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Comparative histopathological analysis of sporadic pediatric papillary thyroid carcinoma from Japan and Ukraine

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Abstract. This study set out to compare structural and invasive characteristics of sporadic papillary thyroid carcinoma (PTC) in age-matched groups of children and adolescents of Japan and Ukraine to provide detailed histopathological analysis of tumors from different geographical areas with different iodine intake. A total of 348 (160 Japanese and 188 Ukrainian) PTCs from patients without radiation history were analyzed initially as a combined pediatric group and then subdivided into childhood (aged ≤ 14 years) and adolescent (aged from 15 to ≤ 18 years) age series. On multivariate comparison, the Japanese pediatric PTC was characterized by a higher sex ratio ($p=1.504E-4$), and a higher frequency of microcarcinoma ($p=0.039$), papillary dominant growth pattern ($p=0.024$), focal oxyphilic cell metaplasia ($p=7.644E-6$), intrathyroid spread ($p=0.010$), lymphatic/vascular invasion ($p=0.01$) and regional lymph node metastases ($p=3.540E-6$). In the Ukrainian group, multifocal ($p=0.004$) and non-encapsulated tumors with the solid-trabecular growth pattern ($p=0.05$) were more frequent. Childhood Japanese PTCs differed from Ukrainian PTCs by more pronounced invasive properties such as lymphatic/vascular invasion and nodal disease, but did not differ by the dominant growth pattern. In adolescents, the differences were detected not only for lymph node metastases, but also for a higher frequency of the papillary dominant pattern in Japanese PTC. Overall, significantly higher frequencies of oxyphilic cell metaplasia and more pronounced invasive features observed in the Japanese PTC in both age-matched series represent the major differences between the tumors from two geographical areas.

Key words: Pediatric papillary thyroid carcinoma, Pathology, Japan, Ukraine, Sporadic thyroid cancer

DIFFERENTIATED THYROID CANCER is rare at young age and accounts for 0.5-3% of all pediatric malignancies [1]. In Japan, according to the Center for Cancer Control and Information Services, National Cancer Center, incidence of thyroid cancer in children 0-19 years old varied age-dependently from 0 to 1.4 per 100,000 during 2002-2012 [2]. In Ukraine, incidence of sporadic thyroid cancer in children aged 4-18 years was from 0.1 to 2.4 per 100,000 during 2006-2014 [3].

Our previous work reported differences in tumor structure and invasive properties between Japanese and Ukrainian sporadic papillary thyroid carcinoma (PTC) in adult patients [4]. The Japanese PTC was characterized by a higher frequency of papillary architecture and invasive features such as extrathyroidal extension and regional lymph node metastases. Ukrainian PTC displayed the higher frequency of solid growth pattern and of oxyphilic cell metaplasia. These differences were ascribed to distinct geographical origin with corresponding country-specific diet and different iodine consumption, and to different genetic backgrounds.

By contrast, single papers on the comparative analysis of Japanese and Belarussian-Ukrainian pediatric PTC pointed at the higher frequency of solid structural component and more frequent invasive

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features in the latter. The higher invasiveness of Belarussian-Ukrainian PTC is at variance with adult PTC. Importantly, however, these comparisons were made between the tumors developing after radiation exposure from the Chernobyl fallouts in Belarus and Ukraine, and sporadic PTC from Japan [5, 6], which are etiologically different.

The aim of this study was to answer whether sporadic pediatric PTC from Ukraine displays the differences in tumor architectonics and invasiveness similar to those seen in sporadic adult tumors or in radiation-related pediatric ones, as compared to sporadic PTC in age-matched group of patients from Japan.

Materials and Methods

Patients

The total number of cases of pediatric PTC was 348, including 160 patients operated at Kuma Hospital (Kobe city, Japan), which is one of the main centers of endocrine surgery in the country, and 188 operated at State Institution “V.P.Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine” (Kiev, Ukraine), a leading research center for study and treatment of thyroid diseases in Ukraine. None of patients had radiation history. All patients from Japan lived in the Prefectures other than Fukushima, and their tumors were not detected during ultrasound screening. Patients from Ukraine were born after the Chernobyl accident since 1987 when radioactive iodine had decomposed and resided in the regions of Ukraine distant from Chernobyl. For each country, all PTCs were firstly analyzed as a whole pediatric group and then subdivided into two age series: children aged ≤ 14 (42 Japanese cases and 98 Ukrainian) and adolescents aged from 15 to ≤ 18 years (118 and 90 cases, respectively) in order to perform a comparison with previously published data [5, 6].

Histopathology

Histopathological examination of hematoxylin/eosin stained paraffin sections was initially performed at the centers of origin by two experienced pathologists (MH and TH at Kuma Hospital, and TB and LZ at the Institute of Endocrinology and Metabolism). The pathological classification was based on the World Health Organization definitions [7].

Joint protocol was developed for the analysis

of morphological characteristics by TB, MH, MI and VS. Tumor size, as a continuous variable, was defined by the largest diameter on macroscopic pathological description. Tumor architecture determined by the dominant histological pattern (papillary, follicular or solid-trabecular when corresponding structure represented $> 50\%$ of tumor section) and invasive characteristics were used as categorical data. Only marked intrathyroid spread over the lobe/lobes was considered positive, including the diffuse-sclerosing variant-like one. Lymphatic and blood vessel invasion were combined into one parameter, the lymphatic/vascular invasion. Extrathyroidal extension included not only tumor invasion to the muscle, but also minimal protrusion beyond the thyroid capsule to adjacent adipose and connective tissues. Distant metastases to the lung were determined by radioactive iodine scans performed following thyroidectomy. No distant metastases to the bone, the brain or other sites were detected. Tumor staging was according to the 7th edition of TNM classification system [8], which assigns minimal extrathyroidal extension pT3 category [4, 9].

Oxyphilic (oncocytic/Hurtle) cell metaplasia was evaluated as absent, focal or severe, including oxyphilic cell PTC. Concomitant nodular or diffuse thyroid pathology was also considered as categorical variables. The analysis of rarer histological subtypes between the two countries was done separately.

TB and MI re-reviewed histological specimens and entered all data digitally into spreadsheets for subsequent statistical analysis.

Statistical analysis

Fisher's exact test for categorical data and Mann-Whitney or Kruskal-Wallis tests for quantitative measurements were used in univariate analyses. Multivariate logistic regression analyses, either binary or multinomial, were adjusted for age at surgery and sex. Calculations were performed using IBM SPSS Statistics Version 21 software (International Business Machines Corp., Armonk, NY, USA); p -values were 2-sided and considered significant if $p \leq 0.05$.

Our previous studies showed that invasive properties of PTC significantly differed between fully encapsulated and non-encapsulated/partially encapsulated tumors [10]. Therefore, separate analyses were performed for all, fully encapsulated and non-encapsulated tumors.

Results

Pediatric Japanese and Ukrainian sporadic PTC

Comparative analysis of pediatric sporadic PTC (all patients) from the two countries showed significantly younger patients' age at surgery in Ukrainian series (Table 1; 14.1 ± 3.2 vs. 16.0 ± 2.8 years, $p=2.150E-10$). In both groups female patients were prevailing, but the relative proportion of male patients was markedly higher in Ukrainian than in Japanese group (F:M ratio 2.6:1 vs. 7.9:1, respectively, $p=1.504E-4$), as was the frequency of fully encapsulated PTC (OR=4.626, $p=0.001$). There was no difference in mean size of tumors from the two countries, although in the Ukrainian group the frequency of non-encapsulated micro-PTC measuring ≤ 10 mm was nearly two times lower as compared to the Japanese (9.0% vs. 18.7%, $p=0.039$ on univariate analysis, Supplementary Table 1).

Ukrainian PTC in comparison with the Japanese tumors also displayed statistically significant differences both in the dominant tumor growth pattern and invasive properties on multivariate analysis adjusted for sex and age. The lower frequency of dominant

papillary growth pattern (OR=0.519, $p=0.024$), focal oxyphilic cell metaplasia (OR=0.191, $p=7.644E-6$), intrathyroid spread (OR=0.509, $p=0.010$), lymphatic/vascular invasion (OR=0.517, $p=0.010$) and regional lymph node metastases (OR=0.290, $p=3.540E-6$) was observed (Table 1). On the other hand, Ukrainian PTCs displayed a higher frequency of tumors with the dominant solid pattern (OR=1.776, $p=0.050$ for non-encapsulated tumors, Supplementary Table 1) and multifocal growth (OR=5.300, $p=0.004$). All these associations were mostly seen for non-encapsulated PTCs, the frequency of which was significantly higher in Ukrainian cases (OR=4.626, $p=0.001$).

When PTCs with the dominant papillary growth pattern were analyzed (Supplementary Table 2), a lower frequency of tumors with important indicators of tumor invasiveness such as lymphatic/vascular invasion (OR=0.519, $p=0.044$) and regional lymph node metastases (OR=0.336, $p=0.005$), as well as with focal oxyphilic cell metaplasia (OR=0.204, $p=4.020E-6$) was observed in the Ukrainian group. PTCs with the solid-trabecular architecture displayed minor differences in tumor invasiveness (Supplementary Table 3),

Table 1 Comparative characteristics of the Japanese and Ukrainian pediatric sporadic papillary thyroid carcinoma (all patients aged ≤ 18 years at surgery)

