Chapter 5

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Comparative pathological analysis of papillary thyroid carcinoma in age-matched groups of patients born before and after Chernobyl

The aim of this chapter is to compare structural characteristics and invasive features of papillary thyroid carcinomas (PTCs) between the groups of patients who were children at the time of the Chernobyl accident and thus were exposed to radioactive iodine in fallout (the radiogenic cancers) and those who were born since 1987 and were not irradiated (so-called sporadic cancers). We recognize that the radiogenic group will inevitably include some cases of non-radiation aetiology, and attempted to minimize these through the process of selection described below.

In Chapter 3 and our previous papers [1-5] it has been shown that thyroid cancer incidence was significantly higher in the six northern Ukraine regions with high levels of contamination by radioactive iodine. Among these, three areas are the most affected: Kiev, Zhytomir, and Chernigov regions. A simple calculation of the number of cases per 1,000 residents in relevant populations for 25 years (from 1986 to 2010) demonstrates evident difference: it is about 3 times higher in those exposed as children and 2 times higher in those exposed as adolescents as compared with less contaminated regions (Table 5.1).

Table 5.1
Number of cases and prevalence per 1,000 of population of thyroid cancer cases in Ukraine in subjects who were children and adolescents at the time of Chernobyl accident

	Children	Adolescents	Total
Whole of Ukraine	5044/11100000=**0.5/1000**	1642/2200000=**0.8/1000**	6686/13300000=**0.5/1000**
21 less or not contaminated regions	2861/8900000=**0.3/1000**	1078/1760000=**0.6/1000**	3939/10660000=**0.4/1000**
3 out of 6 most contaminated regions	1098/1025000=**1.1/1000**	254/195000=**1.3/1000**	1352/1220000=**1.1/1000**

Also, as was reported earlier [6-9], the highest dose-dependent additional incidence was observed in children whose age in 1986 did not exceed 4 years. It therefore is reasonable to assume that the fraction of papillary carcinomas attributable to radiation would be the largest among those whose age at exposure ranged from 0 to 4 years and who at the time of accident were residents of the three most affected regions of Ukraine (Kiev, Chernigov, and Zhytomir regions).

For this reason, for the present investigation we selected pathological data for the period from 1990 to 2010 (see Chapter 4), and included in the analysis only cases diagnosed in residents of the three most contaminated regions who were aged up to 4 years at Chernobyl. These are: 114 out of 272 PTCs in children aged up to 14 years at surgery, 66 out of 225 in adolescents aged from 15 to 18 years at surgery, and 59 out of 361 PTCs in adults aged 19-23 years. Age at surgery in adults was limited from 19 to 23 years since among patients born after Chernobyl no one was older than 23 years in 2010. All 264 PTCs detected in subjects born after the accident were included in the analysis regardless of their place of residence because all these cases are sporadic. Characterstics of the age-matched groups are specified in Table 5.2.

Table 5.2
Age-matched groups of radiogenic and sporadic PTC in the study

	Number of cases		Mean age		F:M	
	Radiogenic	Sporadic	Radiogenic	Sporadic	Radiogenic	Sporadic
Children	114	111	11.6	12.0	68:46=1.5:1	83:28=3.0:1
Adolescents	66	97	16.8	16.8	44:22=2.0:1	72:25=2.9:1
Adults	59	56	21.2	20.8	44:15=2.9:1	46:10=4.6:1

In all groups, both in radiogenic and sporadic PTCs, female patients were prevailing, but in the group of children with radiogenic tumors the proportion of male patients was greater as compared with the group of children with sporadic carcinomas (Table 5.2), with a substantial difference in F:M ratio (1.5:1 vs 3:1, respectively).

There were no significant differences in mean size of tumor when comparing either different age groups or radiogenic and sporadic carcinomas in each age group. In children with radiogenic PTC the frequency of microcarcinomas measuring up to 10 mm was 2.2 times lower as compared to children with sporadic PTC (Table 5.3) suggesting that screening had not shifted tumor size to the lower values in the exposed regions.

Table 5.3
Mean size of radiogenic and sporadic PTC in the study

	Children		Adolescents		Adults	
	Radiogenic	Sporadic	Radiogenic	Sporadic	Radiogenic	Sporadic
Mean size (mm)	23.6	24.0	19.1	23.3	20.6	21.3
≤10 mm: n (%)	7/114(6.1)	5/111(13.5)	14/66(21.2)	16/97(16.5)	13/59(22.0)	13/56(23.2)

It should be emphasized that "architecturally" all PTCs under study, regardless of patients' date of birth or age at diagnosis, were almost all represented by three common histological variants: classical papillary, follicular, solid, and by the mixed-type tumors (herein reffered to as "mixed variant") which comprise combinations of the mentioned growth patterns. The diffuse-sclerosing variant was identified in a small number of cases (mainly among children), and there were isolated cases of Warthin-like and Cribriform-morular variants (Table 5.4). Among the mixed variants of PTC, the papillary-follicular and solid-follicular combinations were most frequent (Table 5.5).

Comparison of radiogenic PTCs selected for the present analysis with all morphologically studied cases in patients born before the Chernobyl accident (described in the previous chapter) shows that such a selection did not result in changes in the distribution of main PTC subtypes, in the ratio of structural components of mixed variant, or frequency of the combined (solid+solid-follicular and papillary+papillary-follicular) variants in all age groups (see Tables 4.4, 4.5 of Chapter 4 and Tables 5.4, 5.5, 5. 6 of this Chapter). Despite the maximum age of adult patients has considerably decreased after selection (from 42 years in the total group to 23 years in the selected group), all significant linear age trends (assessed by the Chi-square test for trend) identified in the previous chapter, were preserved. In the selected groups of PTCs, linear decreasing trends of frequency of solid, solid-follicular and combined (solid+solid-follicular) variants ($p<0.0115$; $p<0.0009$; $p<0.0001$, respectively), and increasing linear trends of frequency of papillary, papillary-follicular and combined (papillary+papillary-follicular) variants in the age series of children-adolescents-adults remained unchanged ($p<0.0001$; $p<0.0013$; $p<0.0001$, respectively). A significant increasing linear age trend was also noted for the frequency of fully encapsulated PTCs ($p<0.0001$, Table 5.7).

The selection had no effect on the invasive properties of radiogenic PTCs either (Table 4.8 of Chapter 4 and Table 5.7 of this Chapter). In the selected cases, significant decreasing linear trends of frequency of intrathyroidal spread and extrathyroidal extension, vascular invasion, regional and distant metastases in the age series of children-adolescents-adults were also confirmed (all trends, $p<0.0001$).

Thus, our selection of cases by patients' age and place of residence at the time of the Chernobyl accident was not associated with significant changes in morphological characteristics of PTCs determined in corresponding age groups for the whole of Ukraine, i.e. there was no detectable selection bias.

