Chapter 4

T Bogdanova, L Zurnadzhy, VA LiVolsi, ED Williams, M Ito, M Nakashima, GA Thomas

Thyroid cancer pathology in Ukraine after Chernobyl

Two main types of thyroid carcinomas may arise from the cells of follicular epithelium: papillary and follicular. These two types differ by their structure (though follicles are often present in papillary carcinomas), molecular-biological characteristics, and clinical behaviour. Besides, medullary thyroid carcinomas (derived from parafollicular neuroendocrine C-cells), as well as poorly differentiated and anaplastic carcinomas may occur in the gland. The two latter types of tumors may develop from preexisting well-differentiated tumors. Nonepithelial tumors developing from lymphoid cells (thyroid lymphoma) or from mesenchymal tissue components (thyroid sarcomas) are also known [1-4].

The following are definitions of the main types of thyroid carcinomas based on the WHO Histological classification [5]:

- papillary thyroid carcinoma (PTC) is a malignant epithelial tumor derived from follicular cells, with characteristic changes in the nuclei (increased size, "ground glass" clearing, pseudo-intranuclear inclusions and grooves);
- follicular thyroid carcinoma (FTC) is an encapsulated or partly encapsulated malignant epithelial tumor, derived from follicular cells, with signs of marked invasion into tumor capsule and/or tumor capsule vessels, without changes in tumor cell nuclei characteristic for PTC;
- medullary thyroid carcinoma (MTC) is a malignant tumor derived from C-cells;
- poorly differentiated thyroid carcinoma (PDTC) is a malignant tumor derived from follicular cells, with signs of decreased differentiation and being an intermediary between well-differentiated (PTC and FTC) and undifferentiated (anaplastic) thyroid carcinoma, both by histological structure, aggressiveness and clinical behaviour;
- anaplastic (undifferentiated) thyroid carcinoma (ATC) is the most malignant epithelial thyroid tumor derived from follicular cells, partly or completely consisting of undifferentiated cells.

According to the above-mentioned classification, the present chapter describes and analyses the main types of thyroid carcinomas which were detected in the group

at increased risk for development of radiation-induced thyroid cancer in the period of a significant rise in its incidence after Chernobyl: 1990-2010 (see Chapter 3). A total of 2,960 cases diagnosed in children and adolescents of Ukraine (aged 0 to 18 years at the time of the Chernobyl accident) as well as in those who were born after the accident are reviewed (Table 4.1).

Morphological characteristics of 2,658 thyroid carcinomas in individuals born before Chernobyl are considered for three age groups: children operated on at the age from 4 to 14 years old, adolescents operated on at the age from 15 to 18 years old, and adults operated on at the age from 19 to 42 years old. Also, a comparative analysis of morphological changes is carried out for four time periods: 1990-1994, 1995-1999, 2000-2004, and 2005-2010 (Table 4.2). Overall, 287 thyroid cancers in children (out of 453 detected in Ukraine, 63.4%), 244 carcinomas in adolescents (out of 527 detected in Ukraine, 46.3%), and 2,127 carcinomas in adults (out of 5,706 detected in Ukraine, 37.3%) were studied for the period 1990-2010. Practically all cancers in children and adolescents included in the analysis have been additionally verified by the international experts, Professors VA LiVolsi and ED Williams, in the framework of joint international projects. Furthermore, 1,512 thyroid carcinomas in children, adolescents and adults operated in 1998-2010 included in the international Chernobyl Tissue Bank have been additionally verified by a Panel of experts-pathologists of the Project (see Chapter 6). It should be noted that since 2001, children born before Chernobyl were no longer registered because they naturally moved over to the age group of "adolescents" who, in turn, moved to the group of "adults" beginning from 2005.

Table 4.1
Total number of thyroid cancer cases under study

	Born before Chernobyl		**Born after Chernobyl**	
Type	number	%	number	%
PTC	2478	93.2	264	87.4
FTC	137	5.1	32	10.6
MTC	39	1.5	6	2.0
PDTC	4	0.2	-	-
Total	**2658**	100	**302**	100
		2960		

PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; MTC – medullary thyroid carcinoma; PDTC – poorly differentiated thyroid carcinoma

As shown in Table 4.2, among all cancers, ***papillary thyroid carcinoma*** was most prevalent, and accounted for more than 90% of cases in all age groups and for all time periods. This fully corresponds to the previously obtained numerous data published by scientists from Ukraine, Belarus, and Russian Federation [6-15], and to the findings of joint scientific projects carried out in cooperation between the affected countries and leading research centres of the world [16-25].

It has been established that PTC was the most common malignant thyroid tumor not only after internal radiation exposure, but also after external exposure of head and neck

area, especially in childhood [1-4,26-30]. Thyroid cancers that had been detected after Hiroshima and Nagasaki A-bombings [31-35] or the hydrogen bomb test in the Marshall Islands were also mainly PTCs [36].

Table 4.2
Number of thyroid cancer cases in patients born before Chernobyl

	Children aged up to 14 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Type	number	%	number	%	number	%	number	%	number	%
PTC	127	97.0	135	93.1	10	90.1	-	-	272	94.8
FTC	2	1.5	6	4.1	-	-	-	-	8	2.8
MTC	2	1.5	4	2.8	1	0.9	-	-	7	2.4
PDTC	-	-	-	-	-		-	-	-	-
Total	**131**	100	**145**	100	**11**	100	-	-	**287**	100
	Adolescents aged from 15 to 18 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	27	96.4	81	92.0	117	91.4	-	-	225	92.2
FTC	1	3.6	7	8.0	10	7.8	-	-	18	7.4
MTC	-	-	-	-	1	0.8	-	-	1	0.4
PDTC	-	-	-	-	-	-	-	-	-	-
Total	**28**	100	**88**	100	**128**	100	-	-	**244**	100
	Adults aged from 19 to 42 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	13	92.9	149	96.8	605	91.5	1214	93.5	1981	93.1
FTC	1	7.1	4	2.6	45	6.8	61	4.7	111	5.2
MTC	-	-	1	0.6	10	1.5	20	1.6	31	1.5
PDTC	-	-	-	-	1	0.2	3	0.2	4	0.2
Total	**14**	100	**154**	100	**661**	100	**1298**	100	**2127**	100
	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	167	96.5	365	94.3	732	91.5	1214	93.5	2478	93.2
FTC	4	2.3	17	4.4	55	6.9	61	4.7	137	5.1
MTC	2	1.2	5	1.3	12	1.5	20	1.6	39	1.5
PDTC	-	-	-	-	1	0.1	3	0.2	4	0.2
Total	**173**	100	**387**	100	**800**	100	**1298**	100	**2658**	100

PTCs in Ukrainian patients varied in size from 0.3 to 75 mm. The analysis shows that the prevalence of tumors sized up to 10 mm (Table 4.3) - when combining all time periods - was increasing significantly and succesively in the age series: children (10/272, 3.7%) – adolescents (27/225, 12.0%) – adults (458/1981, 24.2%), p=0.0001 (here and hereafter, the Chi-square test for trend or Fisher's Exact text are used for comparison of subgroups).

A significant ascending linear trend (p=0.0001) in the frequency of "small" PTCs was also noted for the combined age groups in time elapsed after Chernobyl, i.e. by time periods: 1990-1994 (5/167, 3.0%) – 1995-1999 – (21/365, 5.7%) – 2000-2004 (95/732, 13.0%) – 2005 -2010 (374/1214, 30.8%). An inverse linear relationship was observed in the analysis of the frequency of carcinomas sized more than 40 mm (Table 4.3). The frequency was decreasing gradually and significantly (p=0.0001) both in age series: children (57 out of 272 cases, 20.9%) – adolescents (23 out of 225 cases, 10.2%) – adults (181 out of 1981 cases, 9.1%), and by time periods: 1990-1994 (33/167, 19.8%) – 1995-1999 (60/365, 16.5%) – 2000-2004 (70/732, 9.5%) – 2005-2010 (98/1214, 8.1%).

Analysis of small encapsulated tumors versus non-encapsulated or partly encapsulated did not reveal significant differences in age or time series. By contrast, significant ascending linear age and time trends (p=0.0001) were found for fully encapsulated large tumors (sized more than 40 mm): children (3 out of 57 cases, 5.3%) – adolescents (5 out of 23 cases, 21.7%) – adults (84 out of 181 cases, 46.4%); 1990-1994 (1/33, 3.0%) – 1995-1999 (8/60, 13.3%) – 2000-2004 (26/70, 37.1%) – 2005-2010 (56/98, 57.1%).

For the combined encapsulated tumors of any size, significant ascending linear trends were also noted (p=0.0001): children (21 out of 272 cases, 7.7%) – adolescents (35 out of 225 cases, 15.6%) – adults (582 out of 1981 cases, 29.4%); 1990-1994 (9/149, 6.0%) – 1995-1999 (91/365, 24.9%) – 2000-2004 (172/732, 23.5%) – 2005-2010 (363/1214, 29.9%).

PTC is generally known to display varying histological structures and therefore it is further subdivided into subtypes or variants. According to the WHO Histological classification, these variants include classic papillary, follicular, macrofollicular, solid, oxyphilic-cell, clear-cell, diffuse-sclerosing, tall-cell, columnar-cell, cribriform-morular, and Warthin-like variants. Papillary microcarcinoma is also considered to be a separate variant [5].

With regard to the classic papillary variant, at least 80% of tumors featured typical papillary formations with characteristic fibrovascular core and optically clear ("ground-glass") nuclei (Fig. 4.1 A) containing intranuclear grooves and pseudo-cytoplasmic inclusions. Most of the tumor cells showed positive immunohistochemical staining with antithyroglobulin antibodies (Fig. 4.1 B).

In the *follicular variant of PTC,* typical papillary structures are scarce or absent (Fig. 4.2 A). Cleared nuclei with chromatin localized at the periphery is the main distinctive feature of this subtype. Positive immunohistochemical reaction with antithyroglobulin antibodies, similarly to the classic papillary variant, was observed in most tumor cells (Fig. 4.2 B).

In the *solid variant of papillary thyroid carcinoma*, tumors with alveolar-solid growth pattern were most prevalent (Fig. 4.3 A). Areas with solid-trabecular structures were occasionally observed (Fig. 4.3 B). Papillary structures were generally absent, but small follicular areas could occur. The fact that tumors of this subtype are PTCs is substantiated by the structure of tumor cell nuclei. Intranuclear grooves and nuclear pseudoinclusions were best seen on electron microscopy (Fig. 4.3 D, E). Thyroglobulin in tumor cells, unlike in the classic papillary and follicular variants, was detected only focally (Fig. 4.3 C).

Table 4.3
Size of papillary thyroid carcinomas in patients born before Chernobyl

Size, mm	Children aged up to 14 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	1	0.8	-	-	-	-	-	-	1	0.4
6-10	2	1.6	7	5.2	-	-	-	-	9	3.3
11-20	41	32.3	71	52.6	3	30.0	-	-	115	42.3
21-30	41	32.3	17	12.6	5	50.0	-	-	63	23.2
31-40	15	11.8	10	7.4	2	20.0	-	-	27	9.9
41-50	15	11.8	18	13.4	-	-	-	-	33	12.1
51-60	9	7.0	6	4.4	-	-	-	-	15	5.5
> 60	3	2.4	6	4.4	-	-	-	-	9	3.3
Total	**127**	100	**135**	100	**10**	100	-	-	**272**	100
	Adolescents aged from 15 to 18 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	6	5.1	-	-	6	2.7
6-10	1	3.7	7	8.6	13	11.1	-	-	21	9.3
11-20	10	37.0	38	46.9	51	43.6	-	-	99	44.0
21-30	7	25.9	19	23.5	28	23.9	-	-	54	24.0
31-40	5	18.6	7	8.7	10	8.6	-	-	22	9.8
41-50	1	3.7	6	7.4	8	6.8	-	-	15	6.7
51-60	-	-	3	3.7	-	-	-	-	3	1.3
>60	3	11.1	1	1.2	1	0.9	-	-	5	2.2
Total	**27**	100	**81**	100	**117**	100	-	-	**225**	100
	Adults aged from 19 to 42 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	20	3.3	98	8.1	118	6.0
6-10	1	7.7	7	4.7	56	9.3	276	22.7	340	17.2
11-20	3	23.0	67	43.0	289	47.8	439	36.2	798	40.3
21-30	5	38.5	45	30.2	130	21.5	215	17.7	395	19.9
31-40	2	15.4	10	6.7	49	8.1	88	7.2	149	7.5
41-50	1	7.7	12	8.0	33	5.4	53	4.4	99	5.0
51-60	1	7.7	3	2.0	20	3.3	28	2.3	52	2.6
>60	-	-	5	3.4	8	1.3	17	1.4	30	1.5
Total	**13**	100	**149**	100	**605**	100	**1214**	100	**1981**	100

Continuation of Table 4.3

	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	1	0.6	-	-	26	3.6	98	8.1	125	5.0
6-10	4	2.4	21	5.7	69	9.4	276	22.7	370	14.9
11-20	54	32.3	176	48.2	343	46.9	439	36.2	1012	40.8
21-30	53	31.7	81	22.2	163	22.3	215	17.7	512	20.6
31-40	22	13.2	27	7.4	61	8.3	88	7.2	198	8.0
41-50	17	10.2	36	9.9	41	5.6	53	4.4	147	5.9
51-60	10	6.0	12	3.3	20	2.7	28	2.3	70	2.8
>60	6	3.6	12	3.3	9	1.2	17	1.4	44	1.8
Total	**167**	100	**365**	100	**732**	100	**1214**	100	**2478**	100

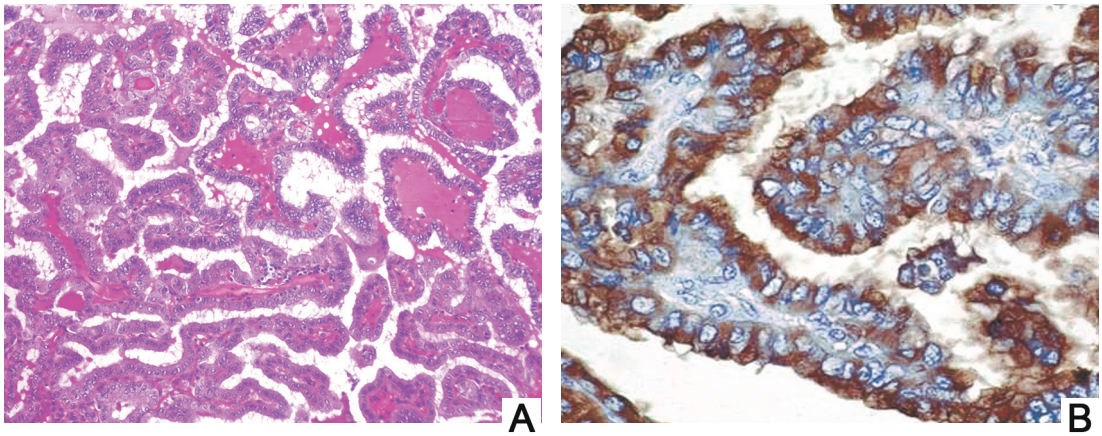

Figure 4.1. Classic papillary carcinoma. (A) Typical papillary structures with well-developed fibrovascular core and cleared tumor cell nuclei. Haematoxylin and eosin, original magnification x100. (B) Strong diffuse cytoplasmic immunostaining for thyroglobulin, original magnification x200.

These three subtypes accounted for more than 50% of all PTCs under study for all age groups and all periods of time (Table 4.4).

Of note, PTCs were not always monomorphic histologically which is a difficulty when ascribing tumors to one of the three main variants. In many cases tumors had a mixed growth pattern (herein referred to as "mixed variant") (Fig. 4.4), comprising a combination of papillary, follicular or solid components (Table 4.5).

Diffuse sclerosing variant was rather rare, 8.7% cases in children in the first period of time (Table 4.4). The frequency of this variant was significantly decreasing (p=0.0001) both in age and time series (Table. 4.4). Tumors with this structure were characterized by:

- diffuse extension of tumoral foci throughout the thyroid
- fibrous-sclerotic changes
- marked thyroiditis
- abundance of psammoma bodies
- foci of squamous-cell metaplasia.

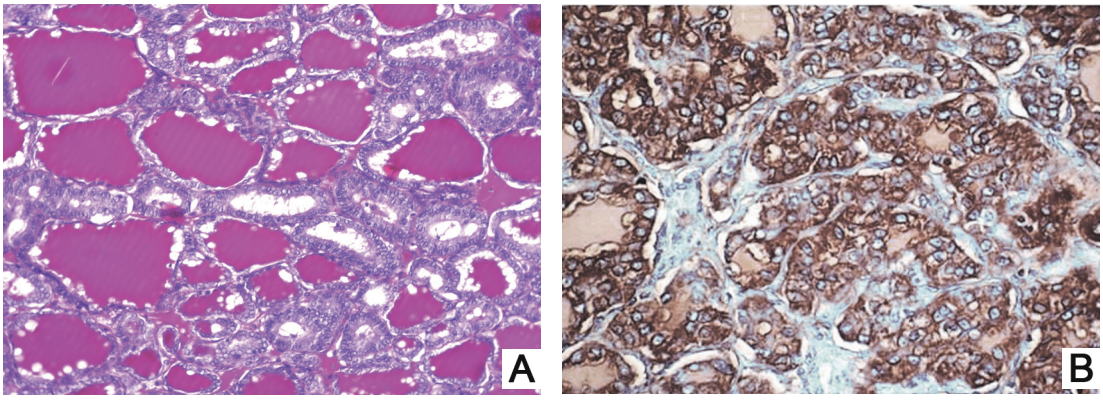

Figure 4.2. Follicular variant of papillary thyroid carcinoma. (A) Diffuse nuclear features of papillary carcinoma. Haematoxylin and eosin, original magnification x100. (B) Strong diffuse cytoplasmic immunostaining for thyroglobulin, original magnification x100.

