifeng Feng[1], Wei Wei[3], Chao Zhang[4], Min Wang[1], Liang Guo[1]

Departments of [1]Plastic Surgery, [2]Ophthalmology, Zhongnan Hospital of Wuhan University, Wuhan 430071, China; [3]Department of Pediatrics, St John Hospital and Medical Center, Detroit 48236, MI, USA; [4]Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China. [*]Equal contributors.

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Abstract: Insular thyroid cancer (ITC) is a relatively rare thyroid malignancy that has an unclear prognosis. Recent studies have indicated that watchful waiting is sufficient for younger patients with more differentiated thyroid lesions such as papillary thyroid microcarcinoma (PTMC). In this study, we investigated the prognosis of younger patients (< 45 and < 55 years old) with ITC and compared their outcomes to patients with PTMC and follicular thyroid microcarcinoma (FTMC). We hypothesized that ITC, like PTMC and FTMC, can be managed with active surveillance in younger patients with this disease. We investigated a large cohort of younger patients with ITC, PTMC, or FTMC who were listed in the Surveillance, Epidemiology, and End Results database between 2004 and 2013. Patient mortality was examined by Kaplan-Meier analyses with log-rank tests and Cox proportional hazards regression analyses. In the study cohort, the rate of cancer-specific mortality per 1000 person-years for younger ITC patients (< 45 and < 55 years) was lower than that for PTMC and FTMC. Kaplan-Meier analyses revealed that the cancer-specific and all-cause mortality rates in younger ITC patients were similar to those of PTMC and FTMC. Similar results were obtained when cases with tumor extension were excluded from the analysis. The unanticipated excellent prognosis of younger patients with ITC challenges the current clinical practice of automatically treating this disease, and offers new implications for management such as pursuing active surveillance instead.

Keywords: Active surveillance, prognosis, ITC, SEER, cancer-specific survival

Introduction

Thyroid cancer is the most common type of endocrine malignancy, and its incidence rate has been rising rapidly in recent decades [1-7]. The most common thyroid cancer subtypes include papillary, follicular, medullary, and anaplastic; moreover, thyroid carcinoma contains many uncommon subtypes such as insular thyroid cancer (ITC), oxyphilic cell thyroid cancer, mixed subtype, and others [5, 8, 9].

ITC is an uncommon thyroid malignancy with a controversial prognosis owing to the relative paucity of data from patients with this disease [10-12]. The estimated incidence of ITC ranges from < 1% to 10% of all thyroid cancers [13-15]. Its morphological characteristics lie between those of well-differentiated carcinoma (papillary or follicular) and undifferentiated or anaplastic carcinoma of the thyroid [16]. ITC histology is characterized by solid nests of small uniform carcinoma cells, small follicles containing thyroglobulin, frequent necrotic foci, and variable but consistently present mitotic activity [12, 17].

Active surveillance is the hottest topic in thyroid cancer area. Papillary thyroid cancers 1 cm or smaller in size, which are also referred to as papillary thyroid microcarcinomas (PTMC), comprise almost 50% of all thyroid carcinomas [18-24]. It was recently suggested that, although the incidence of PTMC is increasing rapidly, it has a very low mortality rate and that the observed rise in incidence was mostly owing to an increase in PTMC detection rates. It has therefore been recommended that observation

Table 1. Baseline characteristics of patients with different histological types (ITC < 45 years, PTMC, and FTMC) treated between 2004 and 2013

Covariate	Level	ITC < 45 years (n=21)	Histological types			
			PTMC (n=31434)	P	FTMC (n=333)	P
Age at diagnosis, (IQR), years		30.7 (24.5-41.5)	52.0 (42.0-61.0)	-	51.0 (41.0-62.0)	-
Median year at diagnosis (IQR)		2008 (2006-2011)	2009 (2007-2012)	0.318	2009 (2007-2011)	0.675
Sex	Female	15 (71.4%)	26119 (83.1%)	0.154	267 (80.2%)	0.334
	Male	6 (28.6%)	5315 (16.9%)		66 (19.8%)	
Race	White	14 (66.7%)	26115 (83.2%)	0.137	271 (81.4%)	0.415
	Black	3 (14.3%)	2115 (6.7%)		30 (9.0%)	
	Other	3 (14.3%)	2803 (8.9%)		24 (7.2%)	
Tumor size, (IQR), mm		35.0 (24.0-49.0)	5.0 (3.0-8.0)	-	8.0 (5.0-10.0)	-
Multifocality	No	17 (81.0%)	21088 (67.1%)	0.033	268 (80.5%)	0.769
	Yes	3 (14.3%)	10097 (32.1%)		57 (17.1%)	
Extension	No	1 8 (85.7%)	30133 (95.9%)	< 0.001	324 (97.3%)	< 0.001
	Yes	2 (9.5%)	1264 (4.0%)		9 (2.7%)	
Radiation	None or refused	5 (23.8%)	24220 (77.1%)	< 0.001	236 (70.9%)	< 0.001
	Performed	16 (76.2%)	7214 (22.9%)		97 (29.1%)	
Surgery	Lobectomy	5 (23.8%)	7706 (24.5%)	0.423	89 (26.7%)	0.540
	Subtotal or near-total thyroidectomy	0 (0%)	1424 (4.5%)		13 (3.9%)	
	Total thyroidectomy	15 (71.4%)	21884 (69.6%)		226 (67.9%)	
Median follow-up time, (IQR), months		56.0 (27.5-76.5)	44.0 (20.0-74.0)	0.466	50.0 (25.0-77.5)	0.808

NOTE: *P*-values were calculated using the chi-squared test or Mann-Whitney U test. Abbreviations: ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; IQR: interquartile range.