	Japan (n=160)		Ukraine (n=188)		p-value (uni)	OR (95% CI) ²	p-value (multi) ³
	Number or value	% or SD ¹	Number or value	% or SD			
Baseline characteristics and tumor histopathology							
Age (mean, years)	16.0	2.8	14.1	3.2	2.150E-10		
Sex (F/M)	142/18	F:M=7.9:1	136/52	F:M=2.6:1	1.504E-4		
Tumor capsule	6	3.7	31	16.5	8.995E-5	4.626 (1.826-11.719)	0.001
Size (mean, mm)	23.4	14.3	24.1	14.3	0.706		
Size ≤ 10 mm	30	18.7	23	12.2	0.101	0.686 (0.367-1.282)	0.237
Dominant pattern							
Papillary	99	61.9	88	46.8	0.005	0.519 (0.375-0.934)	0.024
Follicular	34	21.2	49	26.1	0.315	1.255 (0.736-2.141)	0.405
Solid-trabecular	27	16.9	51	27.1	0.028	1.683 (0.967-2.930)	0.066
Oxyphilic changes	84	52.5	48	25.5	2.903E-7	0.334 (0.207-0.540)	7.606E-6
Concomitant nodular pathology	15	9.4	18	9.6	1.000	1.171 (0.543-2.523)	0.687
Concomitant diffuse pathology	61	38.1	55	29.3	0.088	0.869 (0.539-1.401)	0.565
Tumor invasiveness							
Intrathyroid spread	53	33.1	43	22.9	0.041	0.509 (0.305-0.851)	0.010
Extrathyroidal extension (pT3)	77	48.1	96	51.1	0.593	0.870 (0.551-1.373)	0.550
Multifocality (pTm)	4	2.5	22	11.7	0.001	5.300 (1.728-16.257)	0.004
Lymphatic/vascular invasion	122	76.3	123	65.4	0.034	0.517 (0.313-0.865)	0.010
Lymph node metastases (pN1)	129	80.6	110	58.5	9.448E-6	0.290 (0.171-0.489)	3.540E-6
Distant metastases (M1)	14	8.8	20	10.6	0.591	0.671 (0.299-1.507)	0.334

¹ % for count data, SD for continuous numeric data. ² Corresponding parameters in the Japanese series served as a reference. ³ Adjusted for age and sex. (Here and hereafter in the Tables and Supplementary Tables the numbers in bold indicate statistical significance.)

which was relatively high for both countries, except for the lower frequency of lymph node metastases in the Ukrainian group (OR=0.278, $p=0.035$).

The subdivision of PTCs by one of the three dominant structural components (papillary, follicular or solid-trabecular) demonstrated that in the Japanese group (Supplementary Table 4), focal oxyphilic cell metaplasia specifically associated with the papillary tumor structure ($p<0.03$ for comparisons with all other growth patterns). The frequency of concomitant chronic thyroiditis (OR=2.956, $p=0.031$) and of lymph node metastases (OR=2.656, $p=0.042$) was higher for the tumors with papillary growth than for those with follicular pattern. At the same time, the frequency of extrathyroidal extension of tumors with papillary growth pattern was lower than of PTCs with solid-trabecular structure (OR=0.349, $p=0.024$).

In the Ukrainian group (Supplementary Table 5), dominant follicular growth pattern was associated with the presence of tumor capsule ($p<0.01$ for all comparisons) and with the lower chance of concomitant chronic thyroiditis ($p<0.05$ for all comparisons). Tumors with follicular growth pattern also displayed the lower frequency of severe oxyphilic cell metaplasia

(OR=0.060, $p=0.009$) and of extrathyroidal extension (OR=0.423, $p=0.041$) than those with dominant solid-trabecular structure, and of lymphatic/vascular invasion (OR=0.288, $p=0.035$) as compared with PTCs with the papillary growth pattern. Solid-trabecular structures were associated with the higher frequency of severe oxyphilic cell metaplasia (OR=7.614, $p=0.001$) and, similarly to the Japanese group, of extrathyroidal extension (OR=2.297, $p=0.047$).

Childhood Japanese and Ukrainian sporadic PTC

The results of analysis are presented in Table 2. The relative proportion of male patients was higher in the Ukrainian than in Japanese series, but only for non-encapsulated tumors the ratio was borderline statistically significant (F:M ratio 2.0:1 vs. 5.5:1, respectively, $p=0.050$, Supplementary Table 6). There were no differences in the mean size of tumors or in the frequency of micro-PTC, as well as in the frequency of each of three dominant components (Table 2).

In childhood Ukrainian PTC, similarly to the combined pediatric group, the lower frequency of focal oxyphilic cell metaplasia (OR=0.263, $p=0.003$), intrathyroid spread (OR=0.435, $p=0.040$), lymphatic/

Table 2 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma in children aged ≤ 14 years at surgery

	Japan (<i>n</i> =42)		Ukraine (<i>n</i> =98)		<i>p</i> -value (uni)	OR (95% CI) ²	<i>p</i> -value (multi) ³
	Number or value	% or SD ¹	Number or value	% or SD			
Baseline characteristics and tumor histopathology							
Age (mean, years)	12.1	2.3	11.7	2.6	0.418		
Sex (F/M)	36/6	F:M=6.0:1	68/30	F:M=2.3:1	0.057		
Tumor capsule	3	7.1	19	19.4	0.079	3.495 (0.961-12.709)	0.057
Size (mean, mm)	24.0	14.7	24.2	14.2	0.095		
Size ≤ 10 mm	3	7.1	11	11.2	0.554	1.570 (0.403-6.124)	0.516
Dominant pattern							
Papillary	22	52.4	43	43.9	0.363	0.686 (0.327-1.441)	0.320
Follicular	12	28.6	25	25.5	0.835	0.923 (0.399-2.138)	0.857
Solid-trabecular	8	19.0	30	30.6	0.214	1.813 (0.739-4.447)	0.194
Oxyphilic changes	21	50.0	21	21.4	0.001	0.265 (0.119-0.590)	0.001
Concomitant nodular pathology	3	7.1	9	9.2	1.000	1.230 (0.309-4.905)	0.769
Concomitant diffuse pathology	14	33.3	27	27.6	0.545	0.910 (0.404-2.052)	0.820
Tumor invasiveness							
Intrathyroid spread	17	40.5	23	23.5	0.065	0.435 (0.197-0.961)	0.040
Extrathyroidal extension (pT3)	25	59.5	58	59.2	1.000	0.919 (0.429-1.966)	0.827
Multifocality (pTm)	0	0.0	10	10.2	0.033	ND ⁴	ND
Lymphatic/vascular invasion	37	88.1	66	67.3	0.012	0.253 (0.089-0.721)	0.010
Lymph node metastases (pN1)	35	83.3	63	64.3	0.027	0.342 (0.136-0.861)	0.023
Distant metastases (M1)	7	16.7	15	15.3	0.806	0.766 (0.274-2.140)	0.611

¹ % for count data, SD for continuous numeric data. ² Corresponding parameters in the Japanese series served as a reference. ³ Adjusted for age and sex. ⁴ ND, not determined.

vascular invasion (OR=0.253, $p=0.010$) and regional lymph node metastases (OR=0.342, $p=0.023$) were observed. There were no multifocal tumors in Japanese patients in contrast to 10% in Ukrainian ($p=0.033$). The frequency of distant metastases to the lung in patients from both countries was higher than in the combined group of children and adolescents (8-10% vs. 15-16%, respectively) but no statistically significant difference was observed between the two countries.

Adolescent Japanese and Ukrainian sporadic PTC

Ukrainian patients were markedly younger than Japanese (Table 3; 16.7 ± 1.2 vs. 17.4 ± 1.1 years, respectively, $p=1.381E-5$). Similarly to the combined pediatric group, statistically significant difference was found for sex ratio (F:M ratio 3.1:1 vs. 8.8:1, $p=0.008$), and for the frequencies of fully encapsulated tumors (OR=5.658, $p=0.012$), small non-encapsulated PTC (OR=0.373, $p=0.029$), dominant papillary growth pattern (OR=0.537, $p=0.042$) and focal oxyphilic cell metaplasia (OR=0.288, $p=0.001$) in Ukrainian PTCs.

With regard to tumor invasiveness, significant difference was found only for the frequency of regional lymph

node metastases, which was lower in the Ukrainian series (OR=0.252, $p=4.906E-5$). Multifocality was more frequent in the tumors from Ukraine (OR=3.988, $p=0.025$), in line with the findings in childhood series and in the combined pediatric group.

All differences were confined to the non-encapsulated tumors (Supplementary Table 7).

Age-dependent changes in tumor invasiveness

In both countries, the age-related decline of tumor invasiveness was seen. In Japan (Supplementary Table 8), in non-encapsulated tumors there was a reduction in the frequencies of extrathyroidal extension (OR=0.471, $p=0.050$), lymphatic/vascular invasion (OR=0.210, $p=0.015$), and distant metastases (OR=0.306, $p=0.039$) in adolescents as compared to children. The decrease in tumor size and in the frequency of microcarcinoma was also observed ($p=0.014$ and 0.043 , respectively). In Ukrainian cases (Supplementary Table 9), a reduction in the frequencies of extrathyroidal extension (OR=0.345, $p=0.002$), regional lymph node metastases (OR=0.490, $p=0.043$), and distant metastases (OR=0.306, $p=0.031$) were found for non-encapsulated tumors.

Table 3 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma in adolescents aged from 15 to ≤ 18 years at surgery

	Japan (<i>n</i> =118)		Ukraine (<i>n</i> =90)		<i>p</i> -value (uni)	OR (95% CI) ²	<i>p</i> -value (multi) ³
	Number or value	% or SD ¹	Number or value	% or SD			
Baseline characteristics and tumor histopathology							
Age (mean, years)	17.4	1.1	16.7	1.2	1.381E-5		
Sex (F/M)	106/12	F:M=8.8:1	68/22	F:M=3.1:1	0.008		
Tumor capsule	3	2.5	12	13.3	0.005	5.658 (1.452-22.041)	0.012
Size (mean, mm)	21.9	14.2	24.0	14.5	0.298		
Size ≤ 10 mm	27	22.9	12	13.3	0.106	0.464 (0.210-1.028)	0.059
Dominant pattern							
Papillary	77	65.3	45	50.0	0.033	0.537 (0.295-0.979)	0.042
Follicular	22	18.6	24	26.7	0.181	1.621 (0.803-3.271)	0.178
Solid-trabecular	19	16.1	21	23.3	0.216	1.539 (0.727-3.258)	0.260
Oxyphilic changes	63	53.4	27	30.0	0.001	0.373 (0.200-0.692)	0.002
Concomitant nodular pathology	12	10.2	9	10.0	1.000	1.162 (0.445-3.032)	0.759
Concomitant diffuse pathology	47	39.8	28	31.1	0.244	0.797 (0.428-1.483)	0.474
Tumor invasiveness							
Intrathyroid spread	36	30.5	20	22.2	0.209	0.545 (0.275-1.079)	0.081
Extrathyroidal extension (pT3)	52	44.1	38	42.2	0.888	0.914 (0.506-1.651)	0.766
Multifocality (pTm)	4	3.4	12	13.3	0.016	3.988 (1.191-13.360)	0.025
Lymphatic/vascular invasion	85	72.0	57	63.3	0.229	0.715 (0.382-1.338)	0.294
Lymph node metastases (pN1)	94	79.7	47	52.2	4.408E-5	0.252 (0.129-0.490)	4.906E-5
Distant metastases (M1)	7	5.9	5	5.6	1.000	0.687 (0.190-2.479)	0.566

¹ % for count data, SD for continuous numeric data. ² Corresponding parameters in the Japanese series served as a reference. ³ Adjusted for age and sex.