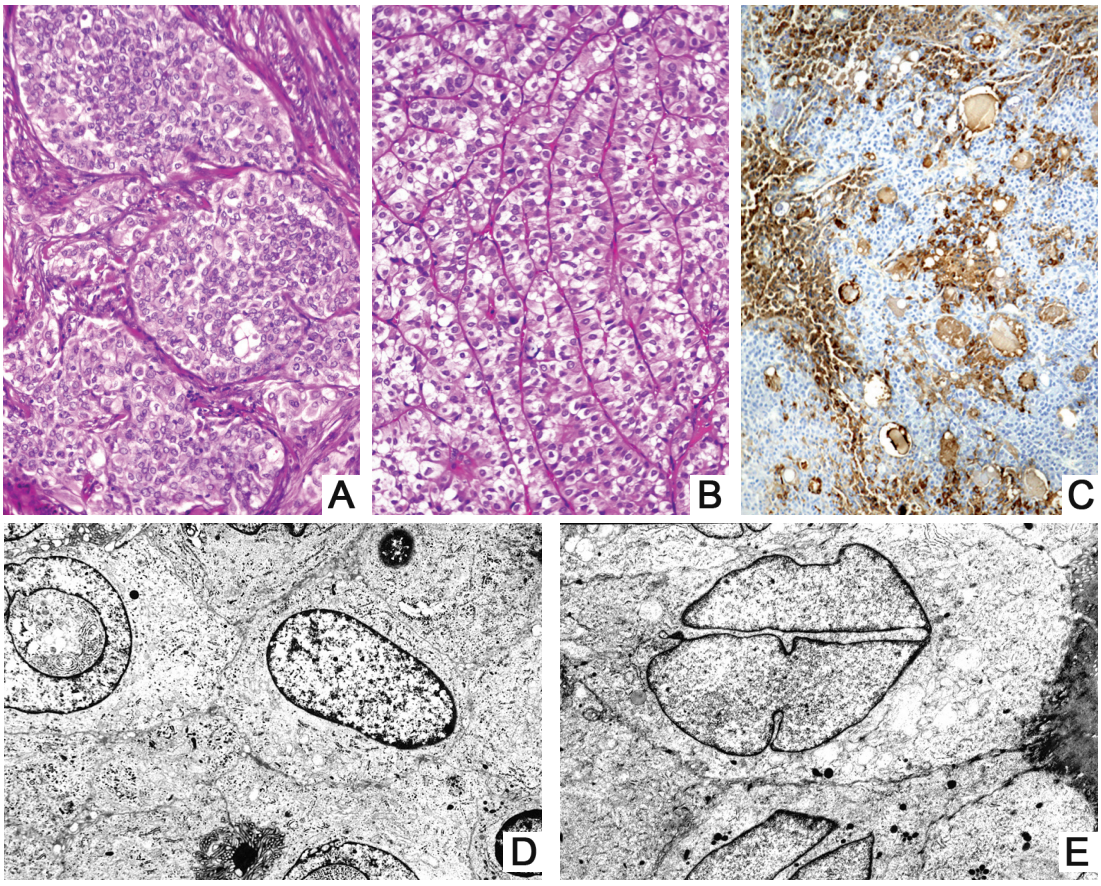

Figure 4.3. Solid variant of papillary thyroid carcinoma. (A) Alveolar-solid growth pattern. Haematoxylin and eosin, original magnification x100. (B) Trabecular growth pattern. Haematoxylin and eosin, original magnification x100. (C) Focal immunostaining for thyroglobulin, original magnification x50. (D) Intranuclear inclusions on electron microscopy, original magnification x5,000. (E) Nuclear grooves on electron microscopy, original magnification x7,000.

Tumoral foci had generally solid or papillary-solid structure. A marked invasion of tumor tissue and psammoma bodies to lymphatic vessels was characteristic (Fig. 4.5).

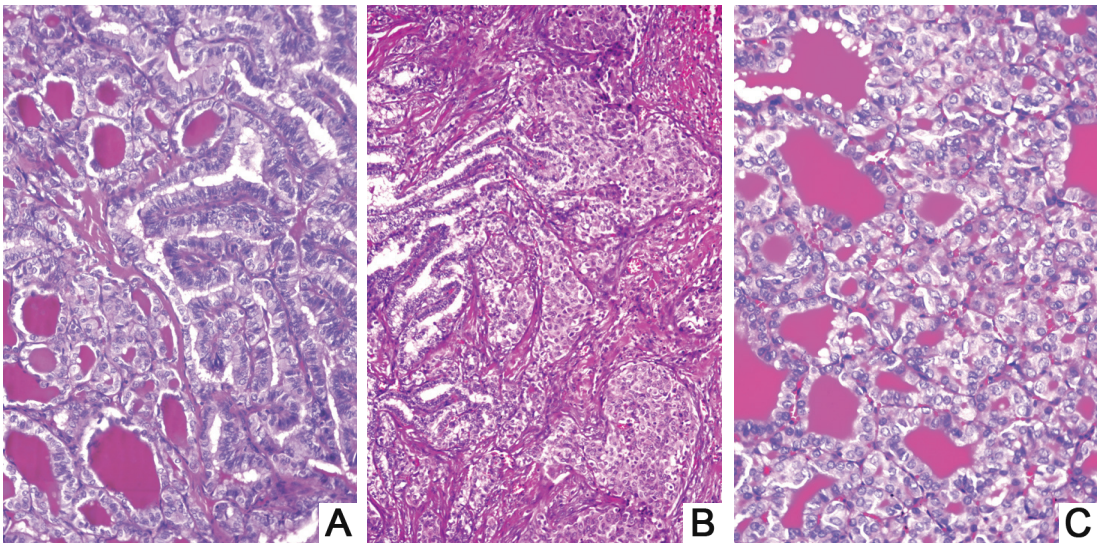

Figure 4.4. Mixed variant of papillary thyroid carcinoma. (A) Papillary-follicular growth pattern. Haematoxylin and eosin, original magnification x100. (B) Papillary-solid growth pattern. Haematoxylin and eosin, original magnification x50. (C) Solid-follicular growth pattern. Haematoxylin and eosin, original magnification x100.

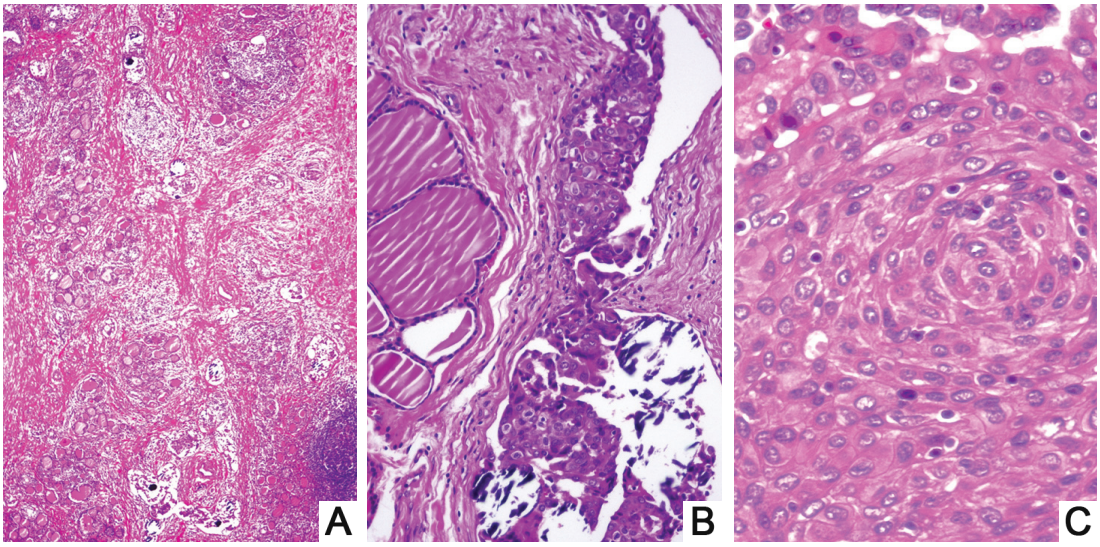

Figure 4.5. Diffuse sclerosing variant of papillary thyroid carcinoma. (A) Diffuse tumor growth, numerous psammoma bodies, marked fibrosis, lymphocytic infiltration. Haematoxylin and eosin, original magnification x20. (B) Tumor aggregates inside lymphatic vessels. Haematoxylin and eosin, original magnification x100. (C) Squamous-cell metaplasia. Haematoxylin and eosin, original magnification x200.

Table 4.4
Subtypes of papillary thyroid carcinomas in patients born before Chernobyl

	Children aged up to 14 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Subtype	Number	%	number	%	number	%	number	%	number	%
PV	9	7.1	19	14.1	2	20.0	-	-	30	11.0
FV	46	36.2	17	12.6	2	20.0	-	-	65	23.9
SV	38	29.9	17	12.6	2	20.0	-	-	57	21.0
Mixed V	23	18.1	76	56.3	4	40.0	-	-	103	37.9
DSV	11	8.7	6	4.4	-	-	-	-	17	6.2
Warthin	-	-	-	-	-	-	-	-	-	-
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	**127**	100	**135**	100	**10**	100	**-**	-	**272**	
	Adolescents aged from 15 to 18 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	4	14.8	21	25.9	23	19.6	-	-	48	21.3
FV	10	37.0	13	16.0	24	20.5	-	-	47	20.9
SV	5	18.5	8	10.0	11	9.4	-	-	24	10.7
Mixed V	8	29.7	35	43.2	58	49.6	-	-	101	44.9
DSV	-	-	4	4.9	-	-	-	-	4	1.8
Warthin	-	-	-	-	1	0.9	-	-	1	0.4
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	**27**	100	**81**	100	**117**	100	**-**	-	**225**	
	Adults aged from 19 to 42 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	2	15.4	54	36.2	223	36.9	388	32.0	667	33.7
FV	6	46.1	30	20.1	102	16.9	194	16.0	332	16.8
SV	2	15.4	12	8.1	25	4.1	79	6.5	118	5.9
Mixed V	3	23.1	51	34.3	242	40.0	541	44.6	837	42.3
DSV	-	-	2	1.3	2	0.3	2	0.1	6	0.3
Warthin	-	-	-	-	11	1.8	8	0.7	19	0.9
Cribriform	-	-	-	-	-	-	2	0.1	2	0.1
Total	**13**	100	**149**	100	**605**	100	**1214**	100	**1981**	100
	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	15	9.0	94	25.8	248	33.9	388	32.0	745	30.0
FV	62	37.1	60	16.4	128	17.5	194	16.0	444	17.9
SV	45	26.9	37	10.1	38	5.2	79	6.5	199	8.1
Mixed V	34	20.4	162	44.4	304	41.5	541	44.6	1041	42.0
DSV	11	6.6	12	3.3	2	0.3	2	0.1	27	1.1
Warthin	-	-	-	-	12	1.6	8	0.7	20	0.8
Cribriform	-	-	-	-	-	-	2	0.1	2	0.1
Total	**167**	100	**365**	100	**732**	100	**1214**	100	**2478**	100

PV – classic papillary variant; FV – follicular variant; SV – solid variant; Mixed V – mixed variant; DSV – diffuse sclerosing variant; Warthin – Warthin-like variant; Cribriform – cribriform-morular variant

Table 4.5
Structural components of mixed variant of papillary thyroid carcinoma in patients born before Chernobyl

	Children aged up to 14 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Structure	Number	%	number	%	number	%	number	%	number	%
PF	3	13.0	12	15.8	1	25.0	-	-	16	15.5
PS	4	17.4	7	9.2	-	-	-	-	11	10.7
PFS	2	8.7	1	1.3	-	-	-	-	3	2.9
SF	14	60.9	56	73.7	3	75.0	-	-	73	70.9
Total	**23**		**76**		**4**	100	**-**	**-**	**103**	100
	Adolescents aged from 15 to 18 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	Number	%	number	%	number	%	number	%	number	%
PF	1	12.5	12	34.9	25	43.1	-	-	38	37.6
PS	-	-	7	20.0	11	19.0	-	-	18	17.8
PFS	-	-	-	-	5	8.6	-	-	5	5.0
SF	7	87.5	16	45.7	17	29.3	-	-	40	39.6
Total	**8**		**35**	100	**58**	100	**-**	**-**	**101**	100
	Adults aged from 19 to 42 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	Number	%	number	%	number	%	number	%	number	%
PF	2	75.0	20	39.2	148	61.2	252	46.6	422	50.4
PS	-	-	11	21.6	32	13.2	100	18.5	143	17.1
PFS	-	-	5	9.8	10	4.1	34	6.2	49	5.9
SF	1	25.0	15	24.4	52	21.5	155	28.7	223	26.6
Total	**3**	100	**51**	100	**242**	100	**541**	100	**837**	100
	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	Number	%	number	%	number	%	number	%	number	%
PF	6	17.6	44	27.2	174	57.2	252	46.6	476	45.7
PS	4	11.8	25	15.4	43	14.1	100	18.5	172	16.5
PFS	2	5.9	6	3.7	15	5.0	34	6.2	57	5.5
SF	22	64.7	87	53.7	72	23.7	155	28.7	336	32.3
Total	**34**	100	**162**	100	**304**	100	**541**	100	**1041**	

PF – papillary-follicular variant; PS – papillary-solid variant; PFS – papillary-follicular-solid variant; SF – solid-follicular variant

According to the literature, the development of PTC with diffuse-sclerosing structure has been associated with previous radiation exposure [1,2,37,38]. However, studies of «post-Chernobyl» carcinomas did not confirm this notion as such tumors were observed in not more than in 7.0-9.0% cases and mostly in children [10,11,16].

In less than 1% of cases, the *Warthin-like variant* (Table 4.4) was found in later periods (2000-2004 and 2005-2010, mostly in adults). Its distinctive feature is a profound intratumoral thyroiditis (Fig. 4.6). Tumors were represented by oxyphilic cells and generally had papillary or papillary-solid structure; they were also characterized by the very strong diffuse immunohistochemical reaction for thyroglobulin (Fig. 4.6 D) and TTF-1 (Fig. 4.6 E). Referring the Warthin-like variant to PTC is justified by enlarged and cleared nuclei (Fig. 4.6 C). The proliferative activity of tumor cells (immunohistochemical reaction with anti-Ki67 antibodies) was not high, less than 5% (Fig. 4.6 F), which is, again, characteristic of PTC in general [3,4]. The lesions ranged in size from 5 to 42 mm, all of them were non-encapsulated. Lymph node metastases were identified in 7 out of 19 cases (36.8%),

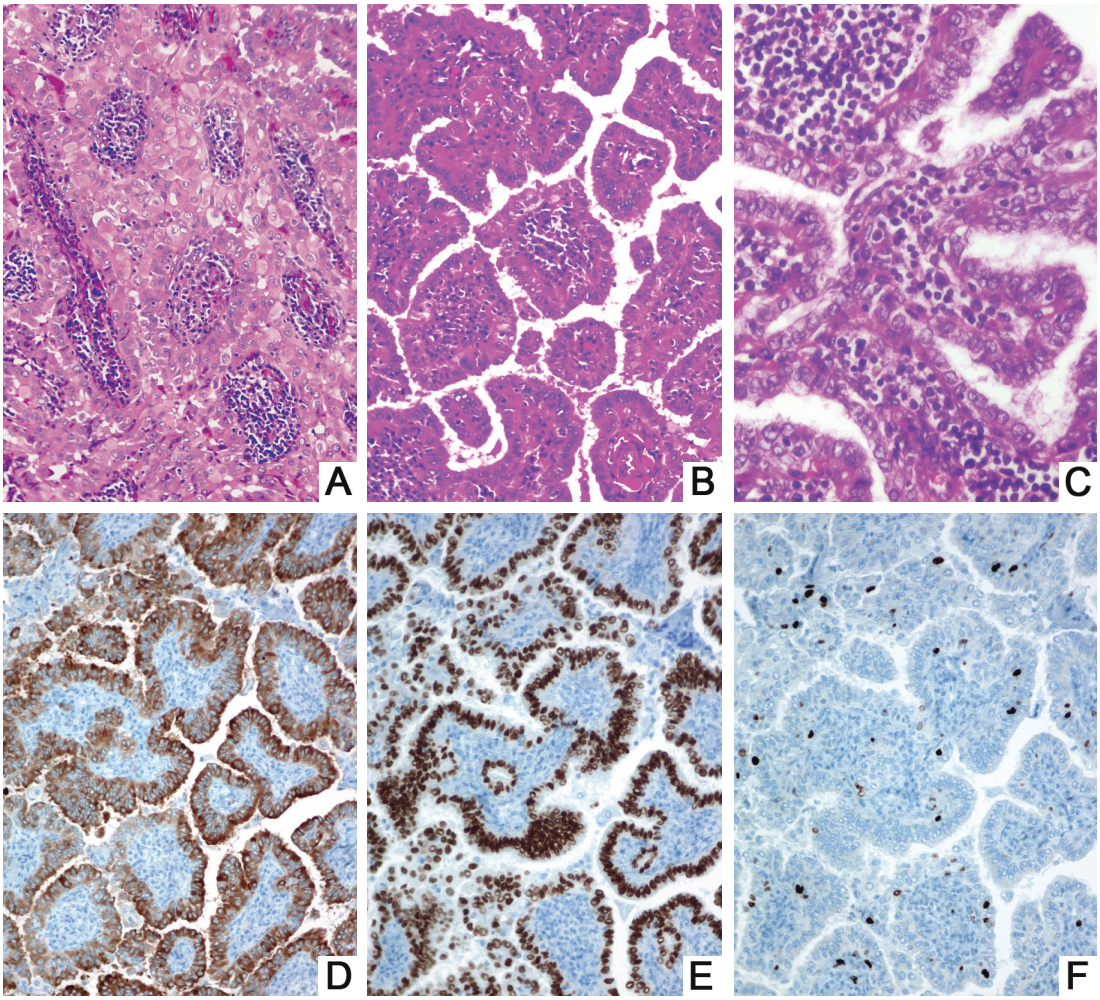

Figure 4.6. Warthin-like variant of papillary thyroid carcinoma. (A, B) Papillary-solid and papillary growth pattern, profound intratumoral thyroiditis. Tumors are represented by oxyphilic cells. Haematoxylin and eosin, original magnification x100. (C) Nuclear features of Warthin-like variant. Haematoxylin and eosin, original magnification x200. (D) Strong diffuse cytoplasmic staining for thyroglobulin, original magnification x100. (E) Strong nuclear reactivity for TTF-1, original magnification x100. (F) Focal nuclear reactivity for Ki67, original magnification x100.

but none showed distant metastases (Table 4.9). Our data are in agreement with the opinion of other authors [39] that these tumors behave similarly to conventional PTCs. The impact of radiation on the development of this subtype is not established yet.