Table 2. Baseline characteristics of patients with different histological types (ITC < 55 years, PTMC and FTMC) treated between 2004 and 2013

Covariate	Level	ITC < 55 years (n=38)	Histological types			
			PTMC (n=31434)	P	FTMC (n=333)	P
Age at diagnosis, (IQR), years		43.0 (34.3-48.3)	52.0 (42.0-61.0)	-	51.0 (41.0-62.0)	-
Median year at diagnosis (IQR)		2009 (2005-2010)	2009 (2007-2012)	0.063	2009 (2007-2011)	0.317
Sex	Female	18 (47.4%)	26119 (83.1%)	< 0.001	267 (80.2%)	< 0.001
	Male	20 (52.6%)	5315 (16.9%)		66 (19.8%)	
Race	White	28 (73.7%)	26115 (83.2%)	0.121	271 (81.4%)	0.594
	Black	6 (15.8%)	2115 (6.7%)		30 (9.0%)	
	Other	3 (2.6%)	2803 (8.9%)		24 (7.2%)	
Tumor size, (IQR), mm		48.5 (35.0-81.3)	5.0 (3.0-8.0)	-	8.0 (5.0-10.0)	-
Multifocality	No	30 (78.9%)	21088 (67.1%)	0.099	268 (80.5%)	0.975
	Yes	7 (18.4%)	10097 (32.1%)		57 (17.1%)	
Extension	No	32 (84.2%)	30133 (95.9%)	< 0.001	324 (97.3%)	< 0.001
	Yes	5 (13.2%)	1264 (4.0%)		9 (2.7%)	
Radiation	None or refused	11 (28.9%)	24220 (77.1%)	< 0.001	236 (70.9%)	< 0.001
	Performed	27 (71.1%)	7214 (22.9%)		97 (29.1%)	
Surgery	Lobectomy	5 (13.2%)	7706 (24.5%)	0.148	89 (26.7%)	0.136
	Subtotal or near-total thyroidectomy	0 (0%)	1424 (4.5%)		13 (3.9%)	
	Total thyroidectomy	32 (84.2%)	21884 (69.6%)		226 (67.9%)	
Median follow-up time, (IQR), months		53.0 (36.8-77.5)	44.0 (20.0-74.0)	0.106	50.0 (25.0-77.5)	0.364

NOTE: *P*-values were calculated using the chi-squared test or Mann-Whitney U test. Abbreviations: ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; IQR: interquartile range.

without immediate surgery for some low-risk patients with PTMC is a more reasonable option [19, 25-28].

The Surveillance, Epidemiology, and End Results (SEER) program is a premier source of cancer surveillance data combined with analytical tools, and is a leading tool in the methodological collection, analysis, interpretation, and dissemination of reliable population-based statistics. In this study, we used the SEER database to investigate our hypothesis that ITC in young patients has a good prognosis, and that a recommendation of active surveillance would suffice for this patient group.

Materials and methods

Study design, participants, and procedures

This study's retrospective protocol was approved by Zhongnan Hospital and Union hospital's ethical review board and complied with the ethical standards of the Declaration of Helsinki, as well as the relevant national and international guidelines. Written informed consent was obtained from each patient. The study cohort was assembled using data recorded between 2004 and 2013 in all 18 registries of the SEER program of the National Cancer Institute. We selected patients with a diagnosis of thyroid cancer, defined by a combination of the International Classification of Diseases for Oncology site code of C73.9 (i.e., thyroid) and diagnostic codes of papillary, follicular, or insular histology as previously described [10]. The diagnostic codes used in the study included "insular carcinoma", "papillary carcinoma", "papillary microcarcinoma", "papillary adenocarcinoma", "follicular adenocarcinoma" and "papillary and follicular adenocarcinoma".

Patients were excluded from analysis if their thyroid malignancies was not of insular, follicular, or papillary histology; if the follicular or papillary thyroid cancer was larger than 1 cm; if insular, follicular, or papillary thyroid cancer presented with lymph node and/or distant metastasis; if patients with ITC were older than 45 or (for subsequent analysis) 55 years old; if patients had a history of another cancer; and if the survival status was unknown.

Statistical analyses

Continuous variables are presented as medians with interquartile ranges (IQR) and categorical variables are presented as numbers with percentages. The chi-square test was used to compare categorical variables and Mann-Whitney U tests was use to compare continuous variables. Patient survival curves were examined by Kaplan-Meier analyses with log-rank tests and Cox proportional hazards regression analyses. Hazard ratios (HRs) were used to show the magnitude of the effect of disease stages on cancer-specific mortality, all-cause mortality and 95% confident intervals (CIs) were used to indicate the significance of the risk. All P values were 2-sided and a $P < .05$ was considered significant. Analyses were performed using SPSS version 22.0, Stata/SE version 12 (Stata Corp) and GraphPad Prism version 6 (GraphPad Software Inc).

Results

Patient characteristics

Of the 98,945 patients with insular, follicular and papillary thyroid cancer identified in the SEER database, 31,795 (38 with ITC, 31434 with PTMC, and 333 with follicular thyroid microcarcinoma [FTMC]) met the inclusion criteria. Baseline demographic and disease characteristics of patients with FTMC, PTMC, and ITC who were under 45 years old or under 55 years old are shown in **Tables 1**, **2**, S1 and S2.

Cancer-specific and all-cause death rates in patients < 45 years with ITC, PTMC, and FTMC

According to the American Joint Committee on Cancer (AJCC) stage system 7.0, the age cut-off was set at 45 years old; therefore, we analyzed the prognoses of younger (< 55 years) patients with ITC, PTMC, and FTMC. The cancer-specific mortality rates per 1000 person-years for younger (< 45 years) patients with ITC, PTMC, and FTMC were 0, 0.24, and 1.39, respectively. The all-cause mortality rates per 1000 person-years for younger (< 45 years) patients with ITC, PTMC, and FTMC were 0, 7.56, and 12.56, respectively (**Table 3**).

We next compared the prognoses of patients with ITC < 45 years to those of patients with PTMC or FTMC who had no tumor extensions; the cancer-specific mortality rates were 0, 0.22, and 0, respectively, while the all-cause mortality rates per 1000 person-years were 0, 7.61, and 11.58, respectively (Table S3).