Considering the frequency of histological subtypes in sporadic PTCs (in patients born after the Chernobyl accident), it should be noted that the linear trends similar to those in radiogenic cancers were not found in age series (Tables 5.4, 5.5, 5.6) except for a decreasing trend in the frequency of solid variant ($p<0.0502$, marginally). Analysis of encapsulated PTCs also showed no age relationship (Table 5.7).

By contrast, invasive properties of sporadic (Table 5.7) as well as of radiogenic PTCs were significantly decreasing in the age series of children-adolescents-adults (intrathyroidal extension, $p<0.0470$; extrathyroidal extension, $p<0.0001$; vascular invasion, $p<0.0008$; regional metastases, $p<0.0004$, distant metastases to the lung, $p<0.0106$).

Conceivably, radiogenic and sporadic papillary carcinomas, when comparison is performed in the age series, are characterized by the same trends for invasive features, but display different character of distribution of main histological subtypes.

Table 5.4
Subtypes of PTC in patients born before (radiogenic) and after Chernobyl (sporadic cancers)

	Children up to 14 y.o. at surgery				Adolescents 15-18 y.o. at surgery				Adults 19-23 y.o. at surgery			
	Radiogenic		Sporadic		Radiogenic		Sporadic		Radiogenic		Sporadic	
	n	%	n	%	n	%	n	%	n	%	n	%
Classic papillary	11	9.6	18	16.2	14	21.2	28	28.9	20	33.3	12	21.4
Follicular	25	21.9	17	15.3	14	21.2	9	9.3	13	22.0	8	14.3
Solid	24	21.1	17	15.3	5	7.6	10	10.3	5	7.5	3	5.3
Mixed	47	41.3	54	48.7	31	47.0	48	49.5	21	35.6	29	51.8
Diffuse-sclerosing	7	6.1	5	4.5	1	1.5	1	1.0	-	-	1	1.8
Warthin-like	-	-	-	-	1	1.5	1	1.0	-	-	2	3.6
Cribriform	-	-	-	-	-	-	-	-	-	-	1	1.8
Total	114	100	111	100	66	100	97	100	59	100	56	100

Table 5.5
Structural combinations of mixed subtypes of PTC in patients born before (radiogenic) and after Chernobyl (sporadic cancers)

	Children up to 14 y.o. at surgery				Adolescents 15-18 y.o. at surgery				Adults 19-23 y.o. at surgery			
	Radiogenic		Sporadic		Radiogenic		Sporadic		Radiogenic		Sporadic	
	n	%	n	%	n	%	n	%	n	%	n	%
Papillary-follicular	9	19.1	20	37.0	13	41.9	19	39.6	12	57.1	7	24.1
Papillary-solid	5	10.6	10	18.5	8	25.8	8	16.7	3	14.3	6	20.7
Papillary-follicular-solid	2	4.3	7	13.0	1	3.2	6	12.5	-	-	4	13.8
Solid-follicular	31	66.0	17	31.5	9	29.0	15	31.2	6	28.6	12	41.4
Total	47	100	54	100	31	100	48	100	21	100	29	100

Table 5.6
PTCs with most prominent solid patterns (SV+SFV) and most prominent papillary patterns (PV+PFV) in patients born before (radiogenic) and after Chernobyl (sporadic cancers)

	Children up to 14 y.o at surgery				Adolescents 15-18 y.o at surgery				Adults 19-23 y.o at surgery			
	Radiogenic		Sporadic		Radiogenic		Sporadic		Radiogenic		Sporadic	
	n	%	n	%	n	%	n	%	n	%	n	%
Solid+Solid-Follicular variants	55/114	48.2	34/111	30.6	14/66	21.2	25/97	25.8	11/59	18.6	15/56	26.8
Papillary+Papillary-Follicular variants	20/114	17.5	38/111	34.2	27/66	40.9	47/97	48.5	32/59	54.2	19/56	33.9

Table 5.7
Invasive proprties and tumor encapsulation in patients born before (radiogenic) and after Chernobyl (sporadic cancers)

	Children up to 14 y.o at surgery				Adolescents 15-18 y.o at surgery				Adults 19-23 y.o at surgery			
	Radiogenic		Sporadic		Radiogenic		Sporadic		Radiogenic		Sporadic	
	n	%	n	%	n	%	n	%	n	%	n	%
Intrathyroidal extension	97	85.1	74	66.7	35	53.0	61	62.9	35	59.3	28	50.0
Extrathyroidal extension	76	66.7	60	54.1	30	45.0	40	41.2	19	32.2	12	21.4
Multifocality	7	6.1	11	9.9	7	10.6	11	11.3	5	8.5	9	16.1
Vascular invasion	97	85.1	79	71.2	44	66.7	64	66.0	27	45.8	24	42.9
Regional metastases	77	67.5	71	64.0	35	53.0	54	55.7	16	27.1	19	33.9
Distant metastases	27	23.8	14	12.6	9	13.6	6	6.2	-	-	1	1.8
Fully encapsulated	6	5.3	22	19.8	10	15.2	15	15.5	19	32.2	15	26.8

Taking into account that earlier comparative analyses of PTC in children and adolescents of Ukraine, Belarus, and Russia born before and after Chernobyl have not revealed substantial morphological differences [10-14], in the present study we used deepened univariate and multivariate statistical approaches to each of the three age-matched groups.

To compare pathological parameters between radiation-induced and sporadic PTC by univariate analysis, Fisher exact test (FT) was used for categorical data, and two-tailed Mann-Whitney test for quantitative measurements.

Univariate statistical analysis of main subtypes of PTC in children (Table 5.8) showed that among radiogenic PTCs the frequency of tumors with solid-follicular strucuture (solid + solid-follicular variants) was significantly higher than that in sporadic PTCs ($p<0.009$). Conversely, the frequency of sporadic PTCs with papillary-follicular structure (papillary + papillary-follicular variants, $p<0.006$) was significantly higher than in radiogenic tumors.

Comparison of invasive features also revealed the most pronounced differences in childhood groups: radiogenic PTCs were characterized by a significantly higher frequency of intrathyroidal extension ($p<0.002$), vascular invasion ($p<0.015$) and distant metastases ($p<0.033$).

In addition, in the group of children with radiogenic PTC, a significantly lower frequency was observed for the fully encapsulated tumors as compared with sporadic PTCs ($p<0.001$), and for the frequency of microcarcinomas sized up to 10 mm, but the difference is not quite statistically significant ($p<0.074$). The groups of children with radiogenic and sporadic PTCs also differed significantly in F:M ratio ($p<0.026$) as mentioned above.