In two cases (female patients aged 26 and 27 years), an even more rare variant of PTC, the *Cribriform-morular*, was identified (0.1%). Tumors were represented by the nodule-like lesions localized between markedly sclerosed stroma (Fig. 4.7 A, 4.7 B). An essential difference between this and other subtypes was the presence of numerous morulas (Fig. 4.7 C, 4.7 D). Tumor areas had solid or follicular structure with the colloid being practically absent in all follicles. In the solid areas, cells were of polygonal shape; nuclei were more dense than in other subtypes and contained a small number of intranuclear inclusions. Immunohistochemical reaction with antithyroglobulin antibodies was practically negative, while the reaction with anti-TTF-1 antibodies was highly intensive and diffuse in tumor cell nuclei but virtually absent in the nuclei of the cells within morulas (Fig. 4.7 E). A highly intensive reaction to ß-catenin was revealed in the nuclei and cytoplasm of tumor cells; staining in morulas was rather weak and had a diffuse pattern (Fig. 4.7 F). Nuclei positive for Ki67 were rare both in tumor and in morular cells (Fig. 4.7 G); weakly positive for TP53 (p53) nuclei were detected in 3-5% of tumor and morular cells (Fig. 4.7 H). The described tumors fully correspond to the data available in the literature [3,4] not only by morphological characteristics, age and gender of patients, but also by the diagnosis of familial adenomatous polyposis (FAP) in these individuals as stated in their medical records. No impact of radiation on the development of this subtype of PTC has been found.

The most aggressive variants according to the literature [1,3,4,37,40], the *Tall-cell* and *Columnar-cell variants*, were not observed among PTCs under study. In three cases in adults (0.3%), only isolated tall-cell areas were noted in the tumors with papillary-trabecular architecture. Columnar-cell areas were detected in an adult patient only in one tumor (0.1%) which was, again, of papillary-trabecular structure. Such areas demonstrated pseudostratified columnar cells with subnuclear and supranuclear cytoplasmic vacuoles (Fig. 4.8 A). Thyroglobulin in such areas was expressed at the apical part of cells and in the narrowed fine intrapapillary space (Fig. 4.8 B); practically all nuclei of tumor cells expressed TTF-1 (Fig. 4.8 C), and only few (2-3%) expressed Ki67 (Fig. 4.8 D). The reaction with anti-TP53 antibodies was negative.

Further, we analyse three main subtypes of PTC (classic papillary, follicular, and solid variants) and tumors with mixed growth pattern for age and time related changes.

In the first five years of a significant rise in thyroid cancer incidence (1990-1994), PTCs in children operated at under 15 years of age (127 out of 167 cases, 76.0%) were the most prevalent. 66.1% of these tumors had follicular and solid structure (Table 4.4). Of note, the follicular variant differed from that described in adults by more roundish nuclei and the presence of solid component (up to 20.0%) in all cases, commonly in the areas of intrathyroidal or extrathyroidal extension. Besides, in the tumors with mixed growth pattern ("mixed variant") in this age group (Table 4.5), the prevalence of the solid-follicular architecture was significantly higher than those of other structural combinations ($p<0.0018$ vs papillary-follicular; $p<0.0058$ vs papillary-solid, and $p<0.0001$ vs papillary-follicular-solid).

Such architectural particularities of tumors in children prompted the introduction of the special solid-follicular "childhood variant" of PTC [38], which combines tumors of solid, follicular, and solid-follicular variants.

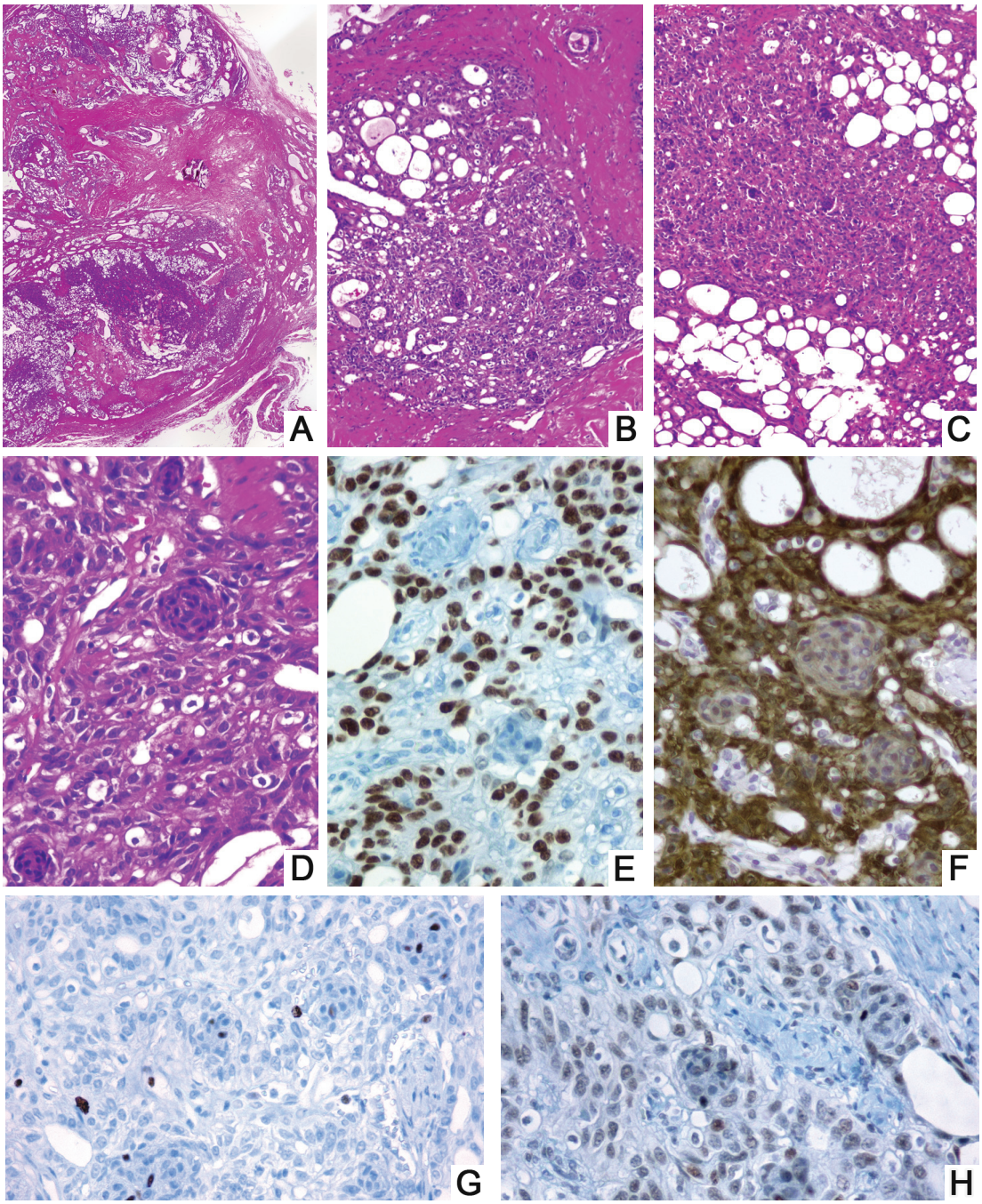

Figure 4.7. Cribriform-morular variant of papillary thyroid carcinoma. (A, B) Nodule-like lesions, marked stromal sclerosis. Haematoxylin and eosin, original magnification x10-panoramic; x50. (C, D) Numerous morulas and empty follicles. Haematoxylin and eosin, original magnification x50; x200. (E) Diffuse strong nuclear reactivity for TTF-1, original magnification x200. (F) Diffuse strong cytoplasmic and nuclear staining for ß-catenin in tumor cells; diffuse and weakly positive staining in morulas. Original magnification x200. (G) Focal nuclear reactivity for Ki67 in tumor and morular cells, original magnification x200. (H) Focal weak nuclear reactivity for TP53 in tumor and morular cells, original magnification x200.

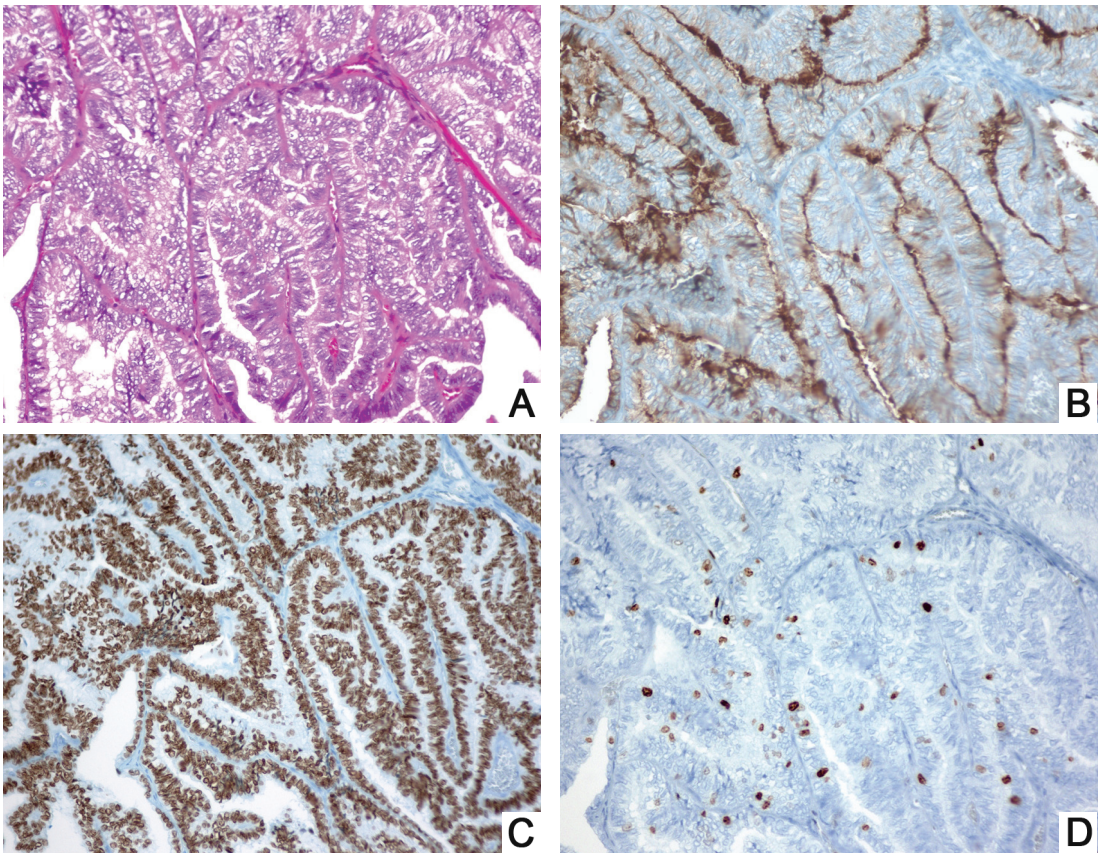

Figure 4.8. Columnar-cell areas of papillary thyroid carcinoma. (A) Papillary-trabecular growth pattern, prominent subnuclear vacuoles, and moderate pseudostratification. Haematoxylin and eosin, original magnification x100. (B) Strong apical cytoplasmic thyroglobulin staining, original magnification x100. (C) Diffuse strong nuclear reactivity for TTF-1, original magnification x100. (D) Focal nuclear reactivity for Ki67, original magnification x100.

During the first decade after Chernobyl, tumors of "childhood variant" accounted for up to 80% in patients operated at the age under 15 years in Ukraine and Belarus. These PTCs were characterized by marked intrathyroidal and extrathyroidal extension, invasion of lymphatic and blood vessels, and very frequent regional metastases [11,17,18,20,41,42]. It should be noted that such a "combined" solid-follicular variant of PTC was much more prevalent among children of Ukraine and Belarus affected by the Chernobyl accident compared to nonexposed children of England and Wales [11,17].

In addition, it has been established in Ukraine that the relative risk of development of "childhood variant" PTC was increasing with thyroid exposure dose: 2.2-fold at the dose 0.05 to 0.2 Gy, 5.2-fold at 0.2 to 1.0 Gy, and 6.7-fold at >1.0 Gy. Overall, the relative risk of development of such tumors at thyroid exposure dose exceeding 0.05 Gy was 3.7 [43].

In children of Russia, the follicular variant of PTC [44] was most common in post-Chernobyl years. No correlation between morphological structure and thyroid exposure dose was found [14].

It has been claimed that the presence of a marked solid component determined the aggressiveness of biological behaviour of PTC in children [16,17,18,20,38,45,46]. In this context, of interest are data obtained later by a group of experts-pathologists (which also included representatives of Ukraine, Belarus and Russia) in the framework of an international project for establishment of the Chernobyl Tissue Bank. The group performed an analysis of the histological structure of PTCs and their latency [47]. Three groups of children have been selected differing by age at exposure, age at surgery, and by the period of latency (defined as time interval between the Chernobyl accident and date of surgery). A significant difference was found in the prevalence of less differentiated (solid) and more differentiated (papillary and follicular) structural components depending on latency. PTCs developing after a short latency were characterized by the more prominent solid component and by more pronounced intrathyroidal and extrathyroidal extension as compared to those occurring after a longer latency. The latter tumors generally displayed papillary-follicular growth pattern and peritumoral fibrosis, which are usually considered to be less aggressive pathological features.

It needs to be emphasized that PTCs with architecturally less differentiated solid areas should not be erroneously assimilated into the poorly differentiated thyroid tumors group [1,3,4,25,30,37,48] as these are different in both histological structure and prognosis.

The same group of pathologists proposed later that the abundance of the solid component in "post-Chernobyl" childhood PTCcould also be influenced by a moderate iodine deficiency observed in the affected countries as compared to England and Wales, and especially to Japan [49].

Since 25 years have already passed after the Chernobyl accident, children who had experienced the strongest impact of radioactive iodine from fallout have already moved over to the age category of "adults" for a long time. Therefore, it appears inappropriate to continue using the term "childhood variant" today; for this reason, our analysis was based on generally accepted PTC subtypes. The highest percentage of tumors with a solid structure, which, as mentioned above, are architecturally less differentiated, was observed in children (21.0%). This is in line with the results of other studes of radiation-induced or sporadic PTC in children [3,4,25,29,46]. The frequency of tumors with classic papillary structure was, on the contrary, the highest in adults (33.7%), with a highly significant age trend (p=0.0001).

The ratio of PTC subtypes significantly changed with time after Chernobyl, i.e. with increasing period of latency. In all age groups the percentage of tumors with solid structure was gradually decreasing while that of classic papillary and, especially, mixed structure was increasing (Table 4.4). Similarly to the age-related changes, time-related linear trends were also highly significant (p=0.0001). Besides, in all age groups combined, the frequency of the solid variant decreased from 26.6% in the first period of observation (1990-1994) to 6.5% in the last period (2005-2010) while the frequency of the classic papillary variant increased from 9.0 to 32.0%. Structural combinations of the mixed variant also markedly changed with time (Table 4.5). The frequency of tumors with solid-follicular structures gradually decreased (from 64.7% in 1990-1994 to 28.7% in 2005-2010), and the percentage of tumors with papillary-follicular structure increased (from 17.6% в 1990-1994 to 46.6% in 2005-2010).