Table 3. Cancer specific and all-cause deaths in patients with different histological types (ITC < 45 years, PTMC, and FTMC)

Histological types	Cancer-Specific Deaths No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
ITC < 45 years	0	0	0	NA	0	0.0	0	NA
PTMC	34	0.1	0.24	0.17-0.34	1006	3.2	7.56	7.10-8.05
FTMC	2	0.6	1.39	0.34-5.58	18	5.4	12.56	7.91-19.93

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

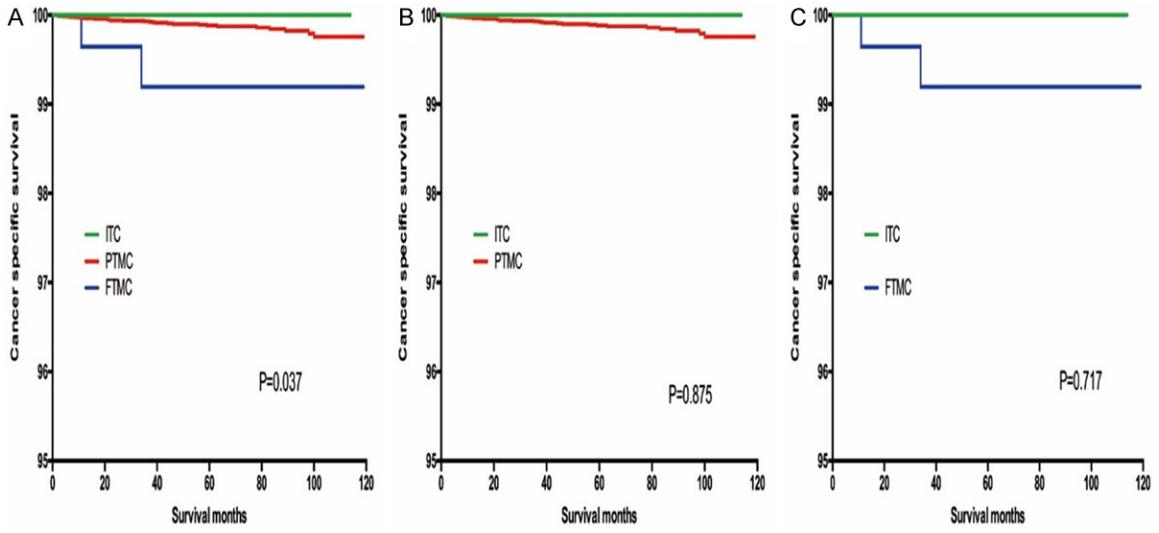

Figure 1. Kaplan Meier curves for cancer-specific survival among patients stratified by subtype: ITC < 45, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

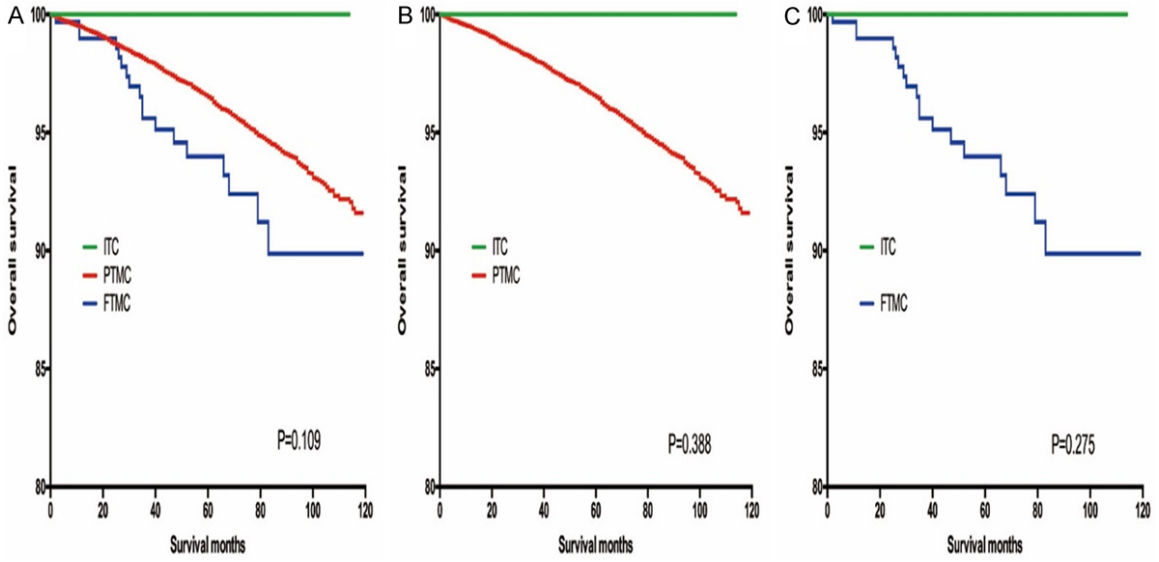

Figure 2. Kaplan Meier curves for all-cause survival among patients stratified by subtype: ITC < 45, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

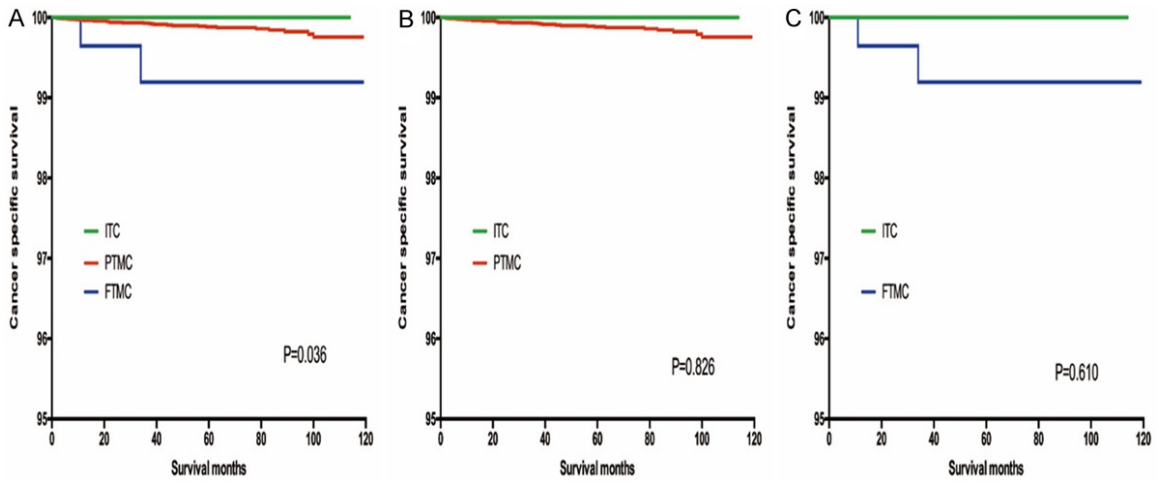

Figure 3. Kaplan Meier curves for cancer-specific survival among patients stratified by subtype: ITC < 55, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