Among adolescents and adults no significant differences between any of the above parameters were observed (Table 5.8).

Multivariate analysis in each age group of patients was performed using standard logistic regression modeling. The following variables were tested:

age at surgery (continuous; years);
sex (categorical, M or F);
tumor size ≤10mm or >10 mm (categorical; yes or no);
complete tumor capsule (categorical; yes or no);
histological subtype (categorical; solid+solid follicular or other);
lymph node metastases (categorical; yes or no);
distant metastasis to the lung (categorical; yes or no);
intrathyroidal spread (categorical; yes or no);
extrathyroidal extension (categorical; yes or no);
multifocality (categorical; yes or no);
vascular invasion (categorical; yes or no).

Non-automatic backward elimination was applied to the full model that initially included all the variables listed above. Once the most appropriate model was determined, the maximum likelihood estimates of the respective parameters and their 95% confidence intervals were calculated.

Multivariate logistic regression analysis (Table 5.9) confirmed significant differences between radiogenic and sporadic PTCs in children. Four parameters (male gender, absence of tumor capsule, solid+solid-follicular tumor architecture, and a higher frequency of intrathyroidal spread) were found to be independently associated with radiogenic PTC. The fifth parameter, the higher frequency of lymph node metastases, showed just marginal association with radiogenic PTCs.

Table 5.8
Univariate statistical analysis of PTCs in patients born before (radiogenic) and after Chernobyl (sporadic cancers) in age-matched groups

Children

Parameters	OR	95% CI	*p*-value
Sex (M vs F)	1.89	1.08-3.35	0.026
Age at operation (years)	0.93	0.83-1.04	0.190
Tumor size (≤10 mm vs >10 mm)	0.42	0.16-1.07	0.074
Tumor capsule (yes vs no)	0.22	0.09-0.58	0.001
Subtype (solid+solid-follicular vs other)	2.11	1.22-3.64	0.009
pN (pN1 vs pN0)	1.14	0.66-1.99	> 0.5
M (M1 vs M0)	2.13	1.06-4.42	0.033
Multifocality (yes vs no)	0.59	0.21-1.56	0.287
Intrathyroidal extension (yes vs no)	2.78	1.47-5.43	0.002
Extrathyroidal extension (yes vs no)	1.67	0.97-2.88	0.063
Vascular invasion (yes vs no)	2.31	1.97-4.47	0.015

Adolescents

Parameters	OR	95% CI	*p*-value
Sex (M vs F)	1.44	0.73-2.86	0.379
Age at operation (years)	1.01	0.76-1.33	> 0.5
Tumor size (≤10 mm vs >10 mm)	0.69	0.29-1.64	0.394
Tumor capsule (yes vs no)	0.92	0.38-2.14	> 0.5
Subtype (solid+solid-follicular vs other)	0.78	0.37-1.63	> 0.5
pN (pN1 vs pN0)	0.92	0.49-1.72	> 0.5
M (M1 vs M0)	2.42	0.83-7.56	0.106
Multifocality (yes vs no)	0.94	0.33-2.52	> 0.5
Intrathyroidal extension (yes vs no)	0.69	0.36-1.29	0.241
Extrathyroidal extension (yes vs no)	1.21	0.64-2.27	> 0.5
Vascular invasion (yes vs no)	1.03	0.53-2.00	> 0.5

Adults

Parameters	OR	95% CI	*p*-value
Sex (M vs F)	1.57	0.64-3.96	0.324
Age at operation (years)	1.28	0.96-1.73	0.097
Tumor size (≤10 mm vs >10 mm)	0.94	0.34-2.53	> 0.5
Tumor capsule (yes vs no)	1.30	0.58-2.94	> 0.5
Subtype (solid+solid-follicular vs other)	0.63	0.26-1.51	0.374
pN (pN1 vs pN0)	0.72	0.32-1.61	0.427
Multifocality (yes vs no)	0.48	0.14-1.50	0.211
Intrathyroidal extension (yes vs no)	1.46	0.70-3.07	0.315
Extrathyroidal extension (yes vs no)	1.74	0.76-4.12	0.191
Vascular invasion (yes vs no)	1.12	0.54-2.35	> 0.5

Table 5.9
Results of multivariate statistical analysis of PTC in patients born before (radiogenic) and after Chernobyl (sporadic cancers) in age-matched groups

Children

Parameters	OR	95% CI	*p*-value
Sex (M vs F)	1.86	1.02-3.43	0.042
Tumor capsule (yes vs no)	0.27	0.09-0.73	0.009
Subtype (solid+solid-follicular vs other)	1.89	1.05-3.33	0.031
pN (yes vs no)	1.89	0.96-3.70	0.064
Intrathyroidal spread (yes vs no)	2.80	1.36-5.98	0.005

Adolescents

Parameters	OR	95% CI	*p*-value
Extrathyroidal extension (yes vs no)	3.00	1.07-9.91	0.037

Adults

Parameters	OR	95% CI	*p*-value
Age at operation (older vs younger)	1.49	1.08-2.12	0.014
pN (yes vs no)	0.34	0.11-0.93	0.034
Multifocality (yes vs no)	0.32	0.08-1.05	0.060
Extrathyroidal extension (yes vs no)	3.56	1.25-1.51	0.017

In adolescents, only a higher chance of extrathyroidal extension in radiogenic PTCs was noted. In adults, the logistic regression revealed a significant association for four parameters: age at surgery, lymph node metastases, and extrathyroidal extension. A higher frequency of extrathyroidal extension was associated with radiogenic PTCs. On the contrary, a higher frequency of lymph node metastases, younger age and higher frequency of multifocality (marginally) were associated with sporadic PTCs (Table 5.9). Of note, univariate statistical analysis showed no significant differences for any of these parameters in adolescents and adults.

Thus, radiogenic papillary carcinomas in each of the age-matched groups had certain differences from sporadic ones. The most pronounced differences were observed in age-matched groups of children; these were confirmed on both univariate and multivariate statistical analyses.

The data obtained suggest that after radiation exposure at the age 0-4 years old, the most rapidly progressing towards clinical manifestations PTCs (latency in subjects operated on in childhood ranged from 3.8 to 13.8 years, mean 9.4 years, Table 5.10) were independently associated with the solid and/or solid-follicular growth pattern, absence of tumor capsule, and such an aggressive morphological feature as intrathyroidal spread as compared to sporadic PTCs in the age-matched group. It should be noted that the higher aggressiveness of radiogenic Chernobyl papillary carcinomas in children of Ukraine and Belarus with a shorter latency was associated with the presence of a marked solid component, as reported in our previous study [15].