Invasive features of PTCs under study (extrathyroidal extension to soft tissues adjacent to the thyroid, regional and distant metastases), and their relationship to tumor size and multifocality as assessed according to the seventh edition of TNM Classification [50], also changed significantly with time after Chernobyl (Table 4.6).

Table 4.6
Size of papillary thyroid carcinomas and the prevalence of lymph node and distant metastases in patients born before Chernobyl

1st period: surgery in 1990-1994

	All age groups						
	N0	N1a	N1b	Total pT		M0	M1
pT/tumor size	number	number	number	number	%	number	number
pT1a (up to 5 mm)	1			1	0.5	1	
pT1a (6-10 mm)	3			3	1.8	3	
pT1am (1-5 mm)							
pT1am (6-10 mm)							
pT1b (11-20 mm)	17	6		23	13.8	23	
pT1bm (11-20 mm)							1
pT2 (21-40 mm)	23	4	2	29	17.4	28	1
pT2m (21-40 mm)							
pT3 (>40 mm)*	8	2	2	12	7.2	11	
pT3m (>40 mm)*							30
pT3 (any size)**	11	13	61	85	50.9	55	13
pT3m (any size)**			14	14	8.4	1	
Total	63 (37.7%)	25 (15.0%)	79 (47.3%)	**167**	**100**	122 (73.1%)	45 (26.9%)

2nd period: surgery in 1995-1999

	All age groups						
	N0	N1a	N1b	Total pT		M0	M1
pT/tumor size	number	number	number	number	%	number	number
pT1a (up to 5 mm)							
pT1a (6-10 mm)	16	1		17	4.7	17	
pT1am (1-5 mm)							
pT1am (6-10 mm)							
pT1b (11-20 mm)	70	22	4	96	26.3	95	1
pT1bm (11-20 mm)	3			3	0.8	3	
pT2 (21-40 mm)	28	14	3	45	12.3	45	
pT2m (21-40 mm)	2			2	0.5	2	
pT3 (>40 mm)*	10	2	1	13	3.6	13	
pT3m (>40 mm)*							
pT3 (any size)**	39	34	92	165	45.2	115	50
pT3m (any size)**			24	24	6.6	3	21
Total	168 (46.0%)	73 (20.0%)	124 (34.0%)	**365**	**100**	293 (80.3%)	72 (19.7%)

Continuation of Table 4.6

3rd period: surgery in 2000-2004

	All age groups						
	N0	N1a	N1b	Total pT		M0	M1
pT/tumor size	number	number	number	number	%	number	number
pT1a (up to 5 mm)	24			24	3.3	24	
pT1a (6-10 mm)	40	6	2	48	6.6	48	
pT1am (1-5 mm)	1	1		2	0.3	2	
pT1am (6-10 mm)	6	2	1	9	1.2	9	
pT1b (11-20 mm)	181	51	17	249	34.0	247	2
pT1bm (11-20 mm)			2	2	0.3	1	1
pT2 (21-40 mm)	75	24	13	112	15.3	110	2
pT2m (21-40 mm)	7	1		8	1.0	8	
pT3 (>40 mm)*	20	1	1	21	2.9	21	
pT3m (>40 mm)*	1			2	0.3	2	
pT3 (any size)**	56	42	128	226	30.9	196	30
pT3m (any size)**	5	6	18	29	3.9	23	6
Total	416 (56.8%)	134 (18.3%)	182 (24.9%)	**732**	**100**	691 (94.4%)	41 (5.6)

4th period: surgery in 2005-2010

	All age groups						
	N0	N1a	N1b	Total pT		M0	M1
pT/tumor size	number	number	number	number	%	number	number
pT1a (up to 5 mm)	79	1	3	83	6.8	83	
pT1a (6-10 mm)	173	24	9	206	17.0	206	
pT1am (1-5 mm)	11	1	1	13	1.1	13	
pT1am (6-10 mm)	30	6	2	38	3.1	38	
pT1b (11-20 mm)	228	62	20	310	25.5	310	
pT1bm (11-20 mm)	32	8	3	43	3.6	43	
pT2 (21-40 mm)	150	25	16	191	15.7	189	2
pT2m (21-40 mm)	16	3	6	25	2.1	25	
pT3 (>40 mm)*	44	11		55	4.5	55	
pT3m (>40 mm)*	9	2		11	0.9	11	
pT3 (any size)**	70	34	88	192	19.8	176	16
pT3m (any size)**	13	8	26	47	3.9	43	4
Total	855 (70.4%)	185 (15.3%)	174 (14.3%)	**1214**	**100**	1192 (98.2%)	22 (1.8%)

*- no extrathyroidal extension; ** - extrathyroidal extension

While during the first period of observation (1990-1994), the signs of extrathyroidal extension were identified in 59.3% cases, their frequency gradually decreased with increasing latency to 23.7% in 2005-2010. Such a tendency was also noted in the analysis of the frequency of regional and distant metastases. The percentage of cases with metastases to lymph nodes decreased from 62.3 to 29.6%, and that of distant metastases to the lung (detected during postoperative treatment of patients with radioiodine), decreased from 26.9 to 1.8%. All the above changes were characterized by significantly descending linear trends (p=0.0001).

The frequency of tumor foci detected in the form of separate lesions in contralateral lobe or sometimes in the affected lobe as well (Tm) in the first three time periods, i.e. during 1990-2004, practically did not differ (Table 4.7): 8.4% (14/167), 7.9% (29/365), and 7.1% (52 cases out of 732). Only in 2005-2010, the frequency of multifocal tumors significantly increased as compared with the first period of time (p=0.0309).

Also, it should be noted that before 2000, the "additional" tumoral foci which did not differ structurally from the main tumor were mostly seen among cases of "aggressive" PTCs sized more than 10 mm with signs of extrathyroidal extension and regional as well as distant metastases (Table 4.6, 4.7 and Fig. 4.9).

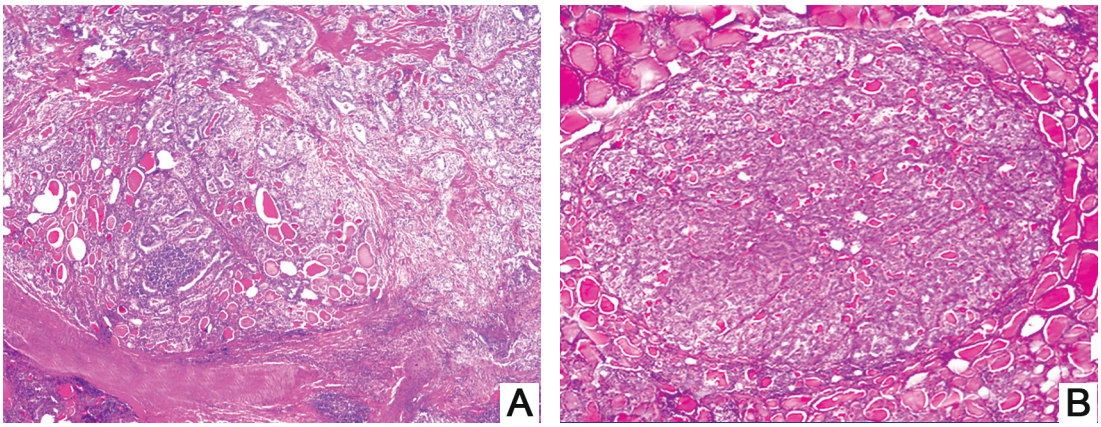

Figure 4.9. Multifocal papillary thyroid carcinoma. (A) Nonencapsulated main tumor sized 15 mm in the left lobe, follicular variant with the solid growth pattern. Haematoxylin and eosin, original magnification x10. (B) Multifocal lesion in the right lobe sized 5 mm with the solid-follicular structure. Haematoxylin and eosin, original magnification x20.

In 2000-2004, and especially in 2005-2010, different foci of multifocal tumors were characterized by variations in size, including microtumors (Table 4.7), by the degree of encapsulation, and by structural and invasive features. For an instance, in the same patient, there might be an encapsulated tumor of mixed structure sized more than 10 mm, and a separate nonencapsulated microtumor of mixed structure in one lobe (Fig. 4.10 A-E). In the contralateral lobe there might be, again, an encapsulated tumor of mixed structure sized more than 10 mm, and a nonencapsulated oxyphilic-cell tumor of the solid structure with signs of marked intratumoral and peritumoral thyroiditis (Fig. 4.10 F-H). In this example tumors are likely to be multiple PTCs developing independently.

Invasive features of PTCs also depended on patients' age. The highest frequency of tumors displaying intrathyroidal and extrathyroidal extension, vascular invasion, regional metastases to cervical lymph nodes and distant metastases to the lung was found in children (Table 4.8). For all these features, significantly descending linear age trends were found (p=0.0001).

Morphological signs of aggressiveness (extrathyroidal extension, vascular invasion, regional metastases) were revealed in all histological subtypes, mostly in nonencapsulated tumors (Table 4.9). In encapsulated PTCs (Fig. 4.11), tumor capsule invasion was observed in most cases, intrathyroidal extension in not more than 40.0%, and was limited only to isolated tumoral foci outside the tumor in adjacent thyroid tissue (Fig. 4.11 D).

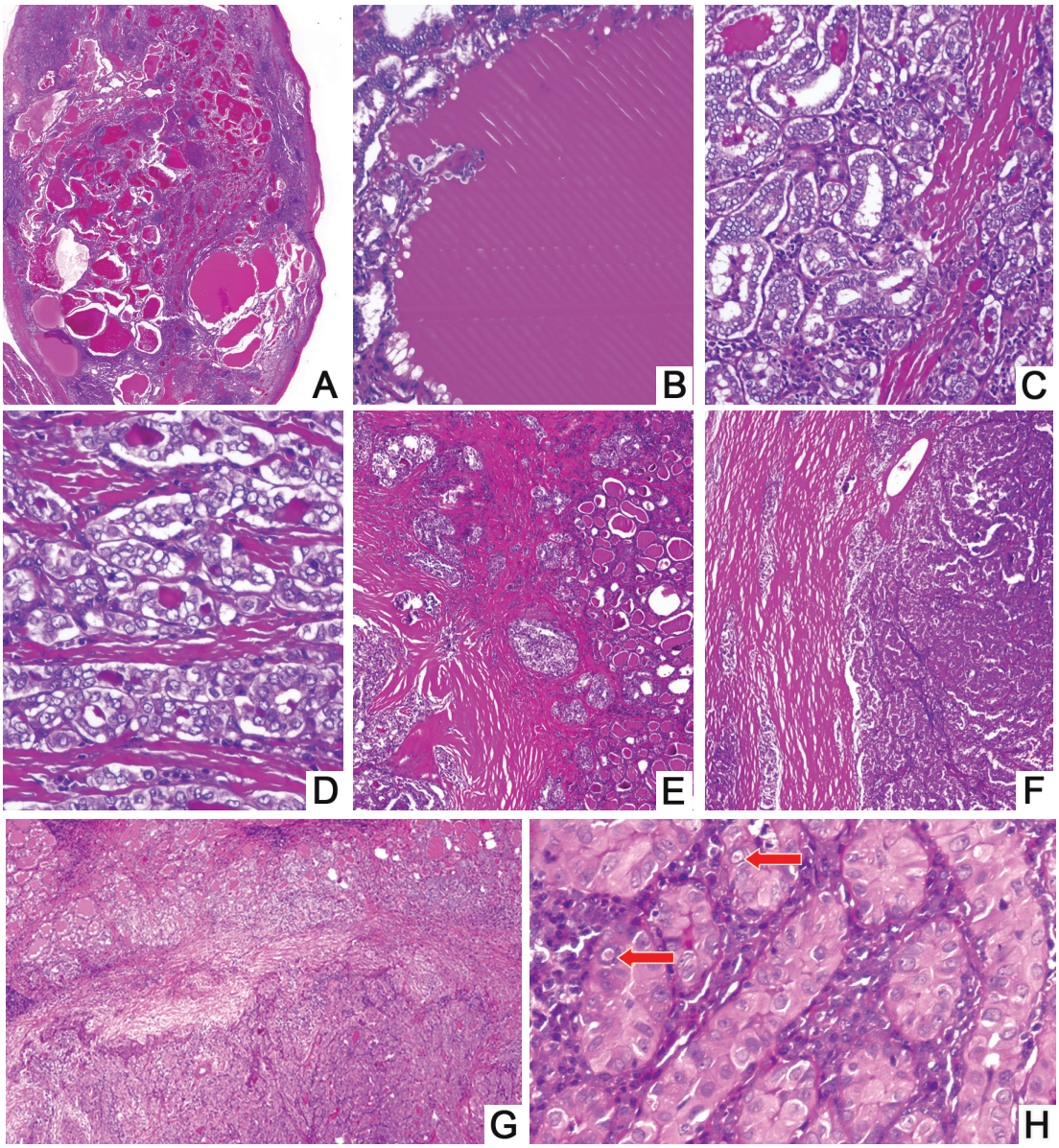

Figure 4.10. Multiple papillary thyroid carcinomas revealed in the same patient. (A) Encapsulated tumor in the right lobe sized 22 mm with the mixed growth pattern. Haematoxylin and eosin, original magnification x10-panoramic. (B) High-power image of the same tumor. Macrofollicular growth pattern. Haematoxylin and eosin, original magnification x100. (C) High-power image of the same tumor. Microfollicular growth pattern. Haematoxylin and eosin, original magnification x100. (D) High-power image of the same tumor, different area. Solid-follicular component between fibrotic stroma. Haematoxylin and eosin, original magnification x200. (E) Nonencapsulated tumor in the right lobe sized 6 mm with the solid-follicular growth pattern and small papillary loci. Marked stromal fibrosis. Haematoxylin and eosin, original magnification x20-panoramic. (F) Encapsulated tumor in the left lobe sized 11 mm with the papillary-solid growth pattern. Evident tumor capsule invasion. Haematoxylin and eosin, original magnification x20. (G) Nonencapsulated oxyphilic-cells tumor in the left lobe sized 9 mm with the solid and trabecular growth pattern. Evident intratumoral and peritumoral thyroiditis. Haematoxylin and eosin, original magnification x20. (H) High-power of the same tumor. Intranuclear pseudoinclusions in oxyphilic tumor cells. Haematoxylin and eosin, original magnification x200.

Extrathyroidal extension was registered only in 1.2% cases in adults among fully encapsulated tumors with subcapsular localization; regional metastases were found in isolated cases in each age group. Regional lymph node metastases in adults were more frequently seen in the classic papillary variant than in follicular or solid variants (Table 4.10). A higher rate of lymph node metastases in encapsulated classical papillary thyroid carcinomas was also reported in an independent study [51]. No distant metastases to the lung in patients with encapsulated PTC were found during the whole period of observation (Table 4.10). This is in excellent agreement with the opinion of J. Rosai: "Papillary thyroid carcinoma totally surrounded by a capsule may still be associated with nodal metastases, but the incidence of distant metastases or tumor death is nearly zero" [4].

Table 4.7
Size of multifocal papillary thyroid carcinomas in patients born before Chernobyl

Biggest lesion, mm	**Children aged up to 14 years at surgery**									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	-	-	-	-	-	-
6-10	-	-	-	-	-	-	-	-	-	-
11-20	3	23.1	1	11.1	-	-	-	-	4	18.2
21-30	4	30.7	-	-	-	-	-	-	4	18.2
31-40	1	7.7	-	-	-	-	-	-	1	4.5
41-50	3	23.1	1	11.1	-	-	-	-	4	18.2
51-60	1	7.7	4	44.5	-	-	-	-	5	22.7
>60	1	7.7	3	33.3	-	-	-	-	4	18.2
Total	**13**	100	**9**	100		**0**	-	-	**22**	100
	Adolescents aged from 15 to 18 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	-	-	-	-	-	-
6-10	-	-	-	-	1	10.0	-	-	1	5.2
11-20	-	-	4	50.0	4	40.0	-	-	8	42.1
21-30	-	-	1	12.5	3	30.0	-	-	4	21.1
31-40	1	100	2	25.0	1	10.0	-	-	4	21.1
41-50	-	-	1	12.5	1	10.0	-	-	2	10.5
51-60	-	-	-	-	-	-	-	-	-	-
>60	-	-	-	-	-	-	-	-	-	-
Total	**1**	100	**8**	100	**10**	100	-	-	**19**	100

Continuation of Table 4.7

	Adults aged from 19 to 42 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	2	4.8	15	8.5	17	7.4
6-10	-	-	-	-	11	26.2	44	24.8	55	23.8
11-20	-	-	5	41.7	10	23.8	62	35.0	77	33.3
21-30	-	-	2	16.7	8	19.0	21	11.9	31	13.4
31-40	-	-	-	-	2	4.8	17	9.6	19	8.2
41-50	-	-	-	-	5	11.9	10	5.6	15	6.5
51-60	-	-	1	8.3	4	9.5	4	2.3	9	3.9
>60	-	-	4	33.3	-	-	4	2.3	8	3.5
Total	**0**	-	**12**	100	**42**	100	**177**	100	**231**	100
	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
up to 5	-	-	-	-	2	3.8	15	8.5	17	6.3
6-10	-	-	-	-	12	23.1	44	24.8	56	20.6
11-20	3	21.4	10	34.5	14	26.9	62	35.0	89	32.7
21-30	4	28.7	3	10.3	11	21.2	21	11.9	39	14.3
31-40	2	14.3	2	6.9	3	5.8	17	9.6	24	8.8
41-50	3	21.4	2	6.9	6	11.5	10	5.6	21	7.7
51-60	1	7.1	5	17.3	4	7.7	4	2.3	14	5.1
>60	1	7.1	7	24.1	-	-	4	2.3	12	4.5
Total	**14**	100	**29**	100	**52**	100	**177**	100	**272**	100

In nonencapsulated PTCs, the most pronounced intrathyroidal extension was noted in the diffuse-sclerosing variant (Fig. 4.5A) apparently stemming from its definition. For patients of all ages with diffuse sclerosing variant of PTC, a high frequency of extrathyroidal extension and metastases to lymph nodes was registered as well (Table 4.9). Metastases most commonly had papillary-solid structure with marked signs of oxyphilic-cell and squamous-cell metaplasia (Fig. 4.12). In children and adolescents with diffuse sclerosing variant of PTC, distant metastases to the lung were also found in 23.5 and 25.0% cases, respectively. These data additionally attest to the aggressive behaviour of this variant of PTC [1,3,4,29], but, as already mentioned above, the small number of cases does not allow establishing a link between such a tumor structure and exposure to Chernobyl fallout.