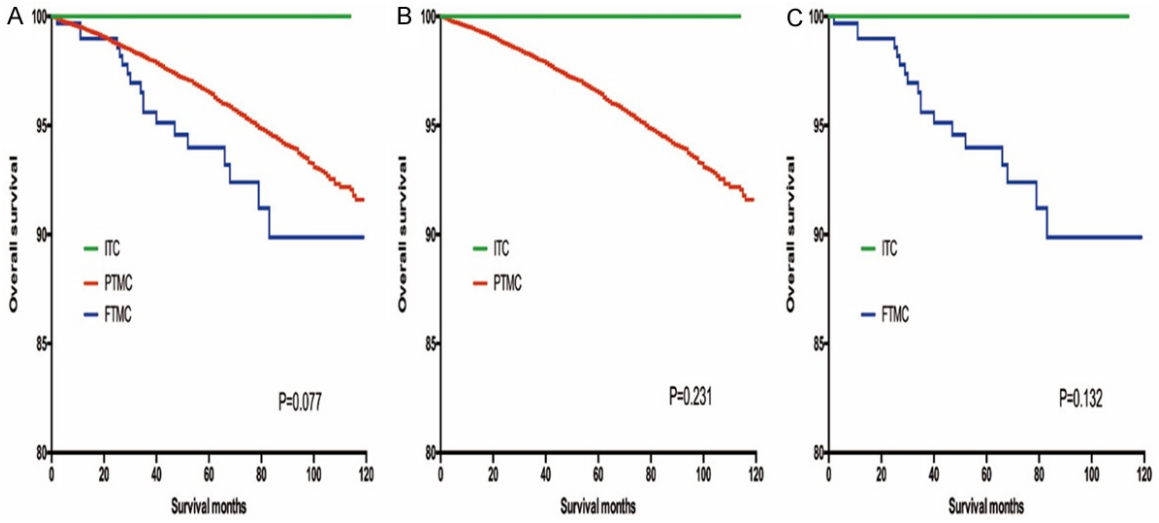

Figure 4. Kaplan Meier curves for all-cause survival among patients stratified by subtype: ITC < 55, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

On Kaplan-Meier analyses, cancer-specific survival curves for patients < 45 years with ITC remained steady during the follow-up period; additionally, curves for both patients with PTMC and FTMC remained flat with only a minimal decline (**Figure 1A-C**). All-cause mortality rates in patients < 45 years with ITC, PTMC, and FTMC did not decline significantly either (**Figure 2A-C**). Similar results for cancer-specific survival curves (**Figure 5A-C**) and all-cause survival curves (**Figure 6A-C**) were obtained for patients under < 45 years with ITC as for patients with PTMC and FTMC without tumor extension.

On univariate Cox regression analyses, the cancer-specific mortality HR for patients with ITC under 45 years was not obtainable as no deaths occurred during the follow-up period. However, the cancer-specific mortality HR for patients with FTMC was 5.29 when compared to those with PTMC. After adjusting for race, sex, and year at diagnosis, the cancer-specific mortality HR in patients with FTMC was 5.01 compared to those with PTMC. Moreover, adjusting for race, sex, yaer at diagnosis, multifocality, extension, surgery, and radiation treatment yielded a cancer-specific mortality HR of 5.05 in patients with FTMC when compared to

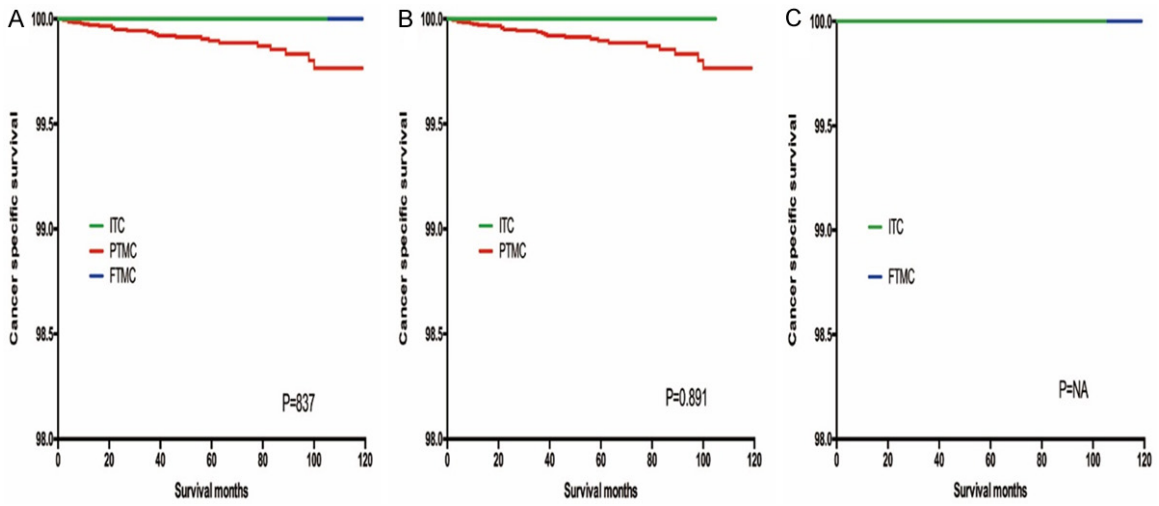

Figure 5. Kaplan Meier curves for cancer-specific survival among patients without extension stratified by subtype: ITC < 45, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