Apparently, the slower development of radiogenic tumors in adolescents and adults (mean latency 14.4 and 18.8 years, respectively, Table 5.10) levels off the differences in histological architectonics seen in children. On multivariate analysis, associations were found only for the greater chance of extrathyroidal extension in adolescents and adults and also for the lower chance of nodal disease in adults, but no correlation was found with tumor morphology in these age groups.

It is worth noting that such a "convergence" of morphological characteristics between radiogenic and sporadic PTCs with increasing patients' age and, naturally, the latency of radiogenic tumors, could perhaps be explained, at least in part, by different thyroid doses received during the Chernobyl accident by children at surgery on one hand, and adolescents and/or adults at surgery on the other. This hypothesis is based on the results of our cohort studies obtained within the Ukrainian-American Project [16]. It was shown that after the 1st screening during the period 1998 to 2000 (mean latency 14.6 years), the number of thyroid cancer cases per 1000 cohort members was the highest (10.2/1000) in the high-dose group in which thyroid doses were more than 1 Gy as compared with the low-dose group with thyroid doses less than 0.3 Gy (1.3/1000, $p<0.0001$). By contrast, after the 4th screening during 2006-08 (mean latency 20.9 years), such tendency was no longer observed (1.2/1000 and 1.5/1000 respectively, $p<0.753$). It therefore seems possible that the rapid progression of radiogenic PTCs in children at surgery might be associated with higher exposure doses as compared with radiogenic tumors in adolescents and adults which are characterized by the longer latency.

To verify this supposition, we analyzed *individual reconstructed ^{131}I thyroid doses* in all cases of radiogenic PTCs which have been calculated by a method described in a recent article [17] and in Chapter 2 of this monograph for thyroid tumors included in the Chernobyl Tissue Bank (CTB). Mean ^{131}I thyroid dose in our cohort which included 239 children aged 0 to 4 years at exposure was 1.016 Gy (95% CI 0.701-1.332; median 0.336 Gy; minimum 0.040 Gy; maximum 24.110 Gy).

In the comparison of three age groups with different latency by the Kruskal-Wallis nonparametric ANOVA, no significant differences between exposure doses were found. Although the median of doses was somewhat decreasing in the series children-adolescents-adults, no significant linear trend was found (Table 5.10). A plausible explanation of the absence of significant differences between thyroid doses would be that all Ukrainian-American cohort members had direct measurements of thyroid activity (see Chapter 2) unlike patients in the present study, who had direct measurements of thyroid activity only in 16.3% cases (39 out of 239). The accuracy of dose estimates in the Ukrainian-American cohort was obviously higher with narrower CI range. In addition, patients distributions by age at the time of Chernobyl (0 to 4 years) and at surgery (4 to 23 years) differed significantly from those included in the Ukrainian-American project [16,18,19] in which the age at exposure exceeded 4 years in most cases, there were practically no patients operated in childhood, and the age of operated adults reached 34 years.

A more detailed analysis of mean thyroid doses for those pathological parameters that distinguished radiogenic PTCs from sporadic ones showed that doses were significantly higher in children/Females comparing with adults/Females. When comparing the doses of females and males, those were higher for males in all age groups, especially in adolescents and adults, but without significant difference (Table 5.11).

Analysis of dose relationship with PTC size (microcarcinoma vs other) demonstrated different trends in children, adolescents and adults. While in children the mean dose for microcarcinomas was insignificantly lower than in PTCs of larger size, in adolescents and adults microcarcinoma was associated with higher doses, and in adolescents such a difference was significant (Table 5.12).

In patients of all age groups with non-encapsulated PTC mean doses were higher than in patients with fully encapsulated tumor (Table 5.13), but significant differences were not found either in children in whom this parameter was strongly associated with radiogenic cancer, or in older patients in whom this association was absent.

For the combined solid + solid-follicular subtypes of PTC, which were associated with radiogenic cancer in children, mean doses did not display statistically significant differences either in the series children-adolescents-adults or when the doses were compared to those for all other subtypes of PTC (Table 5.14).

Morphological features of tumor agressiveness (intrathyroidal spread, extrathyroidal extension, nodal disease), were not associated with significant differences in mean doses in all age groups either. Also, no dose differences were found in patients with or without morphological manifestations of agressiveness (Tables 5.15-5.17). A significantly higher exposure dose was noted only in adolescents without intrathyroidal spread as compared to patients with such or with corresponding adults (Table 5.15).

Tumor multifocality, which was marginally associated with sporadic PTC in adults, was associated in radiogenic carcinomas of this age group with a higher (compared with children and adolescents) exposure dose (Table 5.18) but no significance could be expected taking into account the range of dose estimates from 0.155 to 12.279 Gy in 5 observations.

Table 5.10
Latency and thyroid radiation doses in patients with radiogenic PTC (born before Chernobyl)

	Latency (years)			Doses (Gy)		
Parameters	Children (n=114)	Adolescents (n=66)	Adults (n=59)	Children (n=114)	Adolescents (n=66)	Adults (n=59)
Mean	9.4	14.8	18.9	0.995	1.333	0.704
95 % CI	9.0-9.9	14.3-15.2	18.3-19.4	0.591-1.398	0.487-2.179	0.269-1.139
Minimum	3.8	11.7	14.8	0.048	0.040	0.044
Median	9.4	14.4	18.8	0.406	0.341	0.261
Maximum	13.8	17.9	22.6	16.584	24.110	12.280
p-value			<0.0001			0.226
p-trend			<0.0001			0.467
p-value	<0.0001 [a]			0.801 [a]		
p-value	<0.0001 [b]	<0.0001 [c]		0.098 [b]	0.182 [c]	

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults

Table 5.11
Thyroid radiation doses in females and males with radiogenic PTC (born before Chernobyl)

	Females, doses, Gy			Males, doses, Gy		
Parameters	Children (n=68)	Adolescents (n=44)	Adults (n=44)	Children (n=46)	Adolescents (n=22)	Adults (n=15)
Mean	1.023	0.962	0.459	0.953	2.075	1.317
95 % CI	0.970-1.476	0.320-1.607	0.275-0.714	0.187-1.721	0.208-4.359	0.379-3.014
Minimum	0.048	0.040	0.044	0.057	0.068	0.101
Median	0.459	0.327	0.240	0.329	0.366	0.434
Maximum	13.216	13.286	3.175	16.584	24.110	12.279
p-value			0.046			0.551
p-trend			0.113			0.472
p-value	0.235 [a]			0.234 [d]	0.295 [e]	0.139 [f]
p-value	0.015 [b]	0.217 [c]				

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: female vs male; [e] - adolescents: female vs male; [f] - adults: female vs male;

Table 5.12
Thyroid radiation doses and tumor size in patients with radiogenic PTC (born before Chernobyl)