Discussion

Histopathological features of Japanese childhood PTC were described just in two studies, in which the comparative analyses of radiogenic post-Chernobyl PTC and sporadic Japanese PTC were performed [5, 6]. In both of these publications, differences between the groups from two countries were detected for tumor architecture and invasiveness. Japanese childhood PTC was characterized by the higher frequency of the papillary architecture and the lower frequency of extrathyroidal extension than post-Chernobyl radiogenic tumors. It should be noted that during the study by Williams *et al.* [6], a limited number of sporadic PTCs detected in children born after the Chernobyl accident was also included (23 cases from Belarus, Ukraine and Russia cumulatively), which showed no difference in characteristics from radiogenic childhood post-Chernobyl PTCs. Consequently, the Japanese childhood PTC demonstrated a higher frequency of tumors with the dominant papillary structure and a lower frequency of extrathyroidal extension not only in comparison with post-Chernobyl radiogenic carcinomas, but also with sporadic PTC in children of Belarus, Ukraine and Russia.

By contrast, recent studies in larger series of radiogenic and sporadic Ukrainian and Belarusian PTCs did find certain difference in the morphological and invasive characteristics of pediatric tumors of different etiology [11, 12]. Therefore, in the present work we performed more detailed comparative histopathological analysis of Japanese and Ukrainian sporadic PTC in childhood and adolescent patients using a relatively large number of cases (160 and 188, respectively).

Our analysis, at variance to previous reports, demonstrated that childhood PTC showed no pronounced difference in the ratio of three main dominant growth pattern: papillary, follicular and solid-trabecular (see Table 2). On the other hand, a higher frequency of the papillary dominant growth pattern was observed in the Japanese adolescent PTC and in the combined pediatric group (see Tables 1, 3), similarly to earlier reports [5, 6].

The frequency of PTC with the dominant solid growth pattern was somewhat higher in both childhood and adolescent Ukrainian than in Japanese group, but statistical significance was achieved only in the combined group of pediatric PTC (see Table 1). The reported earlier higher frequency of the solid component in childhood PTC from Ukraine, Belarus and Russia [6], and in PTC of adult patients from Ukraine without radiation

history [4] was considered the major structural difference between Japanese and Ukrainian PTC. This difference has been proposed to be due to iodine deficiency in the areas around Chernobyl, including Ukraine. Less differentiated morphological features (solid-trabecular architecture) were associated with insufficient dietary iodine, whereas more differentiated tumor morphology (dominant papillary pattern) with adequate iodine intake. Iodine deficiency was thought to influence PTC morphology and tumor aggressiveness [6].

The present study did not confirm the above assumption regarding the difference in the architecture of Japanese and Ukrainian childhood PTC. One of the reasons for this may be that in the past, the Japanese pathologists used to classify thyroid tumors with an abundant solid component as poorly differentiated carcinomas. Consequently, such tumors might not have been previously included in the comparative analyses of PTC. Recently published data on the frequency of PTC with the dominant solid structure in Japanese patients aged ≤ 20 years at surgery [13] demonstrate that it is not meaningfully or significantly different from that in our study (8/81 cases, 10% vs. 27/160 cases, 16.9%, respectively, $p=0.177$). Results obtained in this work taken together with those of the previous study of adult PTC patients [4] suggest that iodine deficiency in Ukraine may influence the frequency of PTC with the solid growth pattern in adults, but not in children or adolescents separately.

It is interesting to note that the absence of difference in tumor architecture in childhood patients (see Table 2) and the higher frequency of the dominant papillary growth pattern in adolescents of Japan vs. Ukraine (see Table 3) might be partly explained by the presence of *BRAF*^{V600E} mutation in corresponding tumors, which is known to associate with the papillary tumor structure [14]. Reviewing two relatively recent molecular genetic analyses of Ukrainian [15] and Japanese [16] PTC, we found no statistically significant difference in the prevalence of this mutation between Ukrainian and Japanese sporadic childhood PTC (2/8, 25.0% vs. 3/9 33.3%, respectively; $p=1.000$). On the contrary, the difference was seen in adolescents (4/16, 25% in Ukraine and 18/24, 75% in Japan, $p=0.003$) that corresponds well to the higher frequency of tumors with the papillary architecture in this age subgroup. This explanation should certainly be viewed with caution because of the small size of childhood sample; it requires replication in larger independent groups.

The dominant growth pattern, discussed above, largely reflects the histological subtype/variant of PTC and/or indicates the prevalent structural component of tumors with mixed structure. Rarer PTC subtypes such as diffuse-sclerosing (DSV), Warthin-like (WLV) and tall cell (TCV) variants were identified in a small number of cases. DSV and WLV were observed in the Japanese group in 2 and 2 out of 160 cases (1.3% and 1.3%, respectively), and in 5 and 1 out of 188 Ukrainian cases (2.7%, and 0.5%, respectively), not significantly different between the countries ($p=0.459$ and $p=0.596$, respectively). DSV tumors were represented by the papillary or solid foci spreading to both lobes, and WLV by the dominant papillary growth pattern. TCV was detected only in the Japanese group in 5/160 cases (3.1%, OR=13.334, $p=0.020$ in comparison with the Ukrainian group by univariate analysis). TCV was represented by the dominant papillary growth pattern in 3 cases and by the solid-trabecular structure in 2 cases. Since the number of tumors of the rare PTC subtypes was small in both Japanese and Ukrainian series, they would unlikely have introduced significant bias in the comparative analysis of PTCs from the two countries.

In contrast to very modest difference in tumor architecture, a significantly higher frequency of the indicators of tumor invasiveness found concordantly in the Japanese pediatric (this study) and adult PTC [4] may suggest that iodine-rich diet could be a risk factor for higher morphological tumor aggressiveness in any age group. Noteworthy, the higher frequency of regional lymph node metastases in Japanese PTC was observed both in children and adolescents (see Tables 1-3), further attesting to the validity of a notion on a higher morphological aggressiveness of PTC in young Japanese patients.

Our results are also at variance with the previous report on the higher frequency of extrathyroidal extension in the Ukrainian-Belarusian-Russian childhood PTC as compared to tumors from Japan [6]. The prevalence of PTCs featuring extrathyroidal extension in the Japanese combined pediatric group in our study (77/160, 48.1%) nearly coincides with those in two studies of sporadic pediatric thyroid cancer from Japan: 63/142, 44.4% ($p=0.565$ for difference with our data) [17] and 32/80, 40.0% ($p=0.272$) [13]. We explain the discrepancy with the previous work [6] by a relatively small number of patients with sporadic PTC in it and also by the fact that radiogenic PTC after

Chernobyl apparently displays morphological features of tumor aggressiveness more frequently than sporadic tumors [11, 12].

In conclusion, our study demonstrated that childhood Japanese PTC differed from Ukrainian PTC by more pronounced invasive properties such as lymphatic/vascular invasion and nodal disease, but did not differ by the dominant growth pattern. In adolescents, the difference was detected not only for lymph node metastases, but also for a higher frequency of the papillary dominant pattern in Japanese PTC. Ukrainian PTC displayed more frequent multifocal tumor growth and less frequent oxyphilic cell changes. In the combined pediatric PTC, the higher frequency of tumor invasive features such as intrathyroid spread, lymphatic/vascular invasion and nodal disease, and of the dominant papillary growth pattern in the Japanese group were also confirmed. In addition, it was possible to detect a higher frequency of the solid dominant growth pattern and of multifocal growth, and the lower frequency of oxyphilic cell metaplasia in Ukrainian PTC. The results demonstrate the presence of considerable differences in clinicopathological characteristics of pediatric PTC from Japan and Ukraine, the geographic areas with very different dietary iodine intake.

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Disclosure

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

Supplementary Table 1 Comparative characteristics of the Japanese and Ukrainian pediatric sporadic papillary thyroid carcinoma for all, fully encapsulated and non-encapsulated tumors