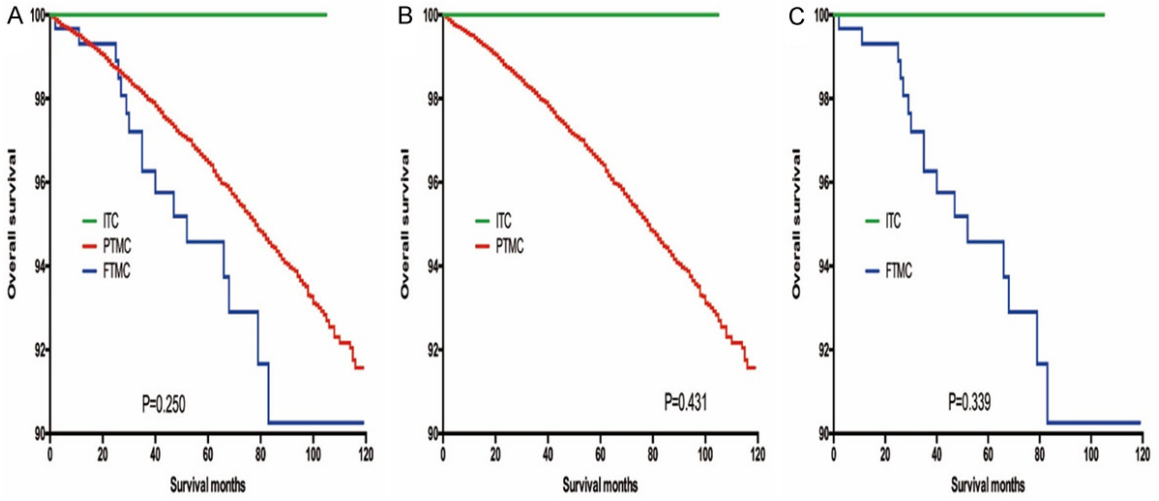

Figure 6. Kaplan Meier curves for all-cause survival without extension among patients stratified by subtype: ITC < 45, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

those with PTMC (**Table 5**). According to univariate Cox regression analyses, the HR for all-cause mortality in patients with FTMC was 1.57 compared to those with PTMC. After adjusting for race, sex, and year at diagnosis, the all-cause mortality HR in patients with FTMC was 1.50 compared to those with PTMC; after adjusting for race, sex, year at diagnosis, multifocality, extension, surgery, and radiation treatment, the cancer-specific mortality of patients with FTMC was 1.46 compared to those with PTMC (**Table 5**). Similar results for all-cause mortality were obtained when comparing patients with FTMC to those with PTMC without tumor extension (Table S5).

Cancer specific deaths and all cause deaths rates for ITC < 55 years, PTMC and FTMC

According to the AJCC stage system 8.0, the age cut-off was set as 55 years old, therefore, we analyzed the prognosis of younger (< 55 years) patients with ITC and PTMC, FTMC. In the study cohort, the cancer-specific mortality rate, per 1000 person-years, for younger (< 55 years) patients with ITC, PTMC and FTMC were 0, 0.24 and 1.39, respectively. The all-cause

Table 4. Cancer specific and all-cause deaths in patients with different histological types (ITC < 55 years, PTMC, and FTMC)

Histological types	Cancer-Specific Deaths No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
ITC < 55 years	0	0	0	NA	0	0	0	NA
CPTC	34	0.1	0.24	0.17-0.34	1006	3.2	7.56	7.10-8.05
FTC	2	0.6	1.39	0.34-5.58	18	5.4	12.56	7.91-19.93

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

Table 5. Hazard ratios for cancer specific and all-cause deaths in patients with different histological types (ITC < 45 years, PTMC, and FTMC)

Histological types	Unadjusted Cox regression		Adjusted 1 Cox regression		Adjusted 1 Cox regression	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Cancer specific mortality						
PTMC	Ref		Ref		Ref	
ITC < 45 years	NA	NA	NA	NA	NA	NA
FTMC	5.29 (1.27-22.03)	0.010	5.01 (1.20-20.90)	0.027	5.05 (1.20-21.27)	0.027
All-cause mortality						
PTMC	Ref		Ref		Ref	
ITC < 45 years	NA	NA	NA	NA	NA	NA
FTMC	1.57 (0.99-2.51)	0.057	1.50 (0.92-2.34)	0.106	1.46 (0.91-2.32)	0.116

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; Adjusted Cox regression 1: adjusted for race, sex, and year at diagnosis. Adjusted Cox regression 2: adjusted for sex, race, year at diagnosis, multifocality, extension, surgery, and radiation treatment.

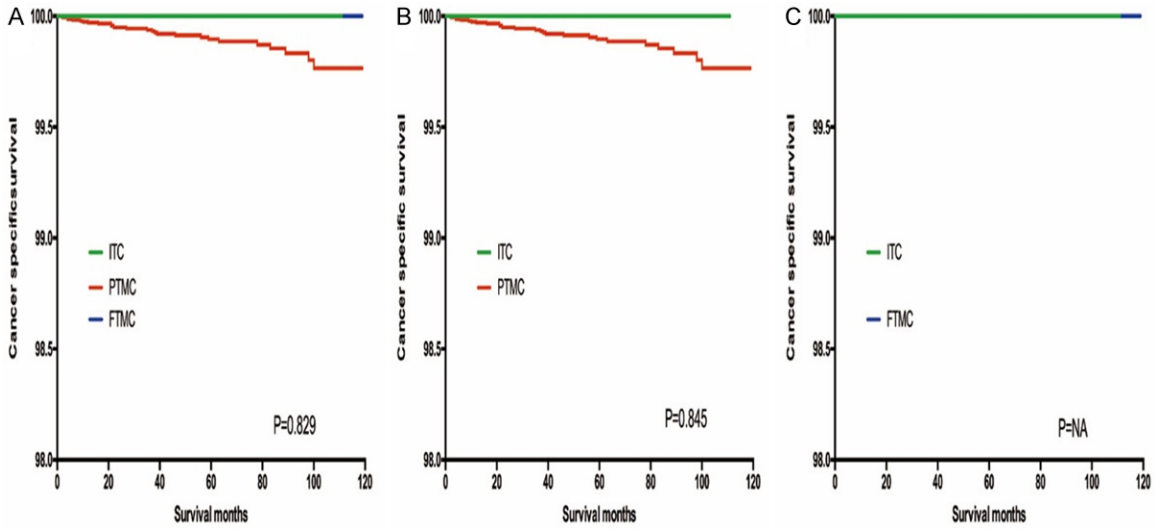

Figure 7. Kaplan Meier curves for cancer-specific survival without extension among patients stratified by subtype: ITC < 55, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

mortality rate, per 1000 person-years, for younger (< 55 years) patients with ITC, PTMC and FTMC were 0, 7.56 and 12.56, respectively (**Table 4**). When we analyzed the prognosis of younger (< 55 years) patients with ITC and PTMC, FTMC who had no tumor extensions; the cancer-specific mortality rate, per 1000 person-years, for younger (< 55 years) patients with ITC, PTMC and FTMC were 0, 0.22 and 0, respectively. While the all-cause mortality rate,