	Size ≤10 mm, doses, Gy			Size ≥11 mm, doses, Gy		
Parameters	Children (n=7)	Adolescents (n=14)	Adults (n=13)	Children (n=107)	Adolescents (n=52)	Adults (n=46)
Mean	0.396	4.323	1.380	1.034	0.528	0.513
95 % CI	0.179-0.612	0.473-8.174	0.620-3.380	0.605-1.464	0.310-0.746	0.304-0.722
Minimum	0.152	0.203	0.087	0.048	0.070	0.044
Median	0.342	2.136	0.274	0.416	0.299	0.259
Maximum	0.715	24.110	12.279	16.584	4.508	3.175
p-value			0.022			0.115
p-trend			0.664			0.084
p-value	0.025 [a]			0.102 [a]		
p-value	0.757 [b]	0.017 [c]		0.086 [b]	0.798 [c]	
p-value				0.645 [d]	0.0006 [e]	0.905 [f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: ≤10 mm vs ≥11 mm; [e] – adolescents: ≤10 mm vs ≥11 mm; [f] - adults: ≤10 mm vs ≥11 mm

Table 5.13
Thyroid radiation doses and full tumor encapsulation in patients with radiogenic PTC (born before Chernobyl)

Parameters	Fully encapsulated, doses, Gy			Non- and partly encapsulated, doses, Gy		
	Children (n=6)	Adolescents (n=10)	Adults (n=19)	Children (n=108)	Adolescents (n=56)	Adults (n=40)
Mean	0.327	0.612	0.362	1.032	1.462	0.866
95 % CI	0.126-0.527	0.092-1.315	0.161-0.563	0.607-1.457	0471-2.454	0.229-1.504
Minimum	0.083	0.087	0.044	0.048	0.040	0.087
Median	0.402	0.327	0.202	0.406	0.359	0.285
Maximum	0.540	3.400	1.626	16.584	24.110	12.279
p-value			0.424			0.732
p-trend			0.534			0.737
p-value	0.635 [a]			0.842 [a]		
p-value	0.849 [b]	0.344 [c]		0.412 [b]	0.642 [c]	
p-value				0.348 [d]	0.838 [e]	0.089 [f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: full encapsulation vs other; [e] – adolescents: full encapsulation vs other; [f] - adults: full encapsulation vs other

Table 5.14
Thyroid radiation doses and combined Solid+Solid-Follicular subtype of PTC in patients born before Chernobyl

Parameters	Solid+Solid-Follicular subtype, doses, Gy			Other subtypes, doses, Gy		
	Children (n=55)	Adolescents (n=14)	Adults (n=11)	Children (n=59)	Adolescents (n=52)	Adults (n=48)
Mean	0.752	0.730	0.716	1.222	1.496	0.701
95 % CI	0.433-1.071	0.315-1.144	0.107-1.325	0.494-1.951	0.424-2.558	0.177-1.226
Minimum	0.056	0.089	0.045	0.048	0.040	0.044
Median	0.369	0.352	0.285	0.428	0.327	0.254
Maximum	6.880	2.160	3.015	16.584	24.110	12.279
p-value			0.855			0.134
p-trend			0.920			0.366
p-value	0.591 [a]			0.417 [a]		
p-value	0.911 [b]	0.966 [c]		0.052 [b]	0.212 [c]	
p-value				0.387 [d]	0.814 [e]	0.654 [f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: SV+SFV vs other; [e] – adolescents: SV+SFV vs other; [f] - adults: SV+SFV vs other

Table 5.15
Thyroid radiation doses and intrathyroidal spread in patients with radiogenic PTC (born before Chernobyl)

Parameters	Intrathyroidal spread, doses, Gy			No intrathyroidal spread, doses, Gy		
	Children (n=97)	Adolescents (n=35)	Adults (n=35)	Children (n=17)	Adolescents (n=31)	Adults (n=21)
Mean	0.973	0.644	0.828	1.121	2.111	0.523
95 % CI	0.573-1.373	0.268-1.021	0.116-1.540	0.486-2.729	0.349-3.873	0.213-0.959
Minimum	0.048	0.040	0.045	0.096	0.072	0.044
Median	0.453	0.292	0.285	0.316	0.428	0.235
Maximum	16.584	4.595	12.279	13.216	24.110	3.175
p-value			0.238			0.067
p-trend			0.692			
p-value	0.120[a]			0.196[a]		
p-value	0.289[b]	0.725[c]		0.308[b]	0.028[c]	
p-value				0.436[d]	0.039[e]	0.436[f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: intrathyroidal spread, yes vs no; [e] – adolescents: intrathyroidal spread, yes vs no; [f] - adults: intrathyroidal spread, yes vs no

Table 5.16
Thyroid radiation doses and extrathyroidal extension in patients with radiogenic PTC (born before Chernobyl)

Parameters	Extrathyroidal extension, doses, Gy			No extrathyroidal extension, doses, Gy		
	Children (n=76)	Adolescents (n=30)	Adults (n=19)	Children (n=38)	Adolescents (n=36)	Adults (n=40)
Mean	0.786	0.726	0.601	1.413	1.839	0.753
95 % CI	0.508-1.063	0.281-1.171	0.204-0.997	0.314-2.513	0.318-3.361	0.128-1.378
Minimum	0.048	0.046	0.045	0.065	0.040	0.044
Median	0.410	0.330	0.285	0.396	0.341	0.259
Maximum	6.880	5.167	3.015	16.584	24.110	12.279
p-value			0.456			0.262
p-trend			0.534			0.391
p-value	0.646[a]			0.987[a]		
p-value	0.372[b]	0.594[c]		0.150[b]	0.175[c]	
p-value				0.648[d]	0.541[e]	0.928[f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: extrathyroidal extension, yes vs no; [e] – adolescents: extrathyroidal extension, yes vs no; [f] - adults: extrathyroidal extension, yes vs no

Table 5.17
Thyroid radiation doses and lymph node metastases in patients with radiogenic PTC (born before Chernobyl)

Parameters	Lymph node metastases, doses, Gy			No lymph node metastases, doses, Gy		
	Children (n=77)	Adolescents (n=35)	Adults (n=16)	Children (n=37)	Adolescents (n=31)	Adults (n=43)
Mean	0.983	0.692	0.642	1.020	2.057	0.727
95 % CI	0.560-1.407	0.294-1.090	0.149-1.135	0.106-1.934	0.296-3.819	0.148-1.306
Minimum	0.048	0.040	0.045	0.065	0.072	0.044
Median	0.416	0.251	0.247	0.397	0.390	0.261
Maximum	13.216	5.167	3.175	16.584	24.110	12.279
p-value			0.176			0.107
p-trend			0.570			0.200
p-value	0.117[a]			0.245[a]		
p-value	0.186[b]	0.855[c]		0.463[b]	0.028[c]	
p-value				0.616[d]	0.021[e]	0.658[f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: lymph node metastases, yes vs no; [e] – adolescents: lymph node metastases, yes vs no; [f] - adults: lymph node metastases, yes vs no