Our review of the three main subtypes of PTC (classic papillary, follicular and solid) and of the mixed-type PTC shows that the identification of the (formerly) "childhood variant" [17,38] which combines - as already pointed out - tumors with solid, follicular, and solid-follicular structures, was pathologically justified. All signs of aggressiveness: vascular invasion, multifocality, extrathyroidal extension, regional lymph node and distant metastases were most pronounced namely in children who had nonencapsulated tumors with such structure (Table 4.9).

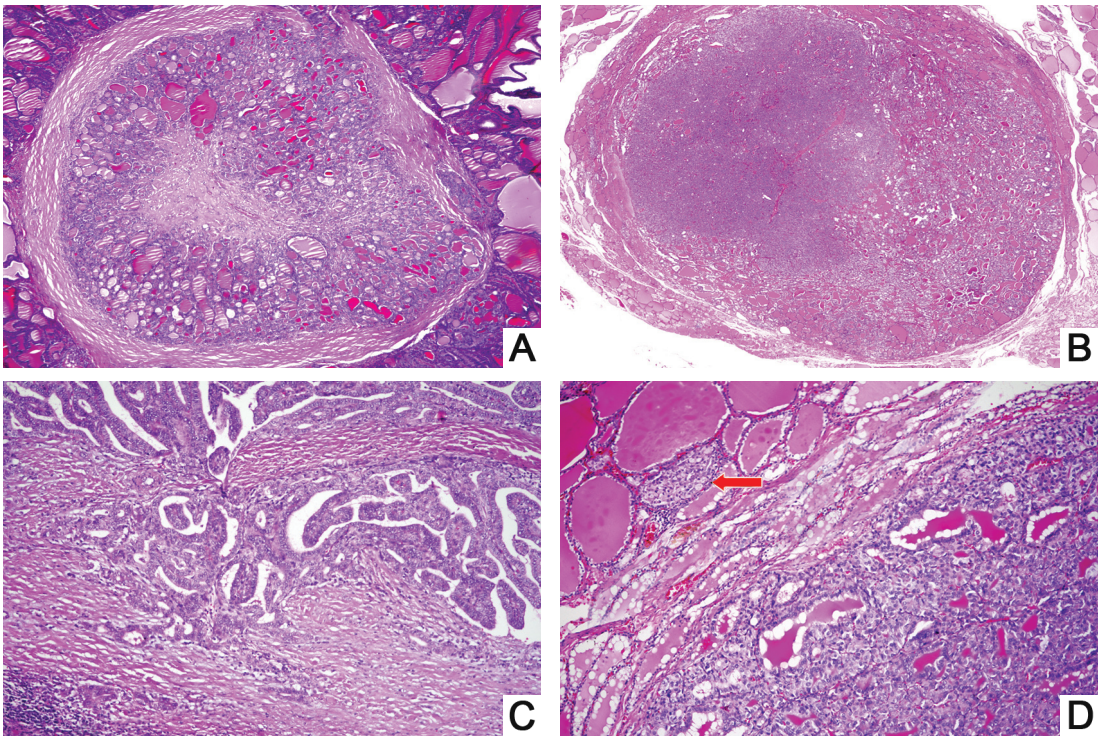

Figure 4.11. Fully encapsulated papillary thyroid carcinomas. (A) Tumor with the follicular growth pattern. Evident tumor capsule invasion and central fibrosis. Haematoxylin and eosin, original magnification x20-panoramic. (B) Tumor with the solid-follicular growth pattern. Haematoxylin and eosin, original magnification x20-panoramic. (C) Tumor with the papillary growth pattern. Tumor capsule invasion. Haematoxylin and eosin, original magnification x50. (D) Tumor with solid-follicular growth pattern. Intrathyroidal extension of the tumor. Haematoxylin and eosin, original magnification x50.

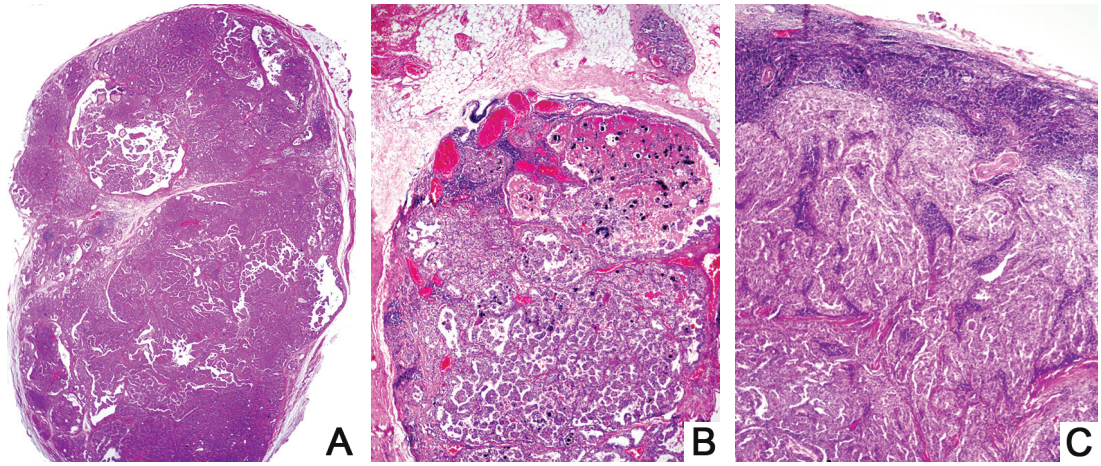

Figure 4.12. Lymph node metastases of the diffuse-sclerosing variant of papillary thyroid carcinomas. (A) Papillary-solid growth pattern. Haematoxylin and eosin, original magnification x10-panoramic. (B) Papillary growth pattern. Cystic changes, numerous psammoma bodies, extra-lymph node extension. Haematoxylin and eosin, original magnification x20. (C) Papillary-solid growth pattern. Evident oxyphilic-cell metaplasia. Haematoxylin and eosin, original magnification x20.

Table 4.8
Invasive properties of papillary thyroid carcinoma in patients born before Chernobyl

Subtype (number)	Intrathyroidal extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
Children aged up to 14 years at surgery														
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (30)	21	70.0	20	66.7	1	3.3	-	-	14	46.7	16	53.3	4	13.3
FV (65)	32	49.2	40	61.5	25	38.5	4	6.2	43	66.2	38	58.5	21	32.3
SV (57)	33	57.9	43	75.4	23	40.4	8	12.3	50	87.7	45	78.9	19	33.3
PFV (16)	8	56.0	9	56.3	1	6.3	1	6.3	8	50.0	11	68.8	4	25.0
PSV (11)	5	45.5	5	45.5	2	18.2	1	9.1	4	36.4	9	81.8	1	9.1
PSFV (3)	2	66.7	1	33.3	-	-	-	-	2	66.7	3	100	-	-
SFV (73)	50	68.5	54	74.0	31	42.5	8	11.0	58	79.5	53	72.6	23	31.5
DSV (17)	17	100	17	100	-	-	-	-	7	41.2	9	52.9	4	23.5
Warthin (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cribriform (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total (272)	168	**61.8**	189	**69.5**	83	**30.5**	22	**8.1**	186	**68.4**	184	**67.6**	76	**27.9**
Adolescents aged from 15 to 18 years at surgery														
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (48)	26	54.2	22	45.8	3	6.3	3	6.3	18	37.5	22	45.8	5	10.4
FV (47)	24	51.1	21	44.7	11	23.4	1	2.1	19	40.4	22	46.8	6	12.8
SV (24)	17	70.8	11	45.8	11	45.8	3	12.5	15	62.5	10	41.7	4	16.7
PFV (38)	17	44.7	13	34.2	5	13.2	4	10.5	16	42.1	20	52.6	5	13.2
PSV (18)	12	66.7	6	33.3	2	11.1	3	16.7	9	50.0	13	72.2	4	22.2
PSFV (5)	3	60.0	3	60.0	1	20.0	-	-	3	60.0	5	100	2	40.0
SFV (40)	26	65.0	20	76.9	9	22.5	5	12.5	21	52.5	22	55.0	12	30.0
DSV (4)	4	100	4	100	-	-	-	-	4	100	4	100	1	25.0
Warthin (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cribriform (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total (225)	129	**57.3**	100	**44.4**	42	**18.7**	19	**8.4**	105	**46.7**	118	**52.4**	39	**17.3**

Continuation of Table 4.8

Subtype (number)	Adults aged from 19 to 42 years at surgery													
	Intrathyroidal extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (667)	200	30.0	203	30.4	29	4.3	69	10.3	133	19.9	225	33.7	10	1.5
FV (332)	100	30.1	58	17.5	49	14.8	38	11.4	63	19.0	79	23.6	8	2.4
SV (118)	40	33.9	39	33.1	37	31.4	17	14.4	41	34.7	35	29.7	6	5.1
PFV (422)	170	40.3	129	30.6	47	11.1	45	10.7	136	32.2	192	45.5	19	4.5
PSV (143)	61	42.7	65	45.5	21	14.7	20	14.0	47	32.9	59	41.3	9	6.3
PSFV (49)	25	51.0	20	41.7	16	32.7	7	14.3	14	28.6	17	34.7	4	8.2
SFV (223)	65	29.1	50	22.4	49	22.0	32	14.3	48	21.5	63	23.8	9	4.0
DSV (6)	6	100	6	100	-	-	-	-	5	83.3	6	100	-	-
Warthin (19)	5	26.3	6	31.6	3	15.8	3	15.8	4	21.1	7	36.8	-	-
Cribriform (2)	2	100	1	50.0	1	50.0	-	-	-	-	1	50.0	-	-
Total (1981)	674	**34.0**	577	**29.1**	252	**12.7**	231	**11.7**	491	**24.8**	674	**34.0**	65	**3.3**

Table 4.9

Invasive properties of nonencapsulated and partly encapsulated papillary thyroid carcinoma in patients born before Chernobyl

Subtype (number)	Children aged up to 14 years at surgery													
	Intrathyroidal extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (26)	18	69.2	17	65.4	1	3.8	-	-	14	53.8	15	57.7	4	15.4
FV (57)	31	54.4	38	66.7	21	36.8	4	7.0	43	75.4	37	64.9	21	36.8
SV (54)	31	57.4	42	77.8	22	40.7	8	14.8	50	92.6	44	81.5	19	35.2
PFV (14)	7	50.0	9	64.3	1	7.1	1	7.1	8	57.1	10	71.4	4	28.6
PSV (11)	5	45.5	5	45.5	2	18.2	1	9.1	4	36.4	9	81.8	1	9.1
PSFV (3)	2	66.7	1	33.3	-	-	-	-	2	66.7	3	100	-	-
SFV (69)	49	71.0	53	71.0	30	43.5	8	11.6	58	84.1	53	76.8	23	33.3
DSV (17)	17	100	17	100	-	-	-	-	7	41.2	9	52.9	4	23.5
Warthin (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cribriform (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total (251)	160	**63.7**	182	**72.5**	77	**30.7**	22	**8.8**	186	**74.1**	180	**71.7**	76	**30.3**

Continuation of Table 4.9

Adolescents aged from 15 to 18 years at surgery

Subtype (num)	Intrathyroidal extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (40)	22	55.0	21	52.5	3	7.5	3	7.5	18	45.0	20	50.0	5	12.5
FV (40)	21	52.5	19	47.5	11	27.5	1	2.5	19	47.5	21	52.5	6	15.0
SV (23)	16	69.5	10	43.5	11	47.8	3	13.0	15	65.2	10	43.5	4	17.4
PFV (31)	15	48.4	12	38.7	5	16.1	3	9.7	16	51.6	20	64.5	5	16.1
PSV (15)	11	73.3	6	40.0	2	13.3	3	20.0	9	60.0	13	86.7	4	26.7
PSFV (5)	3	60.0	3	60.0	1	20.0	-	-	3	60.0	5	100	2	40.0
SFV (31)	23	74.2	18	58.1	7	22.6	5	16.1	21	67.7	22	71.0	12	38.7
DSV (4)	4	100	4	100	-	-	-	-	4	100	4	100	1	25.0
Warthin (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cribriform (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total (190)	115	**60.5**	93	**48.9**	40	**21.1**	18	**9.5**	105	**55.3**	115	**60.5**	39	**20.5**

Adults aged from 19 to 42 years at surgery

	Intrathyroidal extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (499)	145	29.1	170	34.1	21	4.2	57	11.4	129	25.9	210	42.1	10	2.0
FV (178)	73	41.0	48	27.0	24	13.4	16	9.0	63	35.4	72	40.4	8	4.5
SV (74)	33	44.6	36	48.6	24	32.4	13	32.4	40	54.1	33	44.6	6	8.1
PFV (336)	134	39.9	113	33.6	37	11.0	36	10.7	136	40.5	185	55.0	19	5.7
PSV (128)	53	41.4	61	47.7	16	12.5	20	15.6	45	35.2	58	45.3	9	7.0
PSFV (33)	18	54.5	17	51.5	13	39.4	4	12.1	14	42.4	17	51.5	4	12.1
SFV (124)	45	36.3	46	37.1	24	19.4	24	19.4	48	38.7	52	41.9	9	7.3
DSV (6)	6	100	6	100	-	-	-	-	5	83.3	6	100	-	-
Warthin (19)	5	26.3	6	31.6	3	15.8	3	15.8	4	21.1	7	36.8	-	-
Cribriform (2)	2	100	1	50.0	1	50.0	-	-	-	-	1	50.0	-	-
Total (1399)	514	**36.7**	504	**36.0**	163	**11.7**	173	**12.4**	484	**34.6**	641	**45.8**	65	**4.6**

Table 4.10
Invasive properties of fully encapsulated papillary thyroid carcinoma in patients born before Chernobyl

Children aged up to 14 years at surgery

Subtype (number)	Tum capsule invasion		Intrathyroid extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroid extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (4)	4	100	3	75.0	3	75.0	-	-	-	-	-	-	1	25.0	-	-
FV (8)	7	87.5	1	12.5	2	25.0	4	50.0	-	-	-	-	1	12.5	-	-
SV (3)	3	100	2	66.7	1	33.8	1	33.3	-	-	-	-	1	33.3	-	-
PFV (2)	2	100	1	50.0	-	-	-	-	-	-	-	-	1	50.0	-	-
PSV (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PSFV (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SFV (4)	1	25.0	1	25.0	1	25.0	1	25.0	-	-	-	-	-	-	-	-
Total (21)	17	**81.0**	8	**38.1**	7	**33.3**	6	**28.6**	0	**-**	0	**-**	4	**19.0**	0	**-**

Adolescents aged from 15 to 18 years at surgery

Subtype (number)	Tum capsule invasion		Intrathyroid extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroid extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (8)	8	100	4	50.0	1	12.5	-	-	-	-	-	-	2	25.0	-	-
FV (7)	7	100	3	42.9	2	28.6	-	-	-	-	-	-	1	14.8	-	-
SV (1)	1	100	1	100	1	100	-	-	-	-	-	-	-	-	-	-
PFV (7)	7	100	2	28.6	1	14.3	-	-	1	14.3	-	-	-	-	-	-
PSV (3)	3	100	1	33.3	-	-	-	-	-	-	-	-	-	-	-	-
PSFV (0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SFV (9)	9	100	3	33.3	2	22.2	2	22.2	-	-	-	-	-	-	-	-
Total (35)	35	**100**	14	**40.0**	7	**20.0**	2	**5.7**	1	**2.9**	0	**-**	3	**8.6**	0	**-**

Adults aged from 19 to 42 years at surgery

Subtype (number)	Tum capsule invasion		Intrathyroid extension		Lymphatic invasion		Vascular invasion		Multifocality		Extrathyroidal extension		Regional mts		Distant mts	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%	number	%
PV (168)	167	99.4	55	32.7	33	19.6	8	4.8	12	7.1	4	2.4	15	8.9	-	-
FV (154)	129	83.8	27	17.5	10	6.5	25	16.2	22	14.3	-	-	7	4.5	-	-
SV (44)	39	88.6	7	15.9	3	6.8	13	29.5	4	9.1	1	2.3	2	4.5	-	-
PFV (86)	82	95.3	36	41.9	16	18.6	10	11.6	9	10.5	-	-	7	8.1	-	-
PSV (15)	13	86.7	8	53.3	4	26.7	5	33.3	-	-	2	13.3	1	6.7	-	-
PSFV (16)	14	87.5	7	43.8	3	18.8	3	18.8	3	18.8	-	-	-	-	-	-
SFV (99)	82	82.8	20	20.2	4	4.0	25	25.3	8	8.1	-	-	1	1.0	-	-
Total (582)	531	**91.2**	160	**27.5**	73	**12.5**	89	**15.3**	58	**10.0**	7	**1.2**	33	**5.7**	0	**-**

By contrast, in adolescents and adults with tumors of such structural "combination", no signs of the higher aggressiveness were found. This may probably be due to the fact that the architecture of the follicular variant in adolescents and adults differs from that in children. In older patients, the solid component is absent or confined to very small foci in the areas of invasive growth. On the other hand, when combining tumors with the solid and solid-follicular structure in adolescents and adults, the frequency of extrathyroidal extension was significantly higher ($p<0.05$) as compared to other subtypes: in adolescents 66.7% (36/54 cases of the solid and solid-follicular subtypes) vs 50.7% (69/136 cases of other subtypes), and 44.4% (88/198 cases of the solid and solid-follicular subtypes) vs 33.0% (396/1201 cases of other subtypes) in adults. In addition, in the adult group, such a pooling showed a significantly higher frequency, as compared to other subtypes, of vascular invasion ($p<0.001$), multifocality ($p<0.01$) and distant metastases (Table 4.9). Thus, despite the finding that the prevalence of PTCs with the solid and solid-follicular structure was significantly declining with increasing patients' age and latency, morphological signs of aggressiveness in such tumors were still preserved.