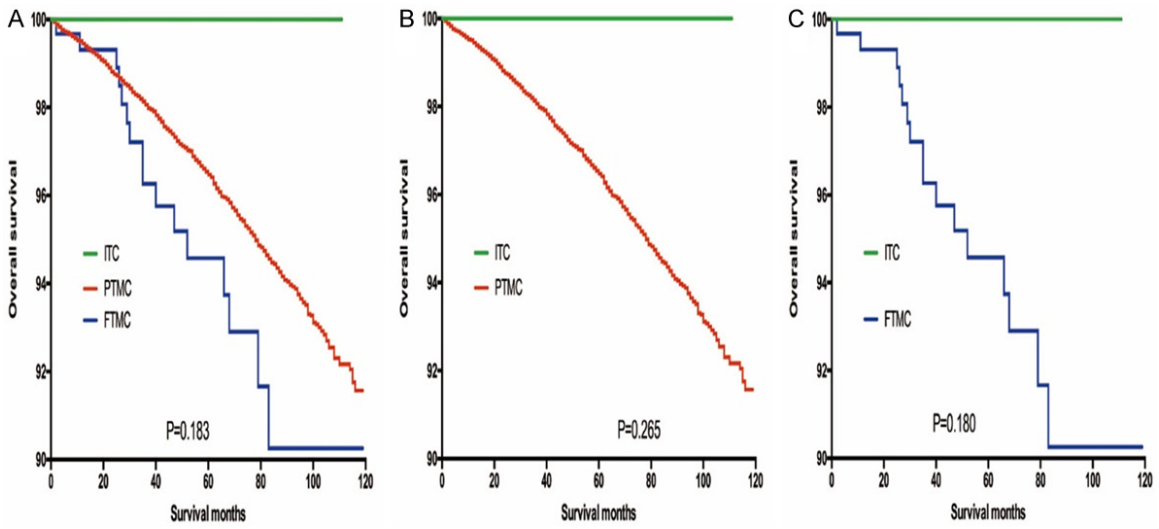

Figure 8. Kaplan Meier curves for all-cause survival without extension among patients stratified by subtype: ITC < 55, PTMC and FTMC (A-C); ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma.

Table 6. Hazard ratios for cancer specific and all-cause deaths in patients with different histological types (ITC < 55 years, PTMC, and FTMC)

Histological types	Unadjusted Cox regression		Adjusted 1 Cox regression		Adjusted 1 Cox regression	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Cancer specific mortality						
PTMC	Ref		Ref		Ref	
ITC < 55 years	NA	NA	NA	NA	NA	NA
FTMC	5.29 (1.27-22.03)	< 0.001	5.01 (1.20-20.90)	0.027	5.05 (1.20-21.27)	0.027
All-cause mortality						
PTMC	Ref		Ref		Ref	
ITC < 55 years	NA	NA	NA	NA	NA	NA
FTMC	1.57 (0.97-2.51)	0.116	1.47 (0.92-2.34)	0.106	1.46 (0.91-2.32)	0.116

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; Adjusted Cox regression 1: adjusted for race, sex, and age at diagnosis. Adjusted Cox regression 2: adjusted for sex, race, year at diagnosis, multifocality, extension, surgery, and radiation treatment.

per 1000 person-years were 0, 7.61 and 11.58, respectively (Table S4).

On Kaplan-Meier analyses, cancer-specific survival curves for patients < 55 years with ITC kept steady during the follow-up period, additionally, curves for both PTMC and FTMC remained flat with only a minimal decline (**Figure 3A-C**). All-cause mortality rates in patients < 55 years with ITC, PTMC and FTMC did not decline significantly either (**Figure 4A-C**). Similar results for cancer-specific survival curves (**Figure 7A-C**) and all-cause survival curves (**Figure 8A-C**) were obtained for the patients with under 55 years with ITC as for patients with PTMC and FTMC without tumor extension.

On univariate Cox regression analyses, similarly, the cancer specific mortality and all-cause mortality rates HR for patients with ITC under 55 years was not obtainable as no deaths occurred during the follow-up period (**Table 6**). The all-cause mortality HR for patients with FTMC was 1.44 when compared to these with PTMC without tumor extension; after adjusting for race, sex and year at diagnosis, the all-cause mortality HR for patients with FTMC was 1.35 compared to these with PTMC without tumor extension; moreover, adjusting for race, sex and year at diagnosis, multifocality, extension, surgery and radiation treatment yielded a cancer specific mortality HR of 1.34 in patients with FTMC when compared to those of PTMC without tumor extension (Table S6).

Discussion

Perhaps owing to improvements in imaging technologies, the incidence of thyroid cancer has been increasing dramatically. Most PTMCs are indolent unless they involve 1 or more high-risk factors such as old age, extrathyroidal and/or extranodal extension, clinical lymph node involvement and/or distant metastasis [1], and large tumor size. To avoid overtreatment, some institutions (including Kuma Hospital) recommend observation for patients with low-risk tumors instead of immediate surgery [19, 29].