Table 5.18
Thyroid radiation doses and multifocality in patients with radiogenic PTC (born before Chernobyl)

Parameters	Multifocality, doses, Gy			No multifocality, doses, Gy		
	Children (n=7)	Adolescents (n=7)	Adults (n=5)	Children (n=107)	Adolescents (n=59)	Adults (n=54)
Mean	0.496	0.888	2.736	1.027	1.386	0.515
95 % CI	0.172-0.821	-0.632-2.409	-3.889-9.361	0.598-1.459	0.448-2.324	0.324-0.703
Minimum	0.150	0.089	0.155	0.048	0.040	0/044
Median	0.457	0.251	0.403	0.397	0.350	0.254
Maximum	1.056	4.595	12.279	16.584	24.110	3.175
p-value			0.642			0.145
p-trend			0.200			0.213
p-value	0.535[a]			0.937[a]		
p-value	>0.999[b]	0.432[c]		0.070[b]	0.093[c]	
p-value				0.944[d]	0.499[e]	0.289[f]

[a] - children vs adolescents; [b] - children vs adults; [c] - adolescents vs adults; [d] - children: multifocality, yes vs no; [e] – adolescents: multifocality, yes vs no; [f] - adults: multifocality, yes vs no

Given mean thyroid doses in patients of three age groups with radiogenic papillary carcinomas did not differ significantly for virtually all morphological characteristics under study, we performed an additional deepened analysis of the dose-response relationship.

Those pathological parameters that appeared to be significant on the multivariate analysis of radiation-induced vs sporadic PTCs were examined for their association with thyroid dose using *univariate and multivariate standard logistic regression modeling*:

$$P(a \mid z) = \frac{1}{1+e^{-z}}$$

where *a* – a pathological parameter and *z* is:

for the univariate analysis

$$z = Const + OR(D_j)$$

where *Const* is a constant, $OR(D_j)$ is the Odds Ratio for the dose group D_i (i=0, .. , 4), relative to the dose group D_0 with the OR=1 (referent group). All exposed patients were subdivided in quartiles thereby determining the dose range for each quartile;

for the multivariate analysis:

$$z = Const + bP_k + OR(D_j)$$

where *Const* is a constant, P_k – pathological parameters, $OR(D_j)$ is the Odds Ratio for the dose group D_j relative to the dose group D_0 with the OR=1 (referent group);

Two types of logistic regression models were applied:

- patients were stratified by eight dose intervals (i=0, .. ,8);
- a threshold dose model (two dose intervals) was used for which the reference dose interval was determined by optimizing the model according to binomial maximum likelihood.

The following pathological parameters (P_k) were tested for the multivariate analysis: age at surgery (continuous; years); sex (categorical, M or F); tumor size ≤10 mm or >10 mm (categorical; yes or no); complete tumor capsule (categorical; no or yes); histological subtype (categorical; solid+solid follicular or other); lymph node metastases (categorical; yes or no); distant metastasis to the lung (categorical; yes or no); intrathyroidal spread (categorical; yes or no); extrathyroidal extension (categorical; yes or no); multifocality (categorical; yes or no).

The linear or linear-quadratic terms for the dose were forcedly introduced as independent variable(s) in addition to the parameters used for the multivariate analysis of radiation-induced vs. sporadic PTCs.

EPICURE software package was used for the analysis. Non-automatic backward elimination was applied to the full model that initially included all the variables listed above. The binomial maximum likelihood estimates and the likelihood-based 95% CI were calculated for parameters of all the above-introduced models. Likelihood ratio statistics were used to calculate *p*-values for the studied effects and to test the statistical significance of the respective parameters. The results of these analyses are presented in Tables 5.19-5.21.

In *children*, the following pathological parameters were significantly different between radiation-induced and sporadic PTCs: absence of full tumor capsule, histological subtype (solid + solid-follicular vs other), intrathyroidal spread (yes vs no), and lymph node metastases (yes vs no), marginally (Table 5.19).

Table 5.19
Univariate and multivariate statistical analyses of association of different pathological parameters in exposed children

Tumor capsule, children

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.1885	1.00	referent	-
0.1885 - < 0.387	0.46	0.02-5.12	> 0.5
0. 387 - < 0.7923	1.50	0.23-12.1	> 0.5
0.7923 – 16.584	NA [a]	NA	NA
p-trend linear regression			> 0.5 [b]
	multivariate, stratified		
Extrathyroidal extension	0.03	0.00-0.26	< 0.001 [c]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
0.110 - < 0.185	NA	NA	
0.185 - < 0.274	NA	NA	
0.274 - < 0.406	0.26	0.01-4.32	0.37
0.406 - < 0.547	1.48	0.12-20.9	> 0.5
0.547 - < 0.851	NA	NA	
0.851 - < 1.907	NA	NA	
1.907 –	NA	NA	
linear dose model *p*-trend			0.1 [b]
	multivariate, dose threshold		
Extrathyroidal extension	0.06	0.00-0.43	0.004 [c]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
≥ 0.110	0.13	0.13-1.21	0.07 [b]

[a] there were no or too few cases in the given dose range to fit the model; [b] indicates non-significant association of full tumor encapsulation with thyroid dose; [c] indicates significantly decreased chance of fully encapsulated tumors among cases with extrathyroidal extension

Continuation of Table 5.19

Histological subtype, children

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.1885	1.00	referent	-
0.1885 - < 0.387	1.64	0.58-4.76	0.35
0.387 - < 0.7923	1.24	0.44-3.58	> 0.5
0.7923 – 16.584	2.06	0.72-6.12	0.18
p-trend linear regression			> 0.5 [a]
	multivariate, stratified		
Extrathyroidal extension	0.23	0.09-0.54	< 0.001 [b]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
0.110 - < 0.185	1.22	0.26-5.94	> 0.5
0.185 - < 0.274	0.97	0.20-4.80	> 0.5
0.274 - < 0.406	1.88	0.40-9.22	0.42
0.406 - < 0.547	1.37	0.29-6.60	> 0.5
0.547 - < 0.851	0.80	0.16-3.81	> 0.5
0.851 - < 1.907	5.07	1.00-31.89	0.05
1.907 –	1.22	0.25-5.94	> 0.5
linear dose model *p*-trend			0.1 [a]
	multivariate, dose threshold		
Extrathyroidal extension	0.24	0.10-0.56	0.002 [b]
Thyroid dose (Gy)			
< 0.851	1.00	referent	-
≥ 0.851	2.03	0.81-5.23	0.31 [a]