	Japan (n=160)		Ukraine (n=188)		p value (uni)	OR (95% CI)	p value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	16.0	2.8	14.1	3.2	2.150E-10		
Fully encapsulated	15.8	1.7	13.5	3.7	0.172		
Non-encapsulated	16.0	2.8	14.2	3.1	3.326E-9		
Sex (F/M)							
All cases	142/18	F:M=7.9:1	136/52	F:M=2.6:1	1.504E-4		
Fully encapsulated	6/0	ND ³	23/8	F:M=2.9:1	0.305		
Non-encapsulated	136/18	F:M=7.6:1	113/44	F:M=2.6:1	3.515E-4		
Tumor capsule					8.995E-5	4.626 (1.826-11.719)	0.001
Full	6	3.7	31	16.5			
Partial/absent	154	96.3	157	83.5			
Size (mean, mm)							
All cases	23.4	14.3	24.1	14.3	0.706		
Fully encapsulated	27.5	11.6	21.9	11.0	0.265		
Non-encapsulated	23.3	14.4	24.5	14.9	0.531		
Size ≤ 10 mm							
All cases	30	18.7	23	12.2	0.101	0.686 (0.367-1.282)	0.237
Fully encapsulated	0	0.0	6	3.2	0.561	ND	ND
Non-encapsulated	30	18.7	17	9.0	0.039	0.569 (0.289-1.118)	0.102
Size >10 mm							
All cases	130	81.3	165	87.8	NC ⁴	NC	NC
Fully encapsulated	6	3.7	25	96.8	NC	NC	NC
Non-encapsulated	124	96.3	140	74.5	NC	NC	NC
Dominant pattern							
Papillary							
All cases	99	61.9	88	46.8	0.005	0.519 (0.375-0.934)	0.024
Fully encapsulated	3	1.9	8	4.3	0.335	0.246 (0.034-1.785)	0.165
Non-encapsulated	96	60.0	80	42.6	0.052	0.693 (0.429-1.120)	0.134
Follicular							
All cases	34	21.2	49	26.1	0.315	1.255 (0.736-2.141)	0.405
Fully encapsulated	2	1.3	17	9.0	0.405	3.319 (0.459-23.986)	0.235
Non-encapsulated	32	20.0	32	17.0	1.000	0.942 (0.525-1.690)	0.841
Solid-trabecular							
All cases	27	16.9	51	27.1	0.028	1.683 (0.967-2.930)	0.066
Fully encapsulated	1	0.6	6	3.2	1.000	1.221 (0.084-17.688)	0.884
Non-encapsulated	26	16.2	45	23.9	0.015	1.776 (0.999-3.159)	0.050
Oxyphilic changes							
All cases	84	52.5	48	25.5	2.903E-7	0.334 (0.207-0.540)	7.606E-6
Fully encapsulated	3	1.9	9	4.8	0.367	0.654 (0.094-4.549)	0.668
Non-encapsulated	81	50.6	39	20.7	5.038E-7	0.307 (0.184-0.512)	5.962E-6
Focal							
All cases	64	40.0	30	16.0	5.461E-7	0.191 (0.084-0.439)	7.644E-6
Fully encapsulated	3	1.9	5	2.7	0.101	0.462 (0.059-3.612)	0.462
Non-encapsulated	61	38.1	25	13.3	3.944E-6	0.280 (0.158-0.495)	1.214E-5
Severe							
All cases	20	12.5	18	9.6	0.394	0.841 (0.408-1.737)	0.640
Fully encapsulated	0	0.0	4	2.1	1.000	ND	ND
Non-encapsulated	20	12.5	14	7.4	0.279	0.761 (0.351-1.651)	0.490
Concomitant nodular pathology							
All cases	15	9.4	18	9.6	1.000	1.171 (0.543-2.523)	0.687
Fully encapsulated	0	0.0	5	2.7	0.567	ND	ND
Non-encapsulated	15	9.4	13	6.9	0.695	1.084 (0.479-2.453)	0.847
Concomitant diffuse pathology							
All cases	61	38.1	55	29.3	0.088	0.869 (0.539-1.401)	0.565
Fully encapsulated	0	0.0	1	0.5	1.000	ND	ND
Non-encapsulated	61	38.1	54	28.7	0.350	1.034 (0.631-1.693)	0.895
Chronic thyroiditis							
All cases	50	31.3	49	26.1	0.340	1.018 (0.618-1.677)	0.945
Fully encapsulated	0	0.0	1	0.5	1.000	ND	ND
Non-encapsulated	50	31.3	48	25.5	0.807	1.197 (0.716-2.001)	0.492
Intrathyroid spread							
All cases	53	33.1	43	22.9	0.041	0.509 (0.305-0.851)	0.010
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	53	33.1	43	22.9	0.220	0.607 (0.360-1.021)	0.060
Extrathyroidal extension (pT3)							
All cases	77	48.1	96	51.1	0.593	0.870 (0.551-1.373)	0.550
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	77	48.1	96	51.1	0.053	1.177 (0.725-1.910)	0.509
Multifocality (pTm)							
All cases	4	2.5	22	11.7	0.001	5.300 (1.728-16.257)	0.004
Fully encapsulated	0	0.0	4	2.1	1.000	ND	ND
Non-encapsulated	4	2.5	18	9.6	0.003	4.805 (1.532-15.072)	0.007
Lymphatic/vascular invasion							
All cases	122	76.3	123	65.4	0.034	0.517 (0.313-0.865)	0.010
Fully encapsulated	3	1.9	6	3.2	0.140	0.349 (0.049-2.482)	0.293
Non-encapsulated	119	74.4	117	62.2	0.598	0.707 (0.406-1.232)	0.221
Lymph node metastases (pN1)							
All cases	129	80.6	110	58.5	9.448E-6	0.290 (0.171-0.489)	3.540E-6
Fully encapsulated	2	1.3	3	1.6	0.177	0.217 (0.022-2.135)	0.190
Non-encapsulated	127	79.4	107	56.9	0.004	0.369 (0.208-0.655)	0.001
Distant metastases (M1)							
All cases	14	8.8	20	10.6	0.591	0.671 (0.299-1.507)	0.334
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	14	8.8	20	10.6	0.365	0.810 (0.361-1.817)	0.609

¹ % for count data, SD for continuous numeric data. ² Adjusted for age and sex. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm.

Supplementary Table 2 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma with the dominant papillary growth pattern in the combined pediatric groups

	Japan (n=99)		Ukraine (n=88)		p value (uni)	OR (95% CI)	p value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	16.4	2.5	14.3	3.2	3.882E-8		
Fully encapsulated	16.1	1.3	13.5	3.9	0.220		
Non-encapsulated	16.4	2.5	14.3	3.2	1.263E-7		
Sex (F/M)							
All cases	85/14	F:M=6.1:1	63/25	F:M=2.5:1	0.019		
Fully encapsulated	3/0	ND ³	4/4	F:M=1.0:1	0.236		
Non-encapsulated	82/14	F:M=5.9:1	59/21	F:M=2.8:1	0.060		
Tumor capsule					0.118	2.896 (0.729-11.513)	0.131
Full	3	3.0	8	9.1			
Partial/absent	96	96.3	80	90.9			
Size (mean, mm)							
All cases	22.4	13.4	23.3	15.1	0.954		
Fully encapsulated	33.7	8.3	18.5	10.7	0.133		
Non-encapsulated	22.0	13.4	23.7	15.4	0.742		
Size ≤ 10 mm							
All cases	20	20.2	13	14.8	0.354	0.650 (0.297-1.422)	0.281
Fully encapsulated	0	0.0	2	2.3	1.000	ND	ND
Non-encapsulated	20	20.2	11	12.5	0.239	0.583 (0.258-1.319)	0.196
Size > 10 mm							
All cases	79	79.8	75	85.2	NC ⁴	NC	NC
Fully encapsulated	3	3.0	6	6.8	NC	NC	NC
Non-encapsulated	76	76.8	69	78.4	NC	NC	NC
Oxyphilic changes							
All cases	63	63.6	21	23.9	4.223E-8	0.204 (0.104-0.401)	4.020E-6⁵
Fully encapsulated	1	1.0	2	2.3	1.000	2.000 (0.090-44.350)	0.661
Non-encapsulated	62	62.6	19	21.6	7.156E-8	0.189 (0.094-0.382)	3.317E-6⁵
Focal							
All cases	49	49.5	17	19.3	1.637E-5	0.248 (0.122-0.505)	1.176E-4⁵
Fully encapsulated	1	1.0	2	2.3	1.000	2.000 (0.090-44.350)	0.661
Non-encapsulated	48	48.5	15	17.0	1.745E-5	0.228 (0.109-0.479)	9.331E-5⁵
Severe							
All cases	14	14.1	4	4.5	0.044	0.384 (0.111-1.328)	0.130 ⁵
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	14	14.1	4	4.5	0.046	0.398 (0.116-1.372)	0.145 ⁵
Concomitant nodular pathology							
All cases	9	9.1	9	10.2	0.809	1.129 (0.420-3.031)	0.810
Fully encapsulated	0	0.0	2	2.3	1.000	ND	ND
Non-encapsulated	9	9.1	7	8.0	1.000	0.984 (0.346-2.798)	0.975
Concomitant diffuse pathology							
All cases	43	43.4	29	33.3	0.176	0.734 (0.397-1.357)	0.324
Fully encapsulated	0	0.0	1	1.1	1.000	ND	ND
Non-encapsulated	43	43.4	28	31.8	0.218	0.738 (0.395-1.382)	0.343
Chronic thyroiditis							
All cases	37	37.4	26	29.5	0.281	0.821 (0.436-1.547)	0.542
Fully encapsulated	0	0.0	1	1.1	1.000	ND	ND
Non-encapsulated	37	37.4	25	28.4	0.344	0.819 (0.430-1.561)	0.544
Intrathyroid spread							
All cases	35	35.4	21	23.9	0.110	0.585 (0.306-1.121)	0.106
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	35	35.4	21	23.9	0.193	0.628 (0.326-1.209)	0.164
Extrathyroidal extension (pT3)							
All cases	42	42.4	42	47.7	0.556	1.236 (0.687-2.223)	0.479
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	42	42.4	42	47.7	0.289	1.401 (0.767-2.558)	0.273
Multifocality (pTm)							
All cases	3	3.0	10	11.4	0.041	4.470 (1.174-17.017)	0.028
Fully encapsulated	0	0.0	1	1.1	1.000	ND	ND
Non-encapsulated	3	3.0	9	10.2	0.039	4.132 (1.068-15.982)	0.040
Lymphatic/vascular invasion							
All cases	75	75.8	54	61.4	0.040	0.519 (0.274-0.982)	0.044
Fully encapsulated	3	3.0	0	0.0	0.006	ND	ND
Non-encapsulated	72	72.7	54	61.4	0.315	0.688 (0.354-1.337)	0.269
Lymph node metastases (pN1)							
All cases	85	85.9	58	65.9	0.002	0.336 (0.156-0.725) ⁵	0.005⁵
Fully encapsulated	2	2.0	2	2.3	0.491	0.500 (0.023-11.088)	0.661
Non-encapsulated	83	83.8	56	63.6	0.009	0.369 (0.165-0.828)	0.016⁵
Distant metastases (M1)							
All cases	7	7.1	10	11.4	0.323	1.669 (0.598-4.662)	0.328
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	7	7.1	10	11.4	0.308	1.787 (0.640-4.985)	0.268

¹ % for count data, SD for continuous numeric data. ² Adjusted for sex unless otherwise specified. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm. ⁵ Adjusted for age and sex.