According to the WHO classification [5], *papillary microcarcinoma* represented by the tumors sized up to 10 mm is considered to be an independent subtype. We already noted that the prevalence of microcarcinomas in the groups under study was significantly rising with increasing age of patients and latency (Table 4.3), i.e. time elapsed after Chernobyl. The presence of the "full" capsule (Fig. 4.13 A) was found in 20.8% tumors sized up to 5 mm (26/125) and in 22.4% (83/170) sized from 6 to 10 mm, i.e. most "small" tumors were nonencapsulated (Fig. 4.13 B-C).

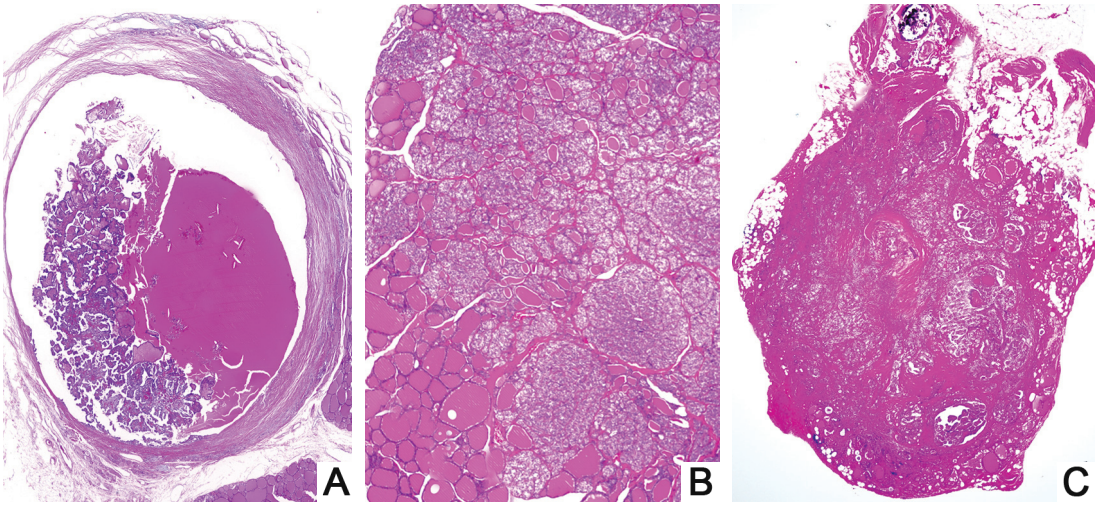

Figure 4.13. Papillary microcarcinomas. (A) Fully encapsulated tumor sized 7 mm with the papillary growth pattern. Haematoxylin and eosin, original magnification x20-panoramic. (B) Nonencapsulated tumor sized 7 mm with the solid growth pattern. Tumoral extension to the thyroid capsule and adjacent thyroid tissue. Haematoxylin and eosin, original magnification x20. (C) Tumor sized 5 mm with the papillary-solid growth pattern. Extrathyroidal extension, marked intratumoral fibrosis. Haematoxylin and eosin, original magnification x10.

Microcarcinomas, similarly to large size PTCs, may have different structure: classic papillary (Fig. 4.13 A), follicular, solid (Fig. 4.13 B) or mixed (Fig. 4.13 C). No statistically significant predominance of any histological variant – among both encapsulated and nonencapsulated tumors – was found in microcarcinomas (Table 4.11, 4.12).

The invasive features of microcarcinoma depended on tumor size and encapsulation. Encapsulated tumors sized up to 5 mm, regardless of architecture, were minimally invasive in all 26 cases. Although tumor cells might display signs of invasion into the tumor capsule, not a single case showed spread outside its limits; there were no signs of vascular invasion or metastases to lymph nodes. In three cases (11.5%) diagnosed during the last period of observation microtumors were multiple, as was mentioned above.

Table 4.11
Subtypes of fully encapsulated micro-PTC in patients born before Chernobyl

sized from 1 to 5 mm

All age groups

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Subtype	number	%	number	%	number	%	number	%	number	%
PV	-	-	-	-	2	40.0	7	33.3	9	34.7
FV	-	-	-	-	1	20.0	7	33.3	8	30.8
SV	-	-	-	-	-	-	1	4.8	1	3.8
PFV	-	-	-	-	-	-	2	9.5	2	7.7
PSV	-	-	-	-	1	20.0	1	4.8	2	7.7
PSFV	-	-	-	-	-	-	1	4.8	1	3.8
SFV	-	-	-	-	1	20.0	2	9.5	3	11.5
Warthin	-	-	-	-	-	-	-	-	-	-
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	-	-	-	-	**5**	100	**21**	100	**26**	100

sized from 6 to 10 mm

All age groups

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	-	-	3	30.0	5	35.7	15	25.0	23	27.4
FV	-	-	2	20.0	4	28.6	12	20.0	18	21.4
SV	-	-	1	10.0	-	-	9	15.0	10	11.9
PFV	-	-	2	20.0	3	21.5	10	16.7	15	17.8
PSV	-	-	2	20.0	1	7.1	2	3.3	5	6.0
PSFV	-	-	-	-	-	-	5	8.3	5	6.0
SFV	-	-	-	-	1	7.1	7	11.7	8	9.5
Warthin	-	-	-	-	-	-	-	-	-	-
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	-	-	**10**	100	**14**	100	**60**	100	**84**	100

Encapsulated microcarcinomas sized from 6 to 10 mm were also minimally invasive in general. However, in two cases out of 84 (2.4%), in the presence of follicular or papillary-follicular structures, there were metastases to lymph nodes (N1a); in 7 cases (8.3%) signs of lymphatic invasion, and in 7 cases (8.3%) multiple microtumors were seen.

Nonencapsulated microcarcinomas, similarly to the tumors of larger size, were characterized by the more pronounced invasive features as compared to encapsulated ones. Even very small tumors (up to 5 mm) of the follicular, solid, and mixed structure displayed signs of moderate intrathyroidal spread in 11.1% cases (11/99), lymphatic invasion in 8.1% (8/99), vascular invasion in 1.0% (1/99), extrathyroidal extension in 2.0% (2/99, Fig. 4.13C), and metastases to lymph nodes (N1a) in 6.1% of cases (6/99).

Table 4.12
Subtypes of nonencapsulated and partly encapsulated micro-PTC in patients born before Chernobyl

sized from 1 to 5 mm

Subtype	**All age groups**									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	1	100	-	-	7	33.3	10	13.0	18	18.2
FV	-	-	-	-	6	28.5	17	22.1	23	23.2
SV	-	-	-	-	1	4.8	9	11.7	10	10.1
PFV	-	-	-	-	3	14.3	13	16.9	16	16.2
PSV	-	-	-	-	1	4.8	9	11.7	10	10.1
PSFV	-	-	-	-	1	4.8	-	-	1	1.0
SFV	-	-	-	-	2	9.5	18	23.3	20	20.2
Warthin	-	-	-	-	-	-	1	1.3	1	1.0
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	**1**	100	-	-	**21**	100	**77**	100	**99**	100

sized from 6 to 10 mm

	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PV	-	-	2	18.2	21	38.2	75	34.7	98	34.3
FV	1	25.0	1	9.1	8	14.5	28	13.0	38	13.3
SV	2	50.0	1	9.1	1	1.8	10	4.6	14	4.9
PFV	-	-	2	18.2	15	27.3	47	21.8	64	22.4
PSV	-	-	2	18.2	5	9.1	26	12.0	33	11.5
PSFV	-	-	-	-	-	-	9	4.2	9	3.1
SFV	1	25.0	3	27.2	5	9.1	20	9.2	29	10.1
Warthin	-	-	-	-	-	-	1	0.5	1	0.4
Cribriform	-	-	-	-	-	-	-	-	-	-
Total	**4**	100	**11**	100	**55**	100	**216**	100	**286**	100

Invasiveness of the tumors sized from 6 to 10 mm was significantly higher compared to that of microcarcinomas sized up to 5 mm: intrathyroidal extension was observed in 22.0% (63 out of 286 cases, p=0.0178); lymphatic invasion in 24.8% (71/286, p=0.0003); extrathyroidal extension in 16.1% (46/286, p=0.0001); lymph node metastases in 23.3% (67/286, p=0.0001). However, all these were significantly lower than in nonencapsulated

carcinomas sized more than 10 mm for all age groups (Table 4.9). It should be emphasized that not in a single case of PTC sized up to 10 mm distant metastases to the lung were detected in the course of postoperative follow-up of patients.

In Belarus, by contrast with Ukraine, the prevalence of post-Chernobyl microcarcinomas was much higher: 39.2% just in children operated on at the age under 15 years [52,53]; in some cases distant metastases to the lung were identified [54]. Thus, tumor size alone cannot be a determinant of the choice of treatment tactics.

Table 4.13
Concomitant thyroid diseases in patients with micro-PTC born before Chernobyl

sized from 1 to 5 mm

All age groups

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Pathology	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	-	-	-	-	-	-
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	5/26	19.2	19/98	19.4	24/125	19.2
Nodule	-	-	-	-	6/26	23.1	15/98	15.4	21/125	16.8
MNG	1/1	-	-	-	4/26	15.4	18/98	18.4	23/125	18.4
Graves'	-	-	-	-	4/26	15.4	22/98	22.4	26/125	20.8
Chronic thyroiditis	-	-	-	-	4/26	15.4	6/98	6.1	10/125	8.0
Total	1/1	-	0	-	23/26	**88.5**	80/98	**81.6**	104/125	**83.2**

sized from 6 to 10 mm

All age groups

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	-	-	-	-	-	-
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	8/69	11.6	16/276	5.8	24/370	6.5
Nodule	-	-	3/21	14.3	7/69	10.1	29/276	10.5	39/370	10.5
MNG	-	-	2/21	9.5	3/69	4.3	20/276	7.2	25/370	6.8
Graves'	-	-	-	-	-	-	2/276	0.7	2/370	0.5
Chronic thyroiditis	-	-	3/21	14.3	3/69	4.3	62/276	22.4	68/370	18.4
Total	0/4	-	8/21	**38.1**	21/69	**30.4**	129/276	**46.6**	158/370	**42.7**

Modern diagnostic methods allow detection of tumors even of minimal size. Our analysis of the presented material shows that thyroid nodule, multiple nodules, and Graves' disease were the reason for surgical intervention in 75.2% of cases of microcarcinoma sized up to 5 mm, and only in 24.3% cases sized from 6 to 10 mm. In the rest of cases, the papillary microcarcinoma was the main thyroid disease, and the main reason for surgery (Table 4.13). Concomitant chronic thyroiditis (presented in Table 4.13) was not the reason for surgery. Undoubtedly, tumors sized up to 1-2 mm could be detected incidentally only on microscopic examination of histological specimens from operated patients. If surgery was performed

for benign thyroid disease, e.g. multinodular goiter or Graves' disease (Fig. 4.14 A-B), such microcarcinomas are considered to be "occult". The presence of microcarcinomas sized 2 mm and larger may be suspected at a thorough examination of surgical material and during sample selection for subsequent microscopic analysis as demonstrated in the case of follicular adenoma (Fig. 4.14 C).

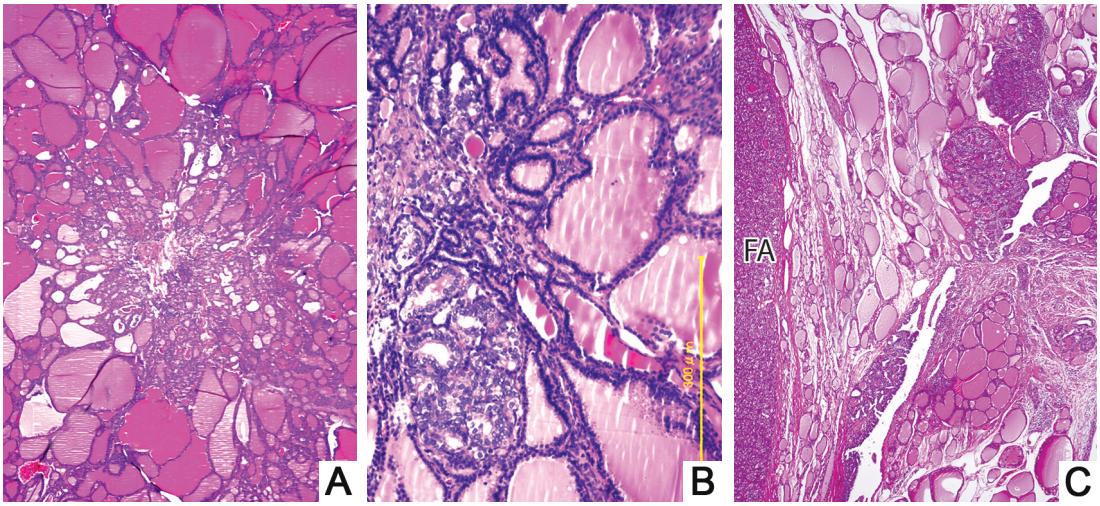

Figure 4.14. Occult papillary microcarcinomas. (A, B) Nonencapsulated micro-PTCs sized 2 mm and 0.3 mm with the follicular growth pattern revealed in patients with Graves' disease. Haematoxylin and eosin, original magnification x20, x100. (C) Nonencapsulated micro-PTCs sized 3 mm with the papillary-follicular growth pattern revealed in patients with follicular adenoma (FA). Haematoxylin and eosin, original magnification x20.

As a whole, our analysis of 2,478 cases of PTC showed the presence of concomitant thyroid disease in children in 11.0%, in adolescents in 16.9%, and in adults in 33.1% cases (Table 4.14). There was a significant ascending age-related linear trend (p=0.0001). The frequency of concomitant thyroid disease was also increasing in time from the first (1990-1994) to the last (2005-2010) period of observation (p=0.0001 for trend).

Besides the concomitant benign thyroid disease, additional coexisting thyroid cancers of smaller size than the PTC were noted in several cases; for this reason such tumors were referred to as "concomitant". In 2 cases these were FTCs and in 2 cases MTCs (Table 4.14). One MTC in a boy who underwent hemithyroidectomy at the age of 7 years for a PTC with the solid structure, was diagnosed at repeated surgery (completion thyroidectomy, neck dissection at level VI) two years later [11,42]. The second MTC, sized 7 mm, was identified in the left lobe of a female patient aged 25 years with a PTC sized 11 mm in the right lobe (Fig. 15 A-C).

Follicular adenomas were concomitant to PTC only in adults, beginning from the period 2000-2004 (2.8%), and their frequency somewhat increased, though insignificantly, in the last period of observation (4.4%).

Solitary and multiple (MNG) hyperplastic nodules were identified in all groups; their frequency significantly increased in a pairwise comparison: from 1.2% in children to 10.2% in adults (p=0.0001), and from 0.6% in 1990-1994 to 12.7% in 2005-2010 (p=0.0001); the ascending linear age and time trends were also significant (p=0.0001).