Aside from low-risk PTMC, non-invasive, well-circumscribed, and encapsulated follicular variant of papillary thyroid carcinoma was also reported to exhibit a markedly indolent clinical course when stringently selected for (i.e., lacking lymph node and distant metastases), and many investigators recommended that it be re-categorized as a benign disease referred to as 'non-invasive follicular thyroid neoplasm with papillary-like nuclear features' [30-33]. Recently, Xu et al. showed that PTMC with a non-invasive, encapsulated follicular variant morphology was biologically indolent, and cautioned against its overtreatment [30].

we analyzed all the histological types (more than 100 types) of thyroid cancer by SEER database, and tried to find out that if any other type of thyroid cancer may be more suitable for active surveillance than PTMC. ITC, which was traditionally considered a poorly differentiated carcinoma with worse outcomes than PTMC, is characterized by a partial loss of thyroidal differentiation. According to the most recent American Thyroid Association guidelines, it occupies a morphologically and behaviorally intermediate category between well-differentiated papillary and follicular carcinomas and fully dedifferentiated anaplastic carcinomas [1, 12]. In our previous study, however, the cancer-specific mortality rate in patients with ITC was lower than in those with classic papillary thyroid cancer but similar to that in patients with follicular thyroid cancer after adjusting for potentially influencing factors using propensity score matching analysis [11]. In fact, it remains debatable whether an insular histology is associated independently with prognosis [14, 17, 34]. As such, our data provided a new perspective concerning the treatment of ITC, especially in categories with excellent prognoses.

In our present study, we included patients with ITC as well as those with PTMC and FTMC with no lymph node and distant metastases and/or tumoral extensions, and found that younger patients with ITC (< 45 years) enjoyed very good prognoses compared to patients with PTMC or FTMC. As the cut-off age was recently revised to 55 years for differentiated thyroid cancers in the AJCC 8.0 guidelines, we reanalyzed ITC patients in the SEER database who were < 55 years, and obtained similar results.

Decaussin et al. demonstrated that patients with well-differentiated thyroid cancer exhibiting an insular component were 17 times more likely to have distant metastases, which is a key marker of poor survival and is known to occur in 4-23% of patients with well-differentiated thyroid cancer. In our previous study, distant metastasis was detected in 22.4% of all patients with ITC, which was a significantly higher rate than those in classic papillary and follicular thyroid cancers (1.3% and 6.0%, respectively) [11]. However, when we excluded patients with distant and lymph node metastases according to the criteria of active surveillance [19, 26, 35], we found that the prognoses of younger patients with ITC (analyzing patients < 45 or < 55 years of age) were similar to those of patients with PTMC; both categories of patients had excellent survival rates.

Hadiza et al. suggested that radioactive iodine treatment was associated with improved survival in patients with ITC even if they had distant metastasis [12]. In our present study, the irradiation rate of younger patients with ITC was indeed higher than those of patients with PTMC and FTMC; however, the cancer-specific and all-cause survival rates were not significantly different between younger ITC and PTMC patients, or between younger ITC and FTMC patients. Therefore, we suggest that younger patients with ITC should also be considered for active surveillance due to their excellent prognoses, with reasonable caution.

Our study had several limitations. First, our data were retrospectively obtained only from the SEER database; the study lacked prospective data of low-risk patients with ITC. Furthermore, our dataset analyzed the prognoses of low-risk patients only according to cancer-specific and all-cause mortality rates with no information on recurrence, which may have

led to overestimation. Another limitation is that family history, vascular invasion, other histologic findings, preoperative ultrasonographic data, and molecular mutations (such as *BRAF*, *RAS*, and *TERT* mutations) were not evaluated or considered in our study. Furthermore, the SEER is a United States-based database, and the findings may not be applicable worldwide.

In summary, we found that younger patients diagnosed with ITC had similar prognoses to those with low-risk PTMC. Our findings offer new implications regarding the understanding of rare histological subtypes of thyroid cancer, and challenges the current clinical practice of indiscriminately treating ITC as a uniformly high-risk disease. Furthermore, our unexpected findings ought to serve as a reference for the planning of future therapies, including active surveillance, by adjusting the intensity of the interventions based on the prognosis of this disease.

Disclosure of conflict of interest

None.

Address correspondence to: Liang Guo and Min Wang, Zhongnan Hospital of Wuhan University, Donghu Road 169, Wuchang District, Wuhan, Hubei Province, China. Tel: +8618062581998; E-mail: guoliangwhzn@163.com (LG); wangminwhzn@163.com (MW)

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Table S1. Baseline characteristics of patients without tumor extension of different histological types (ITC < 45 years, PTMC, and FTMC) treated between 2004 and 2013

Covariate	Level	ITC[a] < 45 years (n=18)	Histological types			
			PTMC[b] (n=30133)	P	FTMC[c] (n=324)	P
Age at diagnosis, (IQR), years		36.0 (21.8-42.3)	52.0 (42.0-61.0)	-	51.0 (41.0-62.0)	-
Median year at diagnosis (IQR)		2008 (2006-2011)	2009 (2007-2012)	0.426	2009 (2007-2011)	0.730
Sex	Female	12 (66.7%)	25035 (83.1%)	0.063	258 (79.6%)	0.189
	Male	6 (33.3%)	5098 (16.9%)		66 (20.4%)	
Race	White	12 (70.6%)	25068 (84.2%)	0.190	263 (81.2%)	0.483
	Black	3 (17.6%)	2073 (7.0%)		29 (9.0%)	
	Other	2 (11.8%)	2638 (8.9%)		24 (7.4%)	
Tumor size, (IQR), mm		35.0 (27.5-48.5)	5.0 (3.0-8.0)	-	8.0 (5.0-9.75)	-
Multifocality	No	14 (82.4%)	20467 (68.4%)	0.216	264 (81.5%)	0.647
	Yes	3 (17.6%)	9455 (31.6%)		53 (16.4%)	
Radiation	None or refused	5 (27.8%)	23662 (78.5%)	< 0.001	233 (71.9%)	< 0.001
	Performed	13 (72.2%)	6471 (21.5%)		91 (28.1%)	
Surgery	Lobectomy	4 (22.2%)	7570 (25.1%)	0.723	86 (26.5%)	0.731
	Subtotal or near-total thyroidectomy	0 (0%)	1384 (4.6%)		13 (4.0%)	
	Total thyroidectomy	14 (77.8%)	20785 (69.0%)		221 (68.2%)	
Median follow-up time, (IQR), months		57.0 (21.5-75.3)	44.0 (20.0-74.0)	0.628	49.0 (25.0-77.0)	0.932

NOTE: *P*-values were calculated using the chi-squared test or Mann-Whitney U test. ITC[a]: ITC < 45 years and without extension; PTMC[b]: PTMC without extension; FTMC[c]: FTMC without extension. Abbreviations: ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; IQR, interquartile range.