[a] indicates non-significant association of histological subtype (solid+solid-follicular) with thyroid dose; [b] indicates significantly decreased chance of tumors with growth pattern other than solid or solid-follicular among cases with extrathyroidal extension

Continuation of Table 5.19

Intrathyroidal spread, children

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.1885	1.00	referent	-
0.1885 - < 0.387	0.38	0.07-1.54	0.18
0.387 - < 0.7923	0.58	0.11-2.61	0.48
0.7923 – 16.584	1.56	0.24-12.61	> 0.5
p-trend linear regression			0.43 [a]
	multivariate, stratified		
pT	8.48	2.05-43.28	0.003 [b]
pN	7.96	1.90-41.07	0.004 [c]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
0.110 - < 0.185	0.96	0.03-20.62	
0.185 - < 0.274	0.78	0.03-13.42	
0.274 - < 0.406	0.21	0.01-3.97	0.37
0.406 - < 0.547	0.68	0.02-11.27	> 0.5
0.547 - < 0.851	1.56	0.05-31.79	
0.851 - < 1.907	3.33	0.08-160.1	
1.907 –	1.52	0.04-54.32	
linear dose model *p*-trend			0.1 [a]
	multivariate, dose threshold		
pT	8.21	2.27-34.17	0.001 [b]
pN	6.54	1.73-28.86	0.001 [c]
Thyroid dose (Gy)			
< 0.547	1.00	referent	-
≥ 0.547	2.80	0.71-13.57	0.147 [a]

[a] indicates non-significant association of intrathyroidal spread with thyroid dose; [b] indicates significantly increased chance of intrathyroidal spread among tumors with advanced pT category; [c] indicates significantly increased chance of intrathyroidal spread among cases featuring lymph node metastases

Continuation of Table 5.19

Lymph node metastases, children

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.1885	1.00	referent	-
0.1885 - < 0.387	0.76	0.24-2.33	> 0.5
0.387 - < 0.7923	0.76	0.24-2.33	> 0.5
0.7923 – 16.584	0.84	0.27-2.65	> 0.5
p-trend linear regression			> 0.5 [a]
	multivariate, stratified		
Sex	2.95	1.03-9.55	0.042 [b]
Tumor capsule	0.11	0.01-0.84	0.034 [c]
M	4.36	1.00-31.23	0.049 [d]
Vascular invasion	0.05	0.01-0.21	0.004 [e]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
0.110 - < 0.185	1.48	0.20-10.8	> 0.5
0.185 - < 0.274	0.89	0.15-5.42	> 0.5
0.274 - < 0.406	2.21	0.26-18.37	0.45
0.406 - < 0.547	2.15	0.29-16.09	0.46
0.547 - < 0.851	0.81	0.15-4.44	> 0.5
0.851 - < 1.907	0.58	0.10-3.49	> 0.5
1.907 –	2.26	0.31-16.42	0.42
linear dose model *p*-trend			> 0.5 [a]
	multivariate, dose threshold		
Sex	2.89	1.05-9.33	0.041 [b]
Tumor capsule	0.15	0.01-0.93	0.036 [c]
M	4.41	1.00-28.41	0.048 [d]
Vascular invasion	0.05	0.01-0.20	< 0.001 [e]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
≥ 0.110	1.56	0.44-4.27	0.72 [a]

[a] indicates non-significant association of lymph node metastases with thyroid dose; [b] indicates significantly higher chance of lymph node metastasis in males; [c] indicates significantly decreased chance of lymph node metastases among cases with fully encapsulated tumor; [d] indicates significantly increased chance of lymph node metastases among cases with distant metastases; [e] indicates significantly decreased chance of lymph node metastases among cases without vascular invasion

In *adolescents*, only one pathological parameter was significantly different between radiation-induced and sporadic PTCs: extrathyroidal extension (yes vs no) (Table 5.20).

Table 5.20
Univariate and multivariate statistical analyses of association of extrathyroidal extension in exposed adolescents

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.1938	1.00	referent	-
0. 1938 - < 0.341	0.70	0.17-2.77	> 0.5
0.341 - < 0.802	1.43	0.36-5.81	> 0.5
0.802 – 24.11	0.45	0.10-1.88	0.28
p-trend linear regression			0.19 [a]
	multivariate, stratified		
pN	7.18	1.76-39.45	0.005 [b]
Vascular invasion	0.11	0.02-0.47	0.002 [c]
Thyroid dose (Gy)			
< 0.095	1.00	referent	-
0.095 - < 0.194	0.61	0.05-6.20	> 0.5
0.194 - < 0.264	1.54	0.13-20.72	> 0.5
0.264 - < 0.341	0.74	0.05-8.96	0.49
0.341 - < 0.425	2.19	0.17-32.21	> 0.5
0.425 - < 0.802	3.42	0.28-49.84	> 0.5
0.802 - < 2.449	0.47	0.04-5.06	0.42
2.449 –	0.67	0.04-10.43	0.37
linear dose model *p*-trend			> 0.5 [a]
	multivariate, dose threshold		
pN	7.18 [b]	1.76-39.45	0.005 [b]
Vascular invasion	0.11 [c]	0.02-0.47	0.002 [c]
Thyroid dose (Gy)			
< 0.194	1.00	referent	-
≥ 0.194	1.88	0.08-23.17	0.52 [a]

[a] indicates non-significant association of extrathyroidal extension with thyroid dose; [b] indicates significantly increased chance of extrathyroidal extension among cases with lymph node metastases; [c] indicates significantly decreased chance of extrathyroidal extension among cases without vascular invasion

In *adults*, the following pathological parameters were significantly different between radiation-induced and sporadic PTCs: extrathyroidal extension (yes vs no), lymph node metastases (yes vs no), and multifocality (yes vs no, marginally) (Table 5.21).