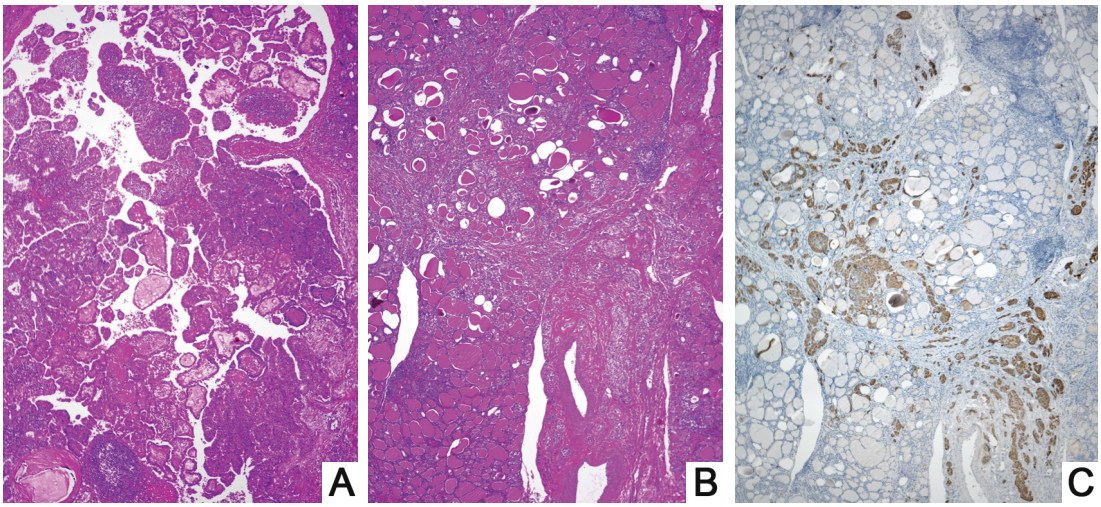

Figure 4.15. Two types of thyroid cancer coexisting in the same patient. (A) Nonencapsulated PTC with the papillary-solid growth pattern. Pronounced oxyphilic-cell metaplasia, Warthin-like loci. Haematoxylin and eosin, original magnification x20. (B) Nonencapsulated micro-medullary thyroid carcinoma with the solid growth pattern. Haematoxylin and eosin, original magnification x20. (C) Immunostaining of same area for calcitonin, original magnification x20.

PTCs in patients with Graves' disease were detected in a small number of cases (1.6%), only in adults and only beginning from 2000, i.e. from the age of 32 years old. These were mainly "occult" cancers or those detected at visual examination of surgical material. PTCs sized more than 10 mm in patients with Graves' disease were identified only in two cases.

The frequency of concomitant marked chronic thyroiditis of grade 3+/4+ (focal thyroiditis of grade 1+/2+ was not taken into account) practically did not differ between children and adolescents (9.6% and 10.7%, respectively) but was significantly increased in adults in a pairwise comparison with both children (p=0.0011) and adolescents (p=0.0105). A significant increase over time was observed between the first and last periods of observation (p=0.0007); the corresponding linear trend was also significant (p=0.0001).

Thus, most morphological characteristics of PTC in children, adolescents and adults who were aged up to 18 years during Chernobyl accident, have two main patterns: age-related and time-related, which displayed significantly descending or ascending linear trends.

Considering other types of thyroid cancer, it should be noted that ***follicular thyroid carcinoma*** (FTC) was detected in Ukraine in a small percentage of cases: 2.8% in children, 7.3% in adolescents, and 5.2% in adults (Table 4.2), similarly to other countries affected by the Chernobyl catastrophe [7,10,14].

The tumors under study represented encapsulated solitary nodules exceeding 2 cm in more than 70% of cases (in all age groups). Tumors sized less than 1 cm were detected in 1 out of 18 cases in adolescents (5.6%) and in 7 out of 111 cases in adults (6.3%). Most FTCs had microfollicular-solid structure. The oxyphilic-cell variant of FTC was not found in children, but was identified in 2 cases in adolescents (11.1%) and in 11 cases (9.9%) in adults. The diagnosis of "follicular thyroid carcinoma" was based on generally accepted criteria: marked "hook-like" or "mushroom-like" expansion through the tumor capsule and/or in blood vessels of the tumor capsule (Fig. 4.16).

Table 4.14
Concomitant thyroid diseases in patients with PTC born before Chernobyl

Children aged up to 14 years at surgery

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Pathology	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	-	-	-	-	-	-
MTC	1/127*	0.8	-	-	-	-	-	-	1/272	0.4
FA	-	-	-	-	-	-	-	-	-	-
Nodule	-	-	1/135	7.4	-	-	-	-	1/272	0.4
MNG	1/127	0.8	1/135	7.4	-	-	-	-	2/272	0.8
Graves'	-	-	-	-	-	-	-	-	-	-
Chronic thyroiditis	8/127	6.3	16/135	11.9	2/10	20.0	-	-	26/272	9.6
Total	10/127	**7.9**	18/135	**13.3**	2/10	**20.0**	**-**	**-**	30/272	**11.0**

* - MTC, 12 mm, n/encaps, sol,T3N0M0

Adolescents aged from 15 to 18 years at surgery

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	1/117*	0.9	-	-	1/225	0.4
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	2/81	2.5	4/117	3.4	-	-	6/225	2.7
Nodule	-	-	2/81	2.5	3/117	2.6	-	-	5/225	2.2
MNG	-	-	1/81	1.8	1/117	0.9	-	-	2/225	0.9
Graves'	-	-	-	-	-	-	-	-	-	-
Chronic thyroiditis	1/27	3.7	9/81	11.1	14/117	12.0	-	-	24/225	10.7
Total	1/27	**3.7**	14/81	**17.3**	23/117	**19.7**	**-**	**-**	38/225	**16.9**

* - FTC, 12 mm, microfol, T1bN0M0

Adults aged from 19 to 42 years at surgery

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	-	-	1/1214*	0.1	1/1981	0.05
MTC	-	-	-	-	-	-	1/1214**	0.1	1/1981	0.05
FA	-	-	-	-	17/605	2.8	53/1214	4.4	70/1981	3.5
Nodule	-	-	3/149	2.0	30/605	5.0	89/1214	7.3	122/1981	6.2
MNG	-	-	2/149	1.3	12/605	2.0	66/1214	5.4	80/1981	4.0
Graves'	-	-	-	-	6/605	1.0	26/1214	2.1	32/1981	1.6
Chronic thyroiditis	1/13	7.7	21/149	14.1	104/605	17.2	224/1214	18.5	350/1981	17.7
Total	1/13	**7.7**	26/149	**17.4**	169/605	**27.9**	460/1214	**37.9**	656/1981	**33.1**

* - FTC, 10 mm, T1aN0M0; ** - MTC, 7 mm, encaps, sol, T1aN0M0

Continuation of Table 4.14

	All age groups									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
FTC	-	-	-	-	1/732	0.1	1/1214	01	2/2478	0.1
MTC	1/167	0.6	-	-	-	-	1/1214	0.1	2/2478	0.1
FA	-	-	2/365	0.5	21/732	2.9	53/1214	4.4	76/2478	3.0
Nodule	-	-	6/365	1.6	33/732	4.5	89/1214	7.3	128/2478	5.2
MNG	1/167	0.6	4/365	1.1	13/732	1.8	66/1214	5.4	84/2478	3.4
Graves'	-	-	-	-	6/732	0.8	26/1214	2.1	32/2478	1.3
Chronic thyroiditis	10/167	6.0	46/365	12.6	120/732	16.4	224/1214	18.5	400/2478	16.1
Total	12/167	**7.2**	58/365	**15.9**	194/732	**26.5**	460/1214	**37.9**	724/2478	**29.2**

Invasion of two and more capsular vessels was found in 108 out of 137 cases (78.8%); therefore, 21.2% of FTCs in children and adolescents born before Chernobyl were minimally invasive. An aggressive widely invasive FTC with extension to extrathyroidal connective tissue and the trachea, with regional metastases to lymph nodes and distant metastases to the lung (pT4aN1aM1) was observed only in one case in an adolescent female patient aged 15 years whom we described earlier [42].

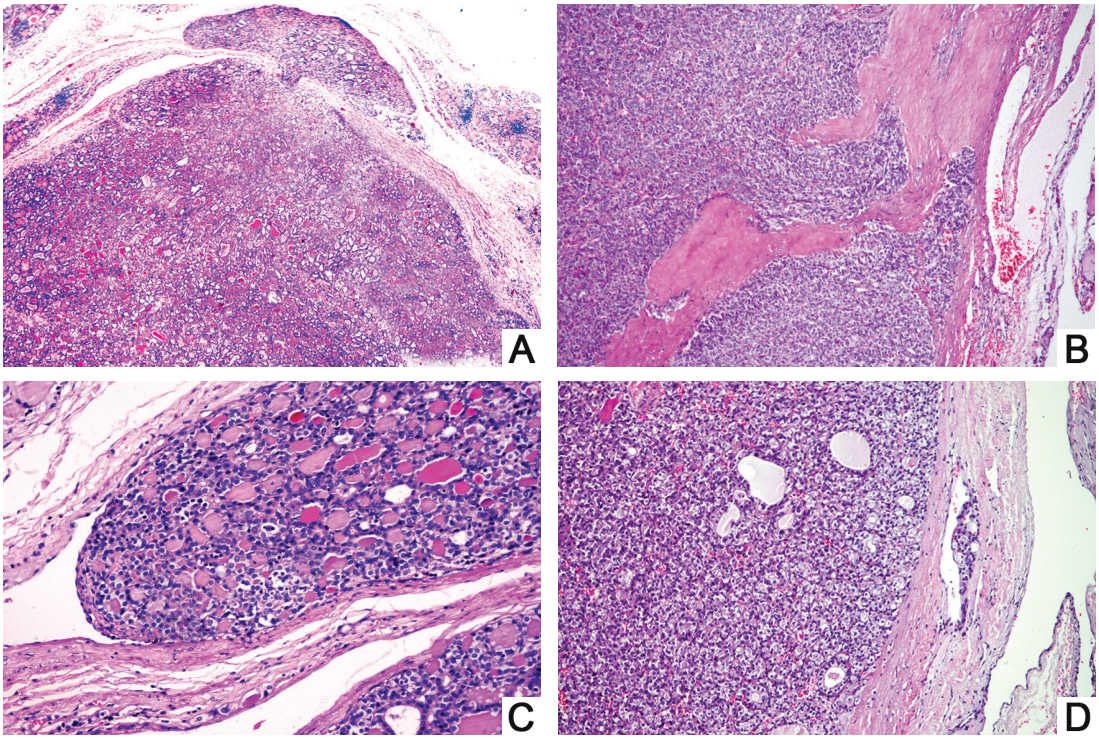

Figure 4.16. Follicular thyroid carcinomas. (A) Mushroom-like expansion through the capsule. Haematoxylin and eosin, original magnification x10. (B) Capsular invasion in a hook-like fashion. Haematoxylin and eosin, original magnification x50. (C, D) Vascular invasion. Aggregates of tumor cells are seen within the vessel lumen attached to the wall and covered by endothelium. Haematoxylin and eosin, original magnification x100, x50.

Among thyroid diseases concomitant to FTC, PTC (represented mostly by microcarcinomas sized up to 10 mm) was detected in 5 adults (Table 4.15). In 1 case, an encapsulated PTC sized 21 mm was smaller than the coexisting FTC nodule (35 mm), and therefore it was referred to the category of "concomitant disease". Solitary and multiple hyperplastic nodules were identified in 5.1%, chronic thyroiditis in the extratumoral tissue in 10.2% of cases.

There are different opinions regarding the impact of radiation exposure on the development of FTC. Some authors suggest the existence of such [3,26,55] while other [56] have not revealed significant link between FTC and previous exposure.

Our analysis of the frequency of FTC in Ukraine after Chernobyl in the group at high risk for radiation-induced thyroid cancer showed no significant differences between different age groups. However, a comparison of the frequency of FTC for different time periods after the accident revealed a significantly increasing linear trend (p=0.0334). Undoubtedly, 137 FTCs comprise too small number as compared to 2,478 PTCs, and further special investigations are needed to draw valid conclusions regarding association with thyroid dose.

Medullary thyroid carcinoma (MTC) in the cohort under study was diagnosed even less frequently: 2.4% in children, 0.4% in adolescents, and 1.5% in adults (Table 4.2). Tumor size varied from 4 to 75 mm; in 84.6% cases (33 out of 39) tumors were nonencapsulated, 87.2% carcinomas (34 out of 39) had the solid structure (Fig. 4.17), and only 12.8% displayed "spindle cell-solid" growth pattern. In all cases there was a positive immunohistochemical reaction with anti-calcitonin antibodies which confirmed the diagnosis of MTC. Seven out of 8 MTCs in children and adolescents (87.5%) were characterized by extrathyroidal extension, metastases to lymph nodes (T3N1bM0); 2 of these patients had distant metastases to the liver and brain (T3N1bM1). In adults, tumor aggressiveness was less pronounced: extrathyroidal extension and regional metastases were found in 12 out of 31 (38.7%) cases, distant metastases to the liver were detected in 1 female patient (3.2%). In the latter patient with MEN 2A syndrome (she had been operated for pheochromocytoma before), a papillary microcarcinoma sized 0.2 cm was identified (Fig. 4.18).

Here we do not analyze MTC in greater detail since many studies of post-Chernobyl thyroid cancer have not revealed any effect of radiation on the risk for development of tumors of this type [7,10,11,14].

Poorly differentiated thyroid carcinoma (PDTC) was diagnosed in 4 cases, all in adult female patients, accounting for 0.2% of all cancers under study (Table 4.2). Two of them were encapsulated, sized 26 and 35 mm, with trabecular-solid structure and invasion into tumor capsule and capsular vessels (T2N0M0). Both carcinomas developed in the presence of PTC as certain tumor areas displayed characteristic nuclear features. Two PDTCs were nonencapsulated, sized 50 and 52 mm, were of the insular and solid structure (T3N1bM0). In case of PDTC with the solid structure, the tumor was widely invasive (Fig. 4.19) with marked intrathyroidal and extrathyroidal extension, and necrotic areas. Tumor cells had signs of oxyphilic-cell metaplasia, were sometimes multinuclear, with marked nucleoli (Fig. 4.19 B). In some tumor areas, a focal positive reaction with anti-thyroglobulin antibodies was revealed (Fig. 4.19 C); the reaction with anti-TTF-1 antibodies was diffuse and strong (Fig. 4.19 D). A high proliferative activity of the tumor was confirmed by the reaction with anti-Ki67 antibodies. In many areas there were more than 50.0% of positively stained nuclei (Fig. 4.19 E). In such areas up to 20.0% of nuclei were also positive for TP53 (Fig. 4.19 F).

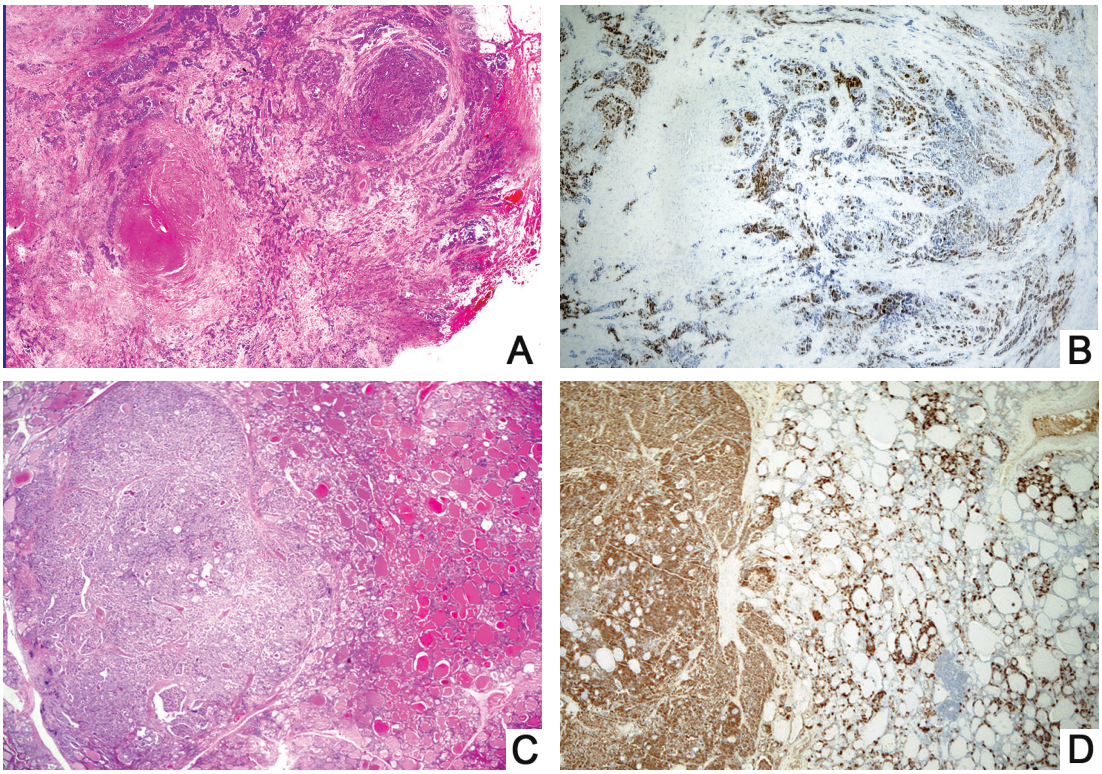

Figure 4.17. Medullary thyroid carcinoma. (A) Tumor with the solid growth pattern, marked stromal fibrosis, extrathyroidal extension and central necrosis. Haematoxylin and eosin, original magnification x10-panoramic. (B) Immunostaining for calcitonin of the same area, original magnification x20. (C) Tumor with the solid growth pattern and vascular invasion. Haematoxylin and eosin, original magnification x10. (D) Immunostaining for calcitonin of the same area. Marked C-cell hyperplasia in peritumoral areas, original magnification x10.