Table S2. Baseline characteristics of patients without extension of different histological types (ITC < 55 years, PTMC and FTMC) treated between 2004 and 2013

Covariate	Level	ITC[a] < 55 years (n=32)	Histological types			
			PTMC[b] (n=30133)	P	FTMC[c] (n=324)	P
Age at diagnosis, (IQR), years		43.0 (32.8-46.8)	52.0 (42.0-61.0)	-	51.0 (41.0-62.0)	-
Median year at diagnosis (IQR)		2009 (2005-2010)	2009 (2007-2012)	0.062	2009 (2007-2011)	0.228
Sex	Female	14 (43.8%)	25035 (83.1%)	< 0.001	258 (79.6%)	< 0.001
	Male	18 (56.3%)	5098 (16.9%)		66 (20.4%)	
Race	White	24 (75.0%)	25068 (84.2%)	0.167	263 (81.2%)	0.660
	Black	5 (15.6%)	2073 (7.0%)		29 (9.0%)	
	Other	2 (6.3%)	2638 (8.9%)		24 (7.4%)	
Tumor size, (IQR), mm		46.0 (35.0-73.0)	5.0 (3.0-8.0)	-	8.0 (5.0-9.75)	-
Multifocality	No	24 (75.0%)	20467 (68.4%)	0.147	264 (81.5%)	0.671
	Yes	7 (21.9%)	9455 (31.6%)		53 (16.4%)	
Radiation	None or refused	10 (31.3%)	23662 (78.5%)	< 0.001	86 (26.5%)	< 0.001
	Performed	22 (68.8%)	6471 (21.5%)		13 (4.0%)	
Surgery	Lobectomy	4 (12.5%)	7570 (25.1%)	0.138	86 (26.5%)	0.139
	Subtotal or near-total thyroidectomy	0 (0%)	1384 (4.6%)		13 (4.0%)	
	Total thyroidectomy	28 (87.5%)	20785 (69.0%)		221 (68.2%)	
Median follow-up time, (IQR), months		55.0 (42.0-78.5)	44.0 (20.0-74.0)	0.095	49.0 (25.0-77.0)	0.279

NOTE: *P*-values were calculated using the chi-squared test or Mann-Whitney U test. ITC[a]: ITC < 55 years and without extension; PTMC[b]: PTMC without extension; FTMC[c]: FTMC without extension. Abbreviations: ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; IQR, interquartile range.

Table S3. Cancer specific and all-cause deaths in patients without extension of different histological types (ITC < 45 years, PTMC, and FTMC)

Histological types	Cancer-Specific Deaths, No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths, No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
ITC[a] < 45 years	0	0	0.0	NA	0	0.0	NA	0
PTMC[b]	30	0.1	0.22	0.15-0.32	970	3.2	7.61	7.13-8.12
FTMC[c]	0	0	0	5.72-7.81	16	4.9	11.58	7.09-18.91

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; ITC[a]: ITC < 45 years and without extension; PTMC[b]: papillary thyroid microcarcinoma without extension; FTMC[c]: follicular thyroid microcarcinoma without extension.

Table S4. Cancer specific and all-cause deaths in patients without extension of different histological types (ITC < 55 years, PTMC, and FTMC)

Histological types	Cancer-Specific Deaths, No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths, No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
ITC[a] < 55 years	0	0	0	NA	0	0	0	NA
PTMC[b]	30	0.1	0.22	0.15-0.32	970	3.2	7.61	7.13-8.12
FTMC[c]	0	0	0	5.72-7.81	16	4.9	11.58	7.09-18.91

ITC: insular thyroid carcinoma; CPTC: classic papillary thyroid cancer; FTC: follicular thyroid carcinoma. ITC[a]: ITC < 55 years and without extension; PTMC[b]: papillary thyroid microcarcinoma without extension; FTMC[c]: follicular thyroid microcarcinoma without extension.

Table S5. Hazard ratios for cancer specific and all-cause deaths in patients without extension of different histological types (ITC < 45 years, PTMC, and FTMC)

Histological types	Unadjusted Cox regression		Adjusted 1 Cox regression		Adjusted 2 Cox regression	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Cancer specific mortality						
PTMC[b]	Ref		Ref		Ref	
ITC[a] < 45 years	NA	NA	NA	NA	NA	NA
FTMC[c]	NA	NA	NA	NA	NA	NA
All-cause mortality						
PTMC[b]	Ref		Ref		Ref	
ITC[a] < 45 years	NA	NA	NA	NA	NA	NA
FTMC[c]	1.44 (0.88-2.37)	0.145	1.35 (0.82-2.21)	0.240	1.34 (0.82-2.20)	0.245

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; ITC[a]: ITC < 45 years and without extension; PTMC[b]: papillary thyroid microcarcinoma without extension; FTMC[c]: follicular thyroid microcarcinoma without extension. Adjusted Cox regression 1: adjusted for race, sex, and age at diagnosis. Adjusted Cox regression 2: adjusted for sex, race, year at diagnosis, multifocality, extension, surgery, and radiation treatment.

Table S6. Hazard ratios for cancer specific and all-cause deaths in patients without extension of different histological types (ITC < 55 years, PTMC, and FTMC)

Histological types	Unadjusted Cox regression		Adjusted 1 Cox regression		Adjusted 2 Cox regression	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Cancer specific mortality						
PTMC[b]	Ref		Ref		Ref	
ITC[a] < 55 years	NA	NA	NA	NA	NA	NA
FTMC[c]	NA	NA	NA	NA	NA	NA
All-cause mortality						
PTMC[b]	Ref		Ref		Ref	
ITC[a] < 55 years	NA	NA	NA	NA	NA	NA
FTMC[c]	1.44 (0.88-2.37)	0.145	1.35 (0.82-2.21)	0.239	1.34 (0.82-2.21)	0.244

ITC: insular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; FTMC: follicular thyroid microcarcinoma; ITC[a]: ITC < 55 years and without extension; PTMC[b]: papillary thyroid microcarcinoma without extension; FTMC[c]: follicular thyroid microcarcinoma without extension. Adjusted Cox regression 1: adjusted for race, sex, and age at diagnosis. Adjusted Cox regression 2: adjusted for sex, race, year at diagnosis, multifocality, extension, surgery, and radiation treatment.