Supplementary Table 3 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma with the dominant solid-trabecular growth pattern in the combined pediatric groups

	Japan (n=27)		Ukraine (n=51)		<i>p</i> value (uni)	OR (95% CI)	<i>p</i> value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	15.6	3.1	14.1	2.9	0.013		
Fully encapsulated	18.1	ND ³	15.3	2.3	0.571		
Non-encapsulated	15.5	3.2	14.0	2.9	0.016		
Sex (F/M)							
All cases	26/1	F:M=26:1	32/19	F:M=1.7:1	0.001		
Fully encapsulated	1/0	ND	3/3	F:M=1.0:1	1.000		
Non-encapsulated	25/1	F:M=25:1	29/16	F:M=1.8:1	0.003		
Tumor capsule					0.411	4.368 (0.481-39.690)	0.190
Full	1	3.7	6	11.8			
Partial/absent	26	96.3	45	88.2			
Size (mean, mm)							
All cases	26.6	16.9	25.0	14.6	0.797		
Fully encapsulated	11.0	ND	25.7	14.9	0.857		
Non-encapsulated	27.2	16.9	24.9	14.7	0.620		
Size ≤ 10 mm							
All cases	5	18.5	5	9.8	0.302	0.521 (0.132-2.055)	0.352
Fully encapsulated	0	0.0	2	3.9	1.000	ND	ND
Non-encapsulated	5	18.5	3	5.9	0.132	0.315 (0.066-1.512)	0.149
Size >10 mm							
All cases	22	81.5	46	90.2	NC ⁴	NC	NC
Fully encapsulated	1	3.7	4	7.8	NC	NC	NC
Non-encapsulated	21	77.8	42	83.4	NC	NC	NC
Oxyphilic changes							
All cases	11	40.7	19	37.3	0.810	0.998 (0.370-2.687)	0.996
Fully encapsulated	1	3.7	4	7.8	1.000	0.0	1.000
Non-encapsulated	10	37.0	15	29.4	0.797	0.892 (0.315-2.521)	0.829
Focal							
All cases	6	22.2	6	11.8	0.323	0.510 (0.140-1.850)	0.305
Fully encapsulated	1	3.7	1	2.0	0.286	0.0	0.995
Non-encapsulated	5	18.5	5	9.8	0.481	0.513 (0.126-2.080)	0.350
Severe							
All cases	5	18.5	13	25.5	0.580	1.702 (0.516-5.614)	0.383
Fully encapsulated	0	0.0	3	5.9	1.000	ND	ND
Non-encapsulated	5	18.5	10	19.6	1.000	1.416 (0.407-4.930)	0.584
Concomitant nodular pathology							
All cases	2	7.4	4	7.8	1.000	1.312 (0.215-7.994)	0.769
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	2	7.4	4	7.8	1.000	1.485 (0.241-9.136)	0.670
Concomitant diffuse pathology							
All cases	9	33.3	16	31.4	1.000	1.018 (0.366-2.827)	0.973
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	9	33.3	16	31.4	1.000	1.212 (0.426-3.452)	0.718
Chronic thyroiditis							
All cases	7	25.9	15	29.4	0.797	1.263 (0.430-3.704)	0.671
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	7	25.9	15	29.4	0.607	1.496 (0.500-4.473)	0.471
Intrathyroid spread							
All cases	10	37.0	14	27.5	0.444	0.566 (0.200-1.604)	0.284
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	10	37.0	14	27.5	0.606	0.657 (0.229-1.886)	0.435
Extrathyroidal extension (pT3)							
All cases	18	66.7	33	64.7	1.000	0.548 (0.184-1.636)	0.281
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	18	66.7	33	64.7	0.787	0.742 (0.230-2.393)	0.617
Multifocality (pTm)							
All cases	1	3.7	4	7.8	0.654	1.840 (0.184-18.360)	0.603
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	1	3.7	4	7.8	0.646	2.076 (0.208-20.759)	0.534
Lymphatic/vascular invasion							
All cases	22	81.5	36	70.6	0.415	0.382 (0.114-1.279)	0.118
Fully encapsulated	0	0.0	1	2.0	1.000	ND	ND
Non-encapsulated	22	81.5	35	68.6	0.552	0.413 (0.106-1.611)	0.203
Lymph node metastases (pN1)							
All cases	20	74.1	28	54.9	0.142	0.278 (0.085-0.906)	0.034 ⁵
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	20	74.1	28	54.9	0.293	0.330 (0.100-1.084)	0.068
Distant metastases (M1)							
All cases	4	14.8	5	9.8	0.711	0.454 (0.099-2.081)	0.309
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	4	14.8	5	9.8	0.716	0.514 (0.112-2.358)	0.392

¹ % for count data, SD for continuous numeric data. ² Adjusted for age unless otherwise specified. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm. ⁵ Adjusted for age and sex.

Supplementary Table 4 Associations of demographic and histopathological characteristics with the dominant growth pattern in the combined pediatric group from Japan

	Papillary (<i>n</i> =99)		Follicular (<i>n</i> =34)		Solid-trabecular (<i>n</i> =27)		<i>p</i> value (uni) ²	OR (95% CI)	<i>p</i> value (multi) ³
	Number or value	% or SD ¹	Number or value	% or SD	Number or value	% or SD			
Age (mean, years)									
All cases	16.4	2.5	15.3	3.1	15.6	3.1	0.096		
Fully encapsulated	16.1	1.3	14.3	0.9	18.1	ND ⁴	0.117		
Non-encapsulated	16.4	2.5	15.3	3.2	15.5	3.2		0.118	
Sex (F/M)									
All cases	85/14	F:M=6.1:1	31/3	F:M=10.3:1	26/1	F:M=26.0:1	0.304		
Fully encapsulated	3/0	ND	2/0	ND	1/0	ND	1.000		
Non-encapsulated	82/14	F:M=5.9:1	29/3	F:M=9.7:1	25/1	F:M=25.0:1	0.348		
Tumor capsule							0.722		NS ⁵
Full	3	3.0	2	5.9	1	3.7			
Partial/absent	96	97.0	32	94.1	26	96.3			
Size (mean, mm)									
All cases	22.4	13.4	23.9	14.6	26.6	16.9	0.556		
Fully encapsulated	33.7	8.3	26.5	12.0	11.0	ND	0.304		
Non-encapsulated	22.0	13.4	23.7	14.9	27.2	16.9	0.393		
Size ≤ 10 mm									
All cases	20	20.2	5	14.7	5	18.5	0.808		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	20	20.2	5	14.7	5	18.5	0.880		NS
Size > 10 mm									
All cases	79	79.8	29	85.3	22	81.5	NC ⁶	NC	NC
Fully encapsulated	3	3.0	2	5.9	1	3.7	NC	NC	NC
Non-encapsulated	76	76.8	27	79.4	21	77.8	NC	NC	NC
Oxyphilic changes									
All cases	63	63.6	10	29.4	11	40.7	0.001	4.166 (1.778-9.762)	0.001 ⁷
Fully encapsulated	1	1.0	1	2.9	1	3.7	0.700	2.488 (1.034-5.988)	0.042 ⁸
Non-encapsulated	62	62.6	9	26.5	10	37.0	4.756E-4	4.562 (1.925-11.242)	0.001 ⁷
Focal									
All cases	49	49.5	9	26.5	6	22.2	0.007	2.659 (1.117-6.328)	0.027 ⁷
Fully encapsulated	1	1.0	1	2.9	1	3.7	0.700	3.253 (1.200-8.816)	0.020 ⁸
Non-encapsulated	48	48.5	8	23.5	5	18.5	0.002	2.948 (1.197-7.263)	0.019 ⁷
Severe								3.999 (1.381-11.582)	0.011 ⁸
All cases	14	14.1	1	2.9	5	18.5	0.121		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	14	14.1	1	2.9	5	18.5	0.118		NS
Concomitant nodular pathology									
All cases	9	9.1	4	11.8	2	7.4	0.859		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	9	9.1	4	11.8	2	7.4	0.858		NS
Concomitant diffuse pathology									
All cases	43	43.4	9	26.5	9	33.3	0.184		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	43	43.4	9	26.5	9	33.3	0.229		NS
Chronic thyroiditis									
All cases	37	37.4	6	17.6	7	25.9	0.091	2.956 (1.103-7.923)	0.031 ⁷
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	37	37.4	6	17.6	7	25.9	0.098	2.932 (1.087-7.912)	0.034 ⁷
Intrathyroid spread									
All cases	35	35.3	8	23.5	10	37.0	0.448		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	35	35.3	8	23.5	10	37.0	0.480		NS
Extrathyroidal extension (pT3)									
All cases	42	42.4	17	50.0	18	66.7	0.075	0.349 (0.139-0.871)	0.024 ⁸
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	42	42.4	17	50.0	18	66.7	0.069	0.335 (0.129-0.867)	0.024 ⁸
Multifocality (pTm)									
All cases	3	3.0	0	0.0	1	3.7	0.628		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	3	3.0	0	0.0	1	3.7	0.629		ND
Lymphatic/vascular invasion									
All cases	75	75.8	25	73.5	22	81.5	0.804		NS
Fully encapsulated	3	3.0	0	0.0	0	0.0	0.050		NS
Non-encapsulated	72	72.7	25	73.5	22	81.5	0.626		NS
Lymph node metastases (pN1)									
All cases	85	85.6	24	70.6	20	74.1	0.085	2.656 (1.035-6.813)	0.042 ⁷
Fully encapsulated	2	2.0	0	0.0	0	0.0	0.400		NS
Non-encapsulated	83	83.8	24	70.6	20	74.1	0.215		NS
Distant metastases (M1)									
All cases	7	7.1	3	8.8	4	14.8	0.443		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	7	7.1	3	8.8	4	14.8	0.370		NS

¹ % for count data, SD for continuous numeric data. ² Kruskal-Wallis or 2x3 Fisher's exact test for continuous or count data, respectively. ³ Multinomial logistic regression. Adjusted for age and sex; only the results with significant *p*-values are shown. ⁴ ND, not determined. ⁵ NS, not significant for any growth pattern. ⁶ NC, not calculated due to data complementarity to size ≤ 10 mm. ⁷ Dominant papillary vs. dominant follicular growth pattern. ⁸ Dominant papillary vs. dominant solid-trabecular growth pattern.