Table 4.15
Concomitant thyroid diseases in patients with FTC born before Chernobyl

	Children aged up to 14 years at surgery									
	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
Pathology	number	%	number	%	number	%	number	%	number	%
PTC	-	-	-	-	-	-	-	-	-	-
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	-	-	-	-	-	-
Nodule	-	-	-	-	-	-	-	-	-	-
MNG	-	-	-	-	-	-	-	-	-	-
Graves'	-	-	-	-	-	-	-	-	-	-
Total	0/2	-	0/6	-	-	-	-	-	0/8	-

Continuation of Table 4.15

Adolescents aged from 15 to 18 years at surgery

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	-	-	-	-	-	-	-	-	-	-
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	2	20.0	-	-	2	11.1
Nodule	-	-	-	-	1	10.0	-	-	1	5.6
MNG	-	-	1	14.3	-	-	-	-	1	5.6
Graves'	-	-	-	-	-	-	-	-	-	-
Chronic thyroiditis	1	-	-	-	1	10.0	-	-	2	11.1
Total	1/1	**-**	1/7	**14.3**	4/10	**40.0**	**-**	**-**	6/18	**33.3**

Adults aged from 19 to 40 years at surgery

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	-	-	-	-	2*	4.4	3*	4.9	5*	4.5
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	1	2.2	-	-	1	0.9
Nodule	-	-	-	-	1	2.2	5	8.2	6	5.4
MNG	-	-	-	-	2	4.4	4	6.6	6	5.4
Graves'	-	-	-	-	-	-	1	1.6	1	0.9
Chronic thyroiditis	-	-	-	-	4	8.9	8	13.1	12	10.8
Total	0/1	**-**	0/4	**-**	10/45	**22.2**	21/61	**34.4**	31/111	**27.9**

* - PTCs: 21 mm, encaps, FV, T2N0M0; 8 mm, partly encaps, FV, T1aN0M0; 7, 6, mm, n/encaps, FV, T1aN0M0; 5 mm, n/encaps, PFV, T1aN0M0

All age groups

	1990-1994		1995-1999		2000-2004		2005-2010		1990-2010	
	number	%	number	%	number	%	number	%	number	%
PTC	-	-	-	-	2	3.6	3	4.9	5	3.6
MTC	-	-	-	-	-	-	-	-	-	-
FA	-	-	-	-	3	5.5	-	-	3	2.2
Nodule	-	-	-	-	2	3.6	5	8.2	7	5.1
MNG	-	-	-	-	2	3.6	4	6.6	7	5.1
Graves'	-	-	-	-	-	-	1	1.6	1	0.7
Chronic thyroiditis	1	25.0	1	5.9	5	9.1	8	13.1	14	10.2
Total	1/4	**25.0**	1/17	**5.9**	14/55	**25.5**	21/61	**34.4**	37/137	**27.0**

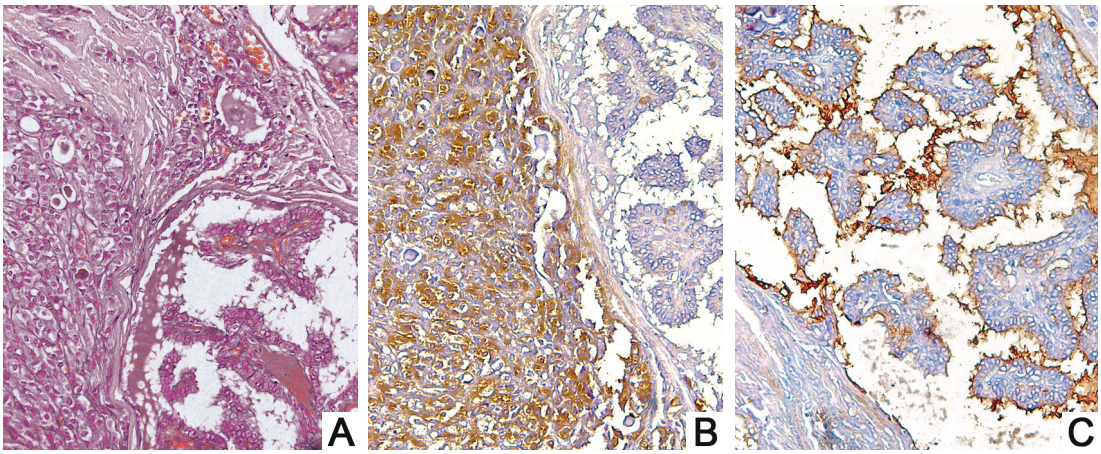

Figure 4.18. Coexistence of two different types of thyroid carcinomas in one patient. (A) Encapsulated papillary microcarcinoma sized 2 mm with the classic growth pattern and cystic changes seen in vicinity to the nonencapsulated medullary thyroid carcinoma with the solid growth pattern. Haematoxylin and eosin, original magnification x100. (B) Immunostaining for calcitonin of the same area, original magnification x100. (C) Immunostaining for thyroglobulin of the same area, original magnification x100.

In the most aggressive among all 4 PDTCs case, microfoci of PTC were also identified (Fig. 4.20). They were characterized by a strong reaction with antibodies to thyroglobulin (Fig. 4.20 D) and TTF-1 (Fig. 4.20 E), but unlike PDTC areas there were only isolated Ki67 positive nuclei (Fig. 4.20 F). TP53 expression was not detected in the PTC areas.

Tumor metastases completely replaced lymphatic nodes, and their structure and immunohistochemical characteristics did not differ from those of the main tumor (Fig. 4.21). The only difference was the lower frequency of nuclei positive for TP53: 5-10% (Fig. 4.21 F).

Modern handbooks of thyroid pathology do not consider the role of radiation in the development of PDTC [3,4]. However, at least some tumors may develop from preexisting well-differentiated PTC or FTC. It could not be ruled out that radiation may promote dedifferentiation of PTC cells. In our series, patients' age was 21 and 24 (encapsulated tumors) and 35 and 38 years old (nonencapsulated tumors), while typical mean age of patients with PDTC specified in handbooks is 55-60 years old. This issue, from our point of view, deserves particular attention in future, because 3 out of 4 cases of PDTC were detected in the last period of follow-up, namely, in 2008-2010.

Summarizing our data on pathology of thyroid cancer in Ukraine in the cohort aged from 0 to 18 years at the time of the Chernobyl accident, it should be noted that for the whole study period (1990-2010) the relative frequency of PTC exceeded 90.0% despite patients' age at surgery increased over this period from 4 (the youngest children operated in 1990) to 42 years old (the oldest adults operated in 2010). Thus, PTC is undoubtedly the type of radiogenic «Chernobyl» cancer; this may be considered a proven fact.

At the same time, a unique "structural portrait" of radiogenic Chernobyl PTC could not been established either by our group in Ukraine, or other authors [14,23,53,57]. Most likely, the development of PTC in patients of the group at risk (0 to 18 years at Chernobyl) followed the common mechanisms of thyroid carcinogenesis (yet displaying a higher or lower frequency of certain genetic abnormalities which correlate with structural changes in the tumor) that presumably underlie sporadic thyroid carcinogenesis.

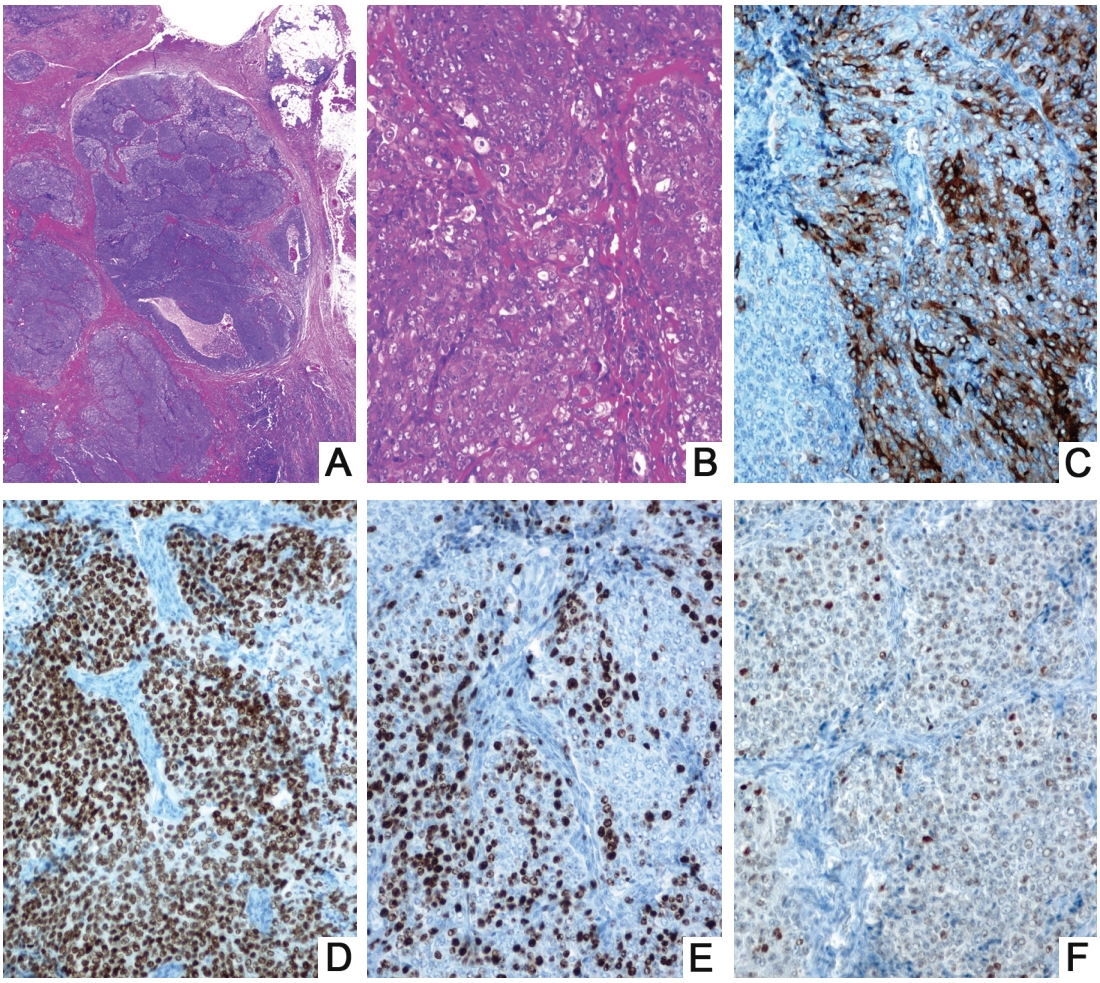

Figure 4.19. Poorly differentiated thyroid carcinoma. (A) Widely invasive nonencapsulated tumor with the solid growth pattern. Marked fibrosis, necrotic foci, extrathyroidal extension. Haematoxylin and eosin, original magnification x10-panoramic. (B) High-power image of the same tumor. Numerous nuclei with prominent nucleoli. Haematoxylin and eosin, original magnification x100. (C) Focal immunostaining for thyroglobulin, original magnification x100. (D) Diffuse strong nuclear reactivity for TTF-1, original magnification x100. (E) Diffuse strong nuclear reactivity for Ki67. Original magnification x100. (F) Moderate nuclear reactivity for TP53, original magnification x100.

Morphological characteristics of PTC are significantly changing with patients' age at surgery and over time after Chernobyl, i.e. with latency. Our analysis provides the evidence for two major patterns (age-related and time-related) seen for most pathological characteristics under study: "ascending" in some cases or "descending" in other linear trends. Significantly descending age and time trends are found for the frequency of architecturally less differentiated solid and solid-follicular subtypes of PTC, and invasive characteristics: intrathyroidal and extrathyroidal extension, vascular invasion, regional metastases to lymph nodes and distant metastases to the lung, which are important and favorable for the postoperative prognosis and patients' quality of life.

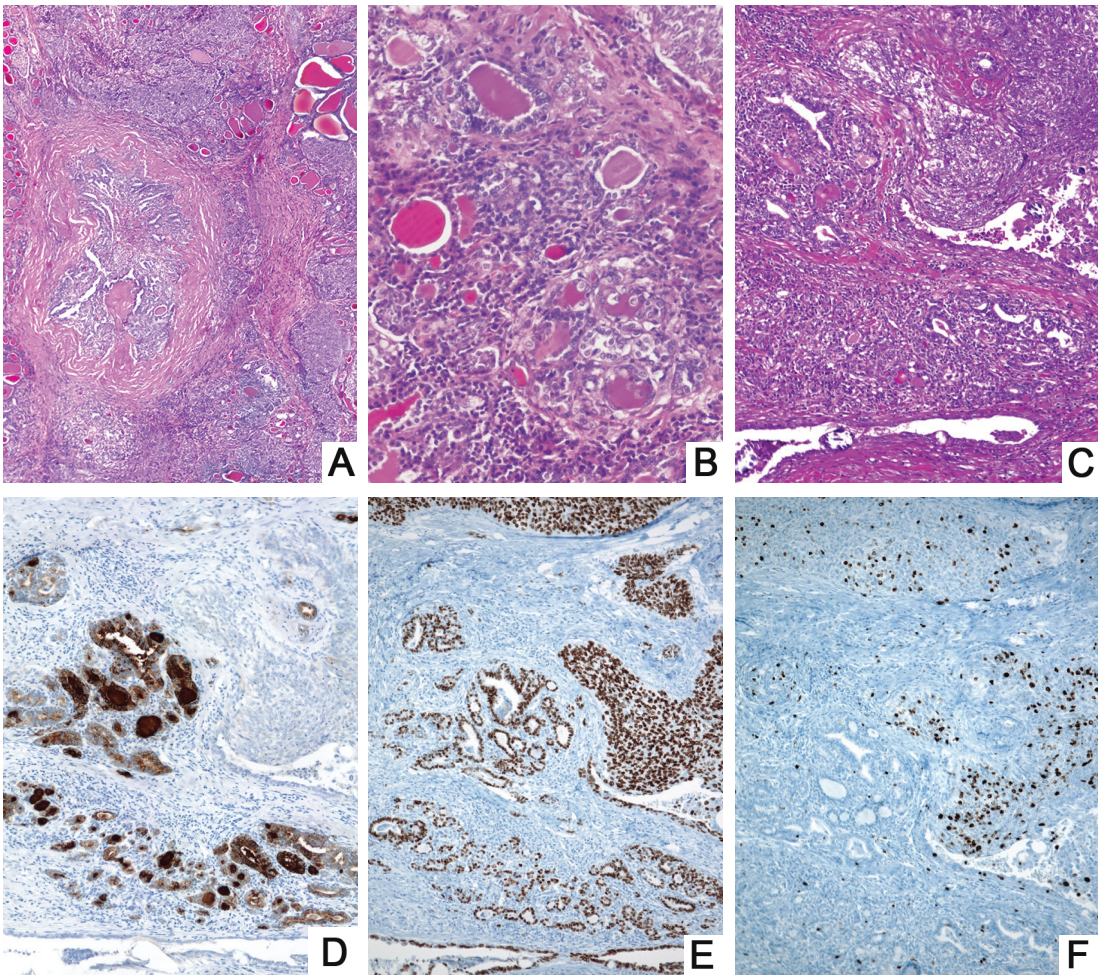

Figure 4.20. Microfoci of papillary thyroid carcinoma in poorly differentiated thyroid carcinoma. (A) Fibrotic area with the papillary-follicular growth pattern. Haematoxylin and eosin, original magnification x50-panoramic. (B) Microfoci with the follicular growth pattern. Haematoxylin and eosin, original magnification x100. (C) Microfoci with the follicular growth pattern and numerous psammoma bodies in lymphatic vessel. Haematoxylin and eosin, original magnification x50. (D) Strong thyroglobulin immunostaining of PTC foci, original magnification x100. (E) Diffuse strong nuclear reactivity for TTF-1 in both PTC and PDTC areas, original magnification x50. (F) Isolated Ki-67 positive nuclei in PTC foci. Original magnification x50.

Ascending linear trends are established for the frequency of structurally more differentiated papillary and papillary-follicular subtypes of PTC, for the prevalence of tumors sized up to 10 mm, and encapsulated tumors. These, again, may be considered as favorable, since "small" and encapsulated PTCs are characterized by significantly weaker invasive features compared with tumors of larger size and nonencapsulated ones. Thus, with increasing time after Chernobyl, PTC, based on its morphological characteristics, clearly becomes less aggressive. It would be difficult, however, to unambiguously determine if this is due only to the increasing patients' age or also to the increasing with age frequency of sporadic PTC.