Table 5.21
Univariate and multivariate statistical analyses of association of different pathological parameters in exposed adults

Lymph node metastases, adults

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.160	1.00	referent	-
0. 160 - < 0.261	0.55	0.09-2.82	0.47
0.261 - < 0.560	0.73	0.14-3.51	> 0.5
0.560 - 12.28	0.74	0.15-3.52	> 0.5
p-trend linear regression			> 0.5 [a]
	multivariate, stratified		
Sex	0.05	0.02-0.53	0.044 [b]
Tumor capsule	0.01	0.00-0.22	0.034 [c]
Vascular invasion	0.02	0.00-0.17	< 0.001 [d]
Thyroid dose (Gy)			
< 0.102	1.00	referent	-
0.102 - < 0.155	0.03	0.00-1.79	0.13
0.155 - < 0.202	0.20	0.00-5.35	0.35
0.202 - < 0.261	0.01	0.00-0.20	0.012
0.261 - < 0.396	0.13	0.00-2.44	0.19
0.396 - < 0.562	0.04	0.00-1.54	0.13
0.562 - < 1.260	0.01	0.00-0.21	0.013
1.260 –	0.12	0.00-3.04	0.23
linear dose model *p*-trend			> 0.5 [a]
	multivariate, dose threshold		
Sex	0.06	0.03-0.51	0.042 [b]
Tumor capsule	0.01	0.00-0.21	0.036 [c]
Vascular invasion	0.02	0.00-0.18	< 0.001 [d]
Thyroid dose (Gy)			
< 0.102	1.00	referent	-
≥ 0.102	0.08	0.00-1.88	0.14 [a]

[a] indicates non-significant association of lymph node metastases with thyroid dose; [b] indicates significantly decreased chance of lymph node metastasis in males; [c] indicates significantly decreased chance of lymph node metastases in cases of fully encapsulated tumors; [d] indicates significantly decreased chance of lymph node metastases among cases without vascular invasion

Continuation of Table 5.21

Multifocality, adults

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.160	1.00	referent	-
0. 160 - < 0.261	NA [a]	NA	NA
0.261 - < 0.560	3.50	0.34-75.98	0.27
0.560 – 12.28	1.00	0.04-26.97	> 0.5
p-trend linear regression			0.12 [b]
	multivariate, stratified		
Tumor size	0.10	0.01-0.69	0.021 [c]
Thyroid dose (Gy)			
< 0.110	1.00	referent	-
0.110 - < 0.185	NA	NA	> 0.5
0.185 - < 0.274	NA	NA	> 0.5
0.274 - < 0.406	NA	NA	> 0.5
0.406 - < 0.547	NA	NA	> 0.5
0.547 - < 0.851	NA	NA	> 0.5
0.851 - < 1.907	NA	NA	> 0.5
1.907 –	NA	NA	> 0.5
Linear/quadratic dose model *p*-trend			0.11 [b]
	multivariate, dose threshold		
Tumor size	0.10	0.01-0.69	0.026 [c]
Thyroid dose (Gy)			
< 0.406	1.00	referent	-
≥ 0.406	4.05	0.49-87.00	0.20 [b]

[a] there were no or too few cases in the given dose range to fit the model; [b] indicates non-significant association of multifocality with thyroid dose; [c] indicates significantly decreased chance of multifocality among small tumors

Continuation of Table 5.21

Extrathyroidal extension, adults

Parameters	OR	95% CI	*p*-value
	univariate		
Thyroid dose (Gy)			
< 0.160	1.00	referent	-
0. 160 - < 0.261	0.80	0.16-3.91	> 0.5
0.261 - < 0.560	1.00	0.21-4.68	> 0.5
0.560 – 12.28	1.00	0.20-4.66	> 0.5
p-trend linear regression			> 0.5 [a]
	multivariate, stratified		
Tumor capsule	0.05	0.00-0.37	0.002 [b]
Vascular invasion	0.08	0.01-0.36	< 0.001 [c]
Thyroid dose (Gy)			
< 0.102	1.00	referent	-
0.102 - < 0.155	0.78	0.02-24.50	> 0.5
0.155 - < 0.202	0.57	0.03-11.74	> 0.5
0.202 - < 0.261	0.23	0.01-4.56	0.32
0.261 - < 0.396	0.51	0.02-9.09	> 0.5
0.396 - < 0.562	0.56	0.03-10.18	> 0.5
0.562 - < 1.260	0.15	0.00-3.24	0.23
1.260 –	0.32	0.02-6.00	0.44
linear dose model *p*-trend			> 0.5 [a]
	multivariate, dose threshold		
Tumor capsule	0.03 [b]	0.00-0.36	0.002 [b]
Vascular invasion	0.07	0.00-0.32	< 0.001 [c]
Thyroid dose (Gy)			
< 0.102	1.00	referent	-
≥ 0.102	0.42	0.04-4.45	0.45 [a]

[a] indicates non-significant association of extrathyroid extension with thyroid dose; [b] indicates significantly decreased chance of extrathyroid extension in encapsulated tumors; [c] indicates significantly decreased chance of extrathyroid extension among cases without vascular invasion.

Thus, as shown by the results of either univariate or any type of multivariate analysis (Tables 5.19-5.21), no evidence of significant association with thyroid dose was found for any pathological parameter tested in all age groups.

The only exception was a marginally significant association of the combined solid + solid-follicular subtype of PTC in children with the dose range from 0.851 to 1.907 Gy (Table 5.19), whose lower limit almost coincides with mean thyroid exposure dose (0.752 Gy) in children with these growth patterns (Table 5.14). In view of recently published results of molecular genetic study of PTCs identified in the Ukrainian-American cohort, which has established a positive association between *RET/PTC* rearrangements and ^{131}I thyroid dose with an inflection point at 1.6 Gy [20], this fact draws attention. Notably, namely *RET/PTC* rearrangements, *RET/PTC3* in particular, are most common among children and are associated with the solid and solid-follicular tumor structure [21, 22].

As a whole, radiogenic papillary carcinomas in children exposed after the Chernobyl accident at the age under 4 years (mean ^{131}I thyroid dose 1.016 Gy) and subdivided by their age at surgery into three groups (children, adolescents and adults) significantly differed from sporadic carcinomas in age-matched groups for a number of morphological parameters. Univariate and multivariate statistical analyses revealed the most substantial differences in both histoarchitectonics and invasive features of radiogenic PTCs, demonstrating their more aggressive behaviour especially well seen in age-matched groups of children. In adolescents and adults, morphological differences between radiogenic and sporadic tumors were found only for isolated parameters and those were revealed only by multivariate analysis.

Such a "convergence" of morphological differences between radiogenic and sporadic PTCs with increasing patients' age (hence the latency of radiogenic tumors), was not associated with the lower thyroid exposure dose or a certain dose range for most morphological manifestations of tumor agressiveness. A significant association was noted only between solid + solid-follicular subtype and a dose range from 0.851 to 1.907 Gy in children, for which an association with *RET/PTC* rearrangements was recently reported [20].

It is quite possible that future molecular genetic investigations employing advanced technologies, e.g next generation sequencing, will discover new genetic/epigenetic alterations unknown at present that are associated with radiation thyroid carcinogenesis, which, in turn, will allow better understanding of the mechanisms underlying more pronounced morphological signs of aggressiveness of radiogenic PTCs with short latency.

Continuous ongoing verifications of thyroid doses in children and adolescents of Ukraine after Chernobyl aimed at the reduction of uncertainties in dose estimates [23, 24] are highly important for the subsequent analyses of dose-response relationship. These would possibly allow establishing more confident associations between morphological parameters and exposure doses.

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