Supplementary Table 5 Associations of demographic and histopathological characteristics with the dominant growth pattern in the combined pediatric group from Ukraine

	Papillary (n=88)		Follicular (n=49)		Solid-trabecular (n=51)		p value (uni) ²	OR (95% CI)	p value (multi) ³
	Number or value	% or SD ¹	Number or value	% or SD	Number or value	% or SD			
Age (mean, years)									
All cases	14.3	3.2	13.8	3.6	14.1	2.9	0.096		
Fully encapsulated	13.5	3.9	12.9	3.9	15.3	2.3	0.117		
Non-encapsulated	14.3	3.2	14.3	3.4	14.0	2.9		0.570	
Sex (F/M)									
All cases	63/25	F:M=2.5:1	41/8	F:M=5.1:1	32/19	F:M=1.7:1	0.061		
Fully encapsulated	4/4	F:M=1.0:1	16/1	F:M=16.0:1	3/3	F:M=1.0:1	0.013		
Non-encapsulated	59/21	F:M=2.8:1	25/7	F:M=3.6:1	29/16	F:M=1.8:1	0.388		
Tumor capsule							<0.0001	5.469 (2.114-14.147)	4.581E-4⁴
Full	8	9.1	17	34.7	6	11.8		4.301 (1.484-12.462)	0.007⁵
Partial/absent	80	90.9	32	65.3	45	88.2		NC ⁶	NC
Size (mean, mm)								NC	NC
All cases	23.3	15.1	24.6	12.7	25.0	14.6	0.556		
Fully encapsulated	18.5	10.7	22.1	9.8	25.7	14.9	0.304		
Non-encapsulated	23.7	15.4	25.9	13.9	24.9	14.7	0.468		
Size ≤ 10 mm									
All cases	13	14.8	5	10.2	5	9.8	0.711		NS ⁷
Fully encapsulated	2	2.3	2	4.1	2	3.9	0.566		NS
Non-encapsulated	11	12.5	3	6.1	3	5.9	0.492		NS
Size > 10 mm									
All cases	75	85.2	44	89.8	46	90.2	NC	NC	NC
Fully encapsulated	6	6.8	15	30.6	4	7.8	NC	NC	NC
Non-encapsulated	69	87.5	29	59.2	42	82.4	NC	NC	NC
Oxyphilic changes									
All cases	21	23.9	8	16.3	19	37.2	0.057	0.318 (0.121-0.837)	0.020⁵
Fully encapsulated	2	2.3	3	6.1	4	7.8	0.124	0.041 (0.002-0.715)	0.028⁵
Non-encapsulated	19	21.6	5	10.2	15	29.4	0.229		NS
Focal									
All cases	17	19.3	7	14.3	6	11.8	0.504		NS
Fully encapsulated	2	2.3	2	4.1	1	2.0	0.942		NS
Non-encapsulated	15	17.0	5	10.2	5	9.8	0.574		NS
Non-encapsulated									
Severe									
All cases	4	4.5	1	2.0	13	25.5	<0.0001	7.614 (2.283-25.388)	0.001⁸
All cases								0.060 (0.007-0.491)	0.009⁵
Fully encapsulated	0	0.0	1	2.0	3	5.9	0.029		ND ⁹
Non-encapsulated	4	4.5	0	0.0	10	19.6	0.001		ND
Concomitant nodular pathology									
All cases	9	10.2	5	10.2	4	7.8	0.948		NS
Fully encapsulated	2	2.3	3	6.1	0	0.0	0.785		ND
Non-encapsulated	7	8.0	2	4.1	4	7.8	1.000		NS
Concomitant diffuse pathology									
All cases	29	33.0	10	20.4	16	31.4	0.287		NS
Fully encapsulated	1	1.1	0	0.0	0	0.0	0.710		ND
Non-encapsulated	28	31.8	10	20.4	16	31.4	0.950		NS
Chronic thyroiditis									
All cases	26	29.5	8	16.3	15	29.4	0.190	0.396 (0.161-0.977)	0.044⁴
All cases								0.355 (0.131-0.967)	0.043⁵
Fully encapsulated	1	1.1	0	0.0	0	0.0	0.710		ND
Non-encapsulated	25	28.4	8	16.3	15	29.4	0.741		NS
Intrathyroid spread									
All cases	21	23.9	8	16.3	14	27.5	0.391		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	21	23.9	8	16.3	14	27.5	0.391		NS
Extrathyroidal extension (pT3)									
All cases	42	47.7	21	42.9	33	64.7	0.065	0.423 (0.185-0.966)	0.041⁵
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	42	47.7	21	42.9	33	64.7	0.065	2.297 (1.011-5.219)	0.047⁸
Multifocality (pTm)									
All cases	10	11.4	8	16.3	4	7.8	0.410		NS
Fully encapsulated	1	1.1	3	6.1	0	0.0	0.792		ND
Non-encapsulated	9	10.2	5	10.2	4	7.8	0.676		NS
Lymphatic/vascular invasion									
All cases	54	61.4	33	67.3	36	70.6	0.522		NS
Fully encapsulated	0	0.0	5	10.2	1	2.0	0.280		ND
Non-encapsulated	54	61.4	28	57.1	35	68.6	0.081	0.288 (0.091-0.914)	0.035⁴
Lymph node metastases (pN1)									
All cases	58	65.9	24	49.0	28	54.9	0.130		NS
Fully encapsulated	2	2.3	1	2.0	0	0.0	0.349		ND
Non-encapsulated	56	63.6	23	47.0	28	54.9	0.589		NS
Distant metastases (M1)									
All cases	10	11.4	5	10.2	5	9.8	1.000		NS
Fully encapsulated	0	0.0	0	0.0	0	0.0	1.000		ND
Non-encapsulated	10	11.4	5	10.2	5	9.8	1.000		NS

¹ % for count data, SD for continuous numeric data. ² Kruskal-Wallis or 2x3 Fisher's exact test for continuous or count data, respectively. ³ Multinomial logistic regression Adjusted for age and sex; only the results with significant *p*-values are shown. ⁴ Dominant follicular vs. dominant papillary growth pattern. ⁵ Dominant follicular vs. dominant solid-trabecular growth pattern. ⁶ NC, not calculated due to data complementarity. ⁷ NS, not significant for any growth pattern. ⁸ Dominant solid-trabecular vs. dominant papillary growth pattern. ⁹ ND, not determined.

Supplementary Table 6 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma for all, fully encapsulated and non-encapsulated tumors in children aged ≤14 years at surgery

	Japan (n=42)		Ukraine (n=98)		p-value (uni)	OR (95% CI)	p value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	12.1	2.3	11.7	2.6	0.418		
Fully encapsulated	14.5	0.6	11.5	3.2	0.087		
Non-encapsulated	11.9	2.3	11.8	2.4	0.721		
Sex (F/M)							
All cases	36/6	F:M=6.0:1	68/30	F:M=2.3:1	0.057		
Fully encapsulated	3/0	ND	15/4	F:M=3.7:1	1.000		
Non-encapsulated	33/6	F:M=5.5:1	53/26	F:M=2.0:1	0.050		
Tumor capsule							
Full	3	7.1	19	19.4	0.079	3.495 (0.961-12.709)	0.057
Partial/absent	39	92.9	79	80.6			
Size (mean, mm)							
All cases	24.0	14.7	24.2	14.2	0.095		
Fully encapsulated	28.0	8.9	22.5	10.3	0.226		
Non-encapsulated	27.6	14.2	24.6	15.0	0.147		
Size ≤ 10 mm							
All cases	3	7.1	11	11.2	0.554	1.570 (0.403-6.124)	0.516
Fully encapsulated	0	0.0	2	2.0	1.000	ND ³	ND
Non-encapsulated	3	7.1	9	9.2	0.748	1.342 (0.329-5.464)	0.682
Size > 10 mm							
All cases	39	92.9	87	88.8	NC ⁴	NC	NC
Fully encapsulated	3	7.1	17	17.3	NC	NC	NC
Non-encapsulated	36	85.7	70	71.4	NC	NC	NC
Dominant pattern							
Papillary							
All cases	22	52.4	43	43.9	0.363	0.686 (0.327-1.441)	0.320
Fully encapsulated	1	2.4	5	5.1	1.000	3.908 (0.127-120.692)	0.436
Non-encapsulated	21	50.0	38	38.8	0.696	0.783 (0.357-1.717)	0.542
Follicular							
All cases	12	28.6	25	25.5	0.835	0.923 (0.399-2.138)	0.857
Fully encapsulated	2	4.8	11	11.2	1.000	0.054 (0.001-6.264)	0.229
Non-encapsulated	10	23.8	14	14.3	0.338	0.661 (0.255-1.711)	0.393
Solid-trabecular							
All cases	8	19.0	30	30.6	0.214	1.813 (0.739-4.447)	0.194
Fully encapsulated	0	0.0	3	3.1	1.000	ND	ND
Non-encapsulated	8	19.0	27	27.6	0.140	1.945 (0.775-4.886)	0.157
Oxyphilic changes							
All cases	21	50.0	21	21.4	0.001	0.265 (0.119-0.590)	0.001
Fully encapsulated	1	2.4	4	4.1	0.469	0.822 (0.042-16.014)	0.897
Non-encapsulated	20	47.6	17	17.3	0.002	0.237 (0.100-0.563)	0.001
Focal							
All cases	16	38.1	13	13.3	0.002	0.263 (0.110-0.626)	0.003
Fully encapsulated	1	2.4	2	2.0	1.000	0.511 (0.025-10.430)	0.663
Non-encapsulated	15	35.7	11	11.2	0.004	0.268 (0.106-0.676)	0.005
Severe							
All cases	5	11.9	8	8.2	0.530	0.574 (0.168-1.956)	0.374
Fully encapsulated	0	0.0	2	2.0	1.000	ND	ND
Non-encapsulated	5	11.9	6	6.1	0.502	0.427 (0.113-1.617)	0.210
Concomitant nodular pathology							
All cases	3	7.1	9	9.2	1.000	1.230 (0.309-4.905)	0.769
Fully encapsulated	0	0.0	5	5.1	0.521	ND	ND
Non-encapsulated	3	7.1	4	4.1	0.683	0.617 (0.126-3.018)	0.551
Concomitant diffuse pathology							
All cases	14	33.3	27	27.6	0.545	0.910 (0.404-2.052)	0.820
Fully encapsulated	0	0.0	1	1.0	1.000	ND	ND
Non-encapsulated	14	33.3	26	26.5	0.837	1.057 (0.450-2.483)	0.899
Chronic thyroiditis							
All cases	11	26.2	25	25.5	1.000	1.173 (0.500-2.749)	0.714
Fully encapsulated	0	0.0	1	1.0	0.340	ND	ND
Non-encapsulated	11	26.2	24	24.5	1.000	1.375 (0.567-3.333)	0.481
Intrathyroid spread							
All cases	17	40.5	23	23.5	0.065	0.435 (0.197-0.961)	0.040
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	17	40.5	23	23.5	0.149	0.536 (0.237-1.211)	0.133
Extrathyroidal extension (pT3)							
All cases	25	59.5	58	59.2	1.000	0.919 (0.429-1.966)	0.827
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	25	59.5	58	59.2	0.392	1.612 (0.678-3.831)	0.280
Multifocality (pTm)							
All cases	0	0.0	10	10.2	0.033	ND	ND
Fully encapsulated	0	0.0	2	2.0	1.000	ND	ND
Non-encapsulated	0	0.0	8	8.2	0.051	ND	ND
Lymphatic/vascular invasion							
All cases	37	88.1	66	67.3	0.012	0.253 (0.089-0.721)	0.010
Fully encapsulated	1	2.4	3	3.1	0.05	0.099 (0.001-8.852)	0.313
Non-encapsulated	36	85.7	63	64.3	0.111	0.315 (0.085-1.167)	0.086
Lymph node metastases (pN1)							
All cases	35	83.3	63	64.3	0.027	0.342 (0.136-0.861)	0.023
Fully encapsulated	1	2.4	3	3.1	0.079	1.107 (0.051-24.078)	0.948
Non-encapsulated	34	81.0	60	61.2	0.224	0.465 (0.157-1.375)	0.166
Distant metastases (M1)							
All cases	7	16.7	15	15.3	0.806	0.766 (0.274-2.140)	0.611
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	7	16.7	15	15.3	1.000	0.982 (0.347-2.780)	0.972

¹ % for count data, SD for continuous numeric data. ² Adjusted for age and sex. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm.

Supplementary Table 7 Comparative characteristics of the Japanese and Ukrainian sporadic papillary thyroid carcinoma for all, fully encapsulated and non-encapsulated tumors in adolescents aged from 15 to ≤18 years at surgery

	Japan (n=118)		Ukraine (n=90)		p value (uni)	OR (95% CI)	p value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	17.4	1.1	16.7	1.2	1.381E-5		
Fully encapsulated	17.1	1.2	16.7	1.3	0.470		
Non-encapsulated	17.4	1.1	16.7	1.2	2.486E-5		
Sex (F/M)							
All cases	106/12	F:M=8.8:1	68/22	F:M=3.1:1	0.008		
Fully encapsulated	3/0	ND ³	8/4	F:M=2.0:1	0.516		
Non-encapsulated	103/12	F:M=8.6:1	60/18	F:M=3.3:1	0.025		
Tumor capsule					0.005	5.658 (1.452-22.041)	0.012
Full	3	2.5	12	13.3			
Partial/absent	115	97.5	78	86.7			
Size (mean, mm)							
All cases	21.9	14.2	24.0	14.5	0.298		
Fully encapsulated	27.0	16.0	20.9	12.4	0.347		
Non-encapsulated	21.8	14.2	24.4	14.8	0.219		
Size ≤ 10 mm							
All cases	27	22.9	12	13.3	0.106	0.464 (0.210-1.028)	0.059
Fully encapsulated	0	0.0	4	4.4	0.516	ND	ND
Non-encapsulated	27	22.9	8	8.9	0.022	0.373 (0.154-0.903)	0.029
Size > 10 mm							
All cases	91	77.1	78	86.7	NC ⁴	NC	NC
Fully encapsulated	3	2.5	8	8.9	NC	NC	NC
Non-encapsulated	88	74.6	70	77.8	NC	NC	NC
Dominant pattern							
Papillary							
All cases	77	65.3	45	50.0	0.033	0.537 (0.295-0.979)	0.042
Fully encapsulated	2	1.7	3	3.3	0.242	0.004 (0.001-16.223)	0.194
Non-encapsulated	75	63.6	42	46.7	0.134	0.662 (0.354-1.241)	0.198
Follicular							
All cases	22	18.6	24	26.7	0.181	1.621 (0.803-3.271)	0.178
Fully encapsulated	0	0.0	6	6.7	0.229	ND	ND
Non-encapsulated	22	18.6	18	20.0	0.588	1.200 (0.567-2.540)	0.634
Solid-trabecular							
All cases	19	16.1	21	23.3	0.216	1.539 (0.727-3.258)	0.260
Fully encapsulated	1	0.8	3	3.3	1.000	0.220 (0.004-13.351)	0.469
Non-encapsulated	18	15.3	18	20.0	0.258	1.566 (0.714-3.435)	0.263
Oxyphilic changes							
All cases	63	53.4	27	30.0	0.001	0.373 (0.200-0.692)	0.002
Fully encapsulated	2	1.7	5	5.6	0.569	0.287 (0.014-6.084)	0.423
Non-encapsulated	61	51.7	22	24.4	0.001	0.347 (0.180-0.669)	0.002
Focal							
All cases	48	40.7	17	18.9	0.001	0.288 (0.143-0.581)	0.001
Fully encapsulated	2	1.7	3	3.3	0.242	0.287 (0.014-6.084)	0.423
Non-encapsulated	46	39.0	14	15.6	0.001	0.253 (0.118-0.542)	4.117E-4
Severe							
All cases	15	12.7	10	11.1	0.831	1.158 (0.458-2.929)	0.756
Fully encapsulated	0	0.0	2	2.2	1.000	ND	ND
Non-encapsulated	15	12.7	8	8.9	0.654	1.186 (0.445-3.164)	0.733
Concomitant nodular pathology							
All cases	12	10.2	9	10.0	1.000	1.162 (0.445-3.032)	0.759
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	12	10.2	9	10.0	0.818	1.304 (0.495-3.432)	0.591
Concomitant diffuse pathology							
All cases	47	39.8	28	31.1	0.244	0.797 (0.428-1.483)	0.474
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	47	39.8	28	31.1	0.548	0.940 (0.496-1.780)	0.849
Chronic thyroiditis							
All cases	39	33.1	24	26.7	0.362	0.965 (0.502-1.853)	0.914
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	39	33.1	24	26.7	0.755	1.135 (0.581-2.217)	0.711
Intrathyroid spread							
All cases	36	30.5	20	22.2	0.209	0.545 (0.275-1.079)	0.081
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	36	30.5	20	22.2	0.423	0.626 (0.313-1.251)	0.185
Extrathyroidal extension (pT3)							
All cases	52	44.1	38	42.2	0.888	0.914 (0.506-1.651)	0.766
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	52	44.1	38	42.2	0.661	1.125 (0.609-2.077)	0.708
Multifocality (pTm)							
All cases	4	3.4	12	13.3	0.016	3.988 (1.191-13.360)	0.025
Fully encapsulated	0	0.0	2	2.2	1.000	ND	ND
Non-encapsulated	4	3.4	10	11.1	0.021	3.553 (1.023-12.341)	0.046
Lymphatic/vascular invasion							
All cases	85	72.0	57	63.3	0.229	0.715 (0.382-1.338)	0.294
Fully encapsulated	2	1.7	3	3.3	0.242	0.295 (0.018-4.915)	0.395
Non-encapsulated	83	70.3	54	60.0	0.747	0.894 (0.458-1.746)	0.742
Lymph node metastases (pN1)							
All cases	94	79.7	47	52.2	4.408E-5	0.252 (0.129-0.490)	4.906E-5
Fully encapsulated	1	0.8	0	0.0	0.200	ND	ND
Non-encapsulated	93	78.8	47	52.2	0.003	0.315 (0.155-0.642)	0.001
Distant metastases (M1)							
All cases	7	5.9	5	5.6	1.000	0.687 (0.190-2.479)	0.566
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	7	5.9	5	5.6	1.000	0.774 (0.214-2.800)	0.697

¹ % for count data, SD for continuous numeric data. ² Adjusted for age and sex. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm.

Supplementary Table 8 Comparison of childhood and adolescent PTC in the Japanese patients

	Children (n=42)		Adolescents (n=118)		p value (uni)	OR (95% CI)	p-value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	12.1	2.3	17.4	1.1	7.267E-22		
Fully encapsulated	14.5	0.6	17.1	1.2	0.100		
Non-encapsulated	11.9	2.3	17.4	1.1	1.196E-20		
Sex (F/M)							
All cases	36/6	F:M=6.0:1	106/12	F:M=8.8:1	0.570		
Fully encapsulated	3/0	ND ³	3/0	ND	ND		
Non-encapsulated	33/6	F:M=5.5:1	103/12	F:M=8.6:1	0.399		
Tumor capsule					0.186	0.320 (0.062-1.664)	0.320
Full	3	7.1	3	2.5			
Partial/absent	39	92.9	115	97.5			
Size (mean, mm)							
All cases	24.0	14.7	21.9	14.2	0.010		
Fully encapsulated	28.0	8.9	27.0	16.0	1.000		
Non-encapsulated	27.6	14.2	21.8	14.2	0.014		
Size ≤ 10 mm							
All cases	3	7.1	27	22.9	0.036	3.845 (1.100-13.440)	0.035
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	3	7.1	27	22.9	0.035	3.661 (1.043-12.849)	0.043
Size > 10 mm							
All cases	39	92.9	91	77.1	NC ⁴	NC	NC
Fully encapsulated	3	7.1	3	2.5	NC	NC	NC
Non-encapsulated	36	85.7	88	74.6	NC	NC	NC
Dominant pattern							
Papillary							
All cases	22	52.4	77	65.3	0.145	1.784 (0.865-3.681)	0.117
Fully encapsulated	1	2.4	2	1.7	1.000	4.000 (0.134-119.230)	0.423
Non-encapsulated	21	50.0	75	63.6	0.252	1.688 (0.799-3.566)	0.170
Follicular							
All cases	12	28.6	22	18.6	0.192	0.564 (0.249-1.276)	0.169
Fully encapsulated	2	4.8	0	0.0	0.400	ND	ND
Non-encapsulated	10	23.8	22	18.6	0.373	0.675 (0.286-1.593)	0.369
Solid-trabecular							
All cases	8	19.0	19	16.1	0.693	0.782 (0.311-1.966)	0.602
Fully encapsulated	0	0.0	1	0.8	1.000	ND	ND
Non-encapsulated	8	19.0	18	15.3	0.469	0.682 (0.268-1.739)	0.423
Oxyphilic changes							
All cases	21	50.0	63	53.4	0.723	1.165 (0.574-2.365)	0.672
Fully encapsulated	1	2.4	2	1.7	1.000	4.000 (0.134-119.230)	0.423
Non-encapsulated	20	47.6	61	51.7	0.855	1.095 (0.527-2.273)	0.808
Focal							
All cases	16	38.1	48	40.7	0.855	1.151 (0.555-2.389)	0.705
Fully encapsulated	1	2.4	2	1.7	1.000	4.000 (0.134-119.230)	0.423
Non-encapsulated	15	35.7	46	39.0	1.000	1.110 (0.522-2.358)	0.787
Severe							
All cases	5	11.9	15	12.7	1.000	1.047 (0.354-3.094)	0.934
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	5	11.9	15	12.7	1.000	0.983 (0.330-2.922)	0.975
Concomitant nodular pathology							
All cases	3	7.1	12	10.2	0.761	1.488 (0.398-5.571)	0.555
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	3	7.1	12	10.2	0.762	1.413 (0.376-5.311)	0.609
Concomitant diffuse pathology							
All cases	14	33.3	47	39.8	0.579	1.278 (0.604-2.706)	0.521
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	14	33.3	47	39.8	0.705	1.176 (0.547-2.529)	0.678
Chronic thyroiditis							
All cases	11	26.2	39	33.1	0.445	1.342 (0.605-2.980)	0.469
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	11	26.2	39	33.1	0.558	1.245 (0.554-2.799)	0.595
Intrathyroid spread							
All cases	17	40.5	36	30.5	0.265	0.652 (0.314-1.356)	0.252
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	17	40.5	36	30.5	0.177	0.595 (0.282-1.256)	0.173
Extrathyroidal extension (pT3)							
All cases	25	59.5	52	44.1	0.106	0.545 (0.266-1.119)	0.098
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	25	59.5	52	44.1	0.063	0.471 (0.222-0.999)	0.050
Multifocality (pTm)							
All cases	0	0.0	4	3.4	0.574	ND	ND
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	0	0.0	4	3.4	0.573	ND	ND
Lymphatic/vascular invasion							
All cases	37	88.1	85	72.0	0.037	0.342 (0.123-0.949)	0.039
Fully encapsulated	1	2.4	2	1.7	1.000	4.000 (0.134-119.230)	0.423
Non-encapsulated	36	85.7	83	70.3	0.008	0.210 (0.060-0.734)	0.015
Lymph node metastases (pN1)							
All cases	35	83.3	94	79.7	0.658	0.789 (0.312-1.997)	0.617
Fully encapsulated	1	2.4	1	0.8	1.000	1.000 (0.034-29.807)	1.000
Non-encapsulated	34	81.0	93	78.8	0.469	0.623 (0.218-1.778)	0.376
Distant metastases (M1)							
All cases	7	16.7	7	5.9	0.053	0.325 (0.106-0.996)	0.049
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	7	16.7	7	5.9	0.047	0.306 (0.099-0.945)	0.039

¹ % for count data, SD for continuous numeric data. ² Adjusted for sex. ³ ND, not determined. ⁴ NC, not calculated due to data complementarity to size ≤ 10 mm.

Supplementary Table 9 Comparison of childhood and adolescent PTC in the Ukrainian patients

	Children (<i>n</i> =98)		Adolescents (<i>n</i> =90)		<i>p</i> value (uni)	OR (95% CI)	<i>p</i> value (multi) ²
	Number or value	% or SD ¹	Number or value	% or SD			
Age (mean, years)							
All cases	11.7	2.6	16.7	1.2	2.661E-32		
Fully encapsulated	11.5	3.2	16.7	1.3	1.417E-8		
Non-encapsulated	11.8	2.4	16.7	1.2	2.870E-27		
Sex (F/M)							
All cases	68/30	F:M=2.3:1	68/22	F:M=3.1:1	0.415		
Fully encapsulated	15/4	F:M=3.7:1	8/4	F:M=2.0:1	0.676		
Non-encapsulated	53/26	F:M=2.0:1	60/18	F:M=3.3:1	0.214		
Tumor capsule					0.326	0.634 (0.228-1.396)	0.258
Full	19	19.4	12	13.3			
Partial/absent	79	80.6	78	86.7			
Size (mean, mm)							
All cases	24.2	14.2	24.0	14.5	0.951		
Fully encapsulated	22.5	10.3	20.9	12.4	0.589		
Non-encapsulated	24.6	15.0	24.4	14.8	0.897		
Size ≤ 10 mm							
All cases	11	11.2	12	13.3	0.664	1.272 (0.527-3.068)	0.593
Fully encapsulated	2	2.0	4	4.4	0.174	3.883 (0.552-27.330)	0.173
Non-encapsulated	9	9.2	8	8.9	1.000	0.924 (0.334-2.553)	0.878
Size > 10 mm							
All cases	87	88.8	78	86.7	NC ³	NC	NC
Fully encapsulated	17	17.3	8	8.9	NC	NC	NC
Non-encapsulated	70	71.4	70	77.8	NC	NC	NC
Dominant pattern							
Papillary							
All cases	43	43.9	45	50.0	0.465	1.286 (0.723-2.288)	0.392
Fully encapsulated	5	5.1	3	3.3	1.000	0.726 (0.120-4.377)	0.727
Non-encapsulated	38	38.8	42	46.7	0.524	1.240 (0.660-2.330)	0.504
Follicular							
All cases	25	25.5	24	26.7	0.869	1.013 (0.524-1.961)	0.969
Fully encapsulated	11	11.2	6	6.7	0.724	0.952 (0.174-5.210)	0.955
Non-encapsulated	14	14.3	18	20.0	0.434	1.347 (0.613-2.959)	0.458
Solid-trabecular							
All cases	30	30.6	21	23.3	0.325	0.714 (0.370-1.376)	0.314
Fully encapsulated	3	3.1	3	3.3	0.653	1.525 (0.234-9.926)	0.659
Non-encapsulated	27	27.6	18	20.0	0.158	0.602 (0.296-1.223)	0.161
Oxyphilic changes							
All cases	21	21.4	27	30.0	0.186	1.601 (0.825-3.109)	0.164
Fully encapsulated	4	4.1	5	5.6	0.253	2.848 (0.563-14.421)	0.206
Non-encapsulated	17	17.3	22	24.4	0.360	1.495 (0.715-3.124)	0.285
Focal							
All cases	13	13.3	17	18.9	0.324	1.520 (0.691-3.345)	0.298
Fully encapsulated	2	2.0	3	3.3	0.350	3.900 (0.494-30.758)	0.196
Non-encapsulated	11	11.2	14	15.6	0.520	1.391 (0.5843-3.11)	0.456
Severe							
All cases	8	8.2	10	11.1	0.621	1.469 (0.549-3.931)	0.444
Fully encapsulated	2	2.0	2	2.2	0.630	1.460 (0.166-12.837)	0.733
Non-encapsulated	6	6.1	8	8.9	0.589	1.459 (0.477-4.464)	0.508
Concomitant nodular pathology							
All cases	9	9.2	9	10.0	1.000	1.039 (0.390-2.769)	0.939
Fully encapsulated	5	5.1	0	0.0	0.128	ND ⁴	ND
Non-encapsulated	4	4.1	9	10.0	0.160	2.162 (0.625-7.480)	0.224
Concomitant diffuse pathology							
All cases	27	27.6	28	31.1	0.632	1.127 (0.594-2.139)	0.715
Fully encapsulated	1	1.0	0	0.0	1.000	ND	ND
Non-encapsulated	26	26.5	28	31.1	0.739	1.037 (0.527-2.041)	0.917
Chronic thyroiditis							
All cases	25	25.5	24	26.7	0.869	0.996 (0.511-1.939)	0.990
Fully encapsulated	1	1.0	0	0.0	1.000	ND	ND
Non-encapsulated	24	24.5	24	26.7	1.000	0.908 (0.450-1.831)	0.787
Intrathyroid spread							
All cases	23	23.5	20	22.2	0.864	0.941 (0.475-1.865)	0.862
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	23	23.5	20	22.2	0.721	0.850 (0.419-1.725)	0.653
Extrathyroidal extension (pT3)							
All cases	58	59.2	38	42.2	0.028	0.507 (0.283-0.907)	0.022
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	58	59.2	38	42.2	0.002	0.345 (0.176-0.675)	0.002
Multifocality (pTm)							
All cases	10	10.2	12	13.3	0.651	1.313 (0.536-3.219)	0.552
Fully encapsulated	2	2.0	2	2.2	0.630	2.167 (0.244-19.276)	0.488
Non-encapsulated	8	8.2	10	11.1	0.626	1.268 (0.470-3.423)	0.640
Lymphatic/vascular invasion							
All cases	66	67.3	57	63.3	0.646	0.830 (0.454-1.518)	0.546
Fully encapsulated	3	3.1	3	3.3	0.653	2.400 (0.355-16.213)	0.369
Non-encapsulated	63	64.3	54	60.0	0.146	0.570 (0.273-1.187)	0.133
Lymph node metastases (pN1)							
All cases	63	64.3	47	52.2	0.105	0.616 (0.343-1.107)	0.105
Fully encapsulated	3	3.1	0	0.0	0.265	ND	ND
Non-encapsulated	60	61.2	47	52.2	0.041	0.490 (0.245-0.977)	0.043
Distant metastases (M1)							
All cases	15	15.3	5	5.6	0.034	0.336 (0.116-0.969)	0.044
Fully encapsulated	0	0.0	0	0.0	ND	ND	ND
Non-encapsulated	15	15.3	5	5.6	0.029	0.306 (0.105-0.895)	0.031

¹ % for count data. SD for continuous numeric data. ² Adjusted for sex. ³ NC, not calculated due to data complementarity to size ≤ 10 mm. ⁴ ND, not determined.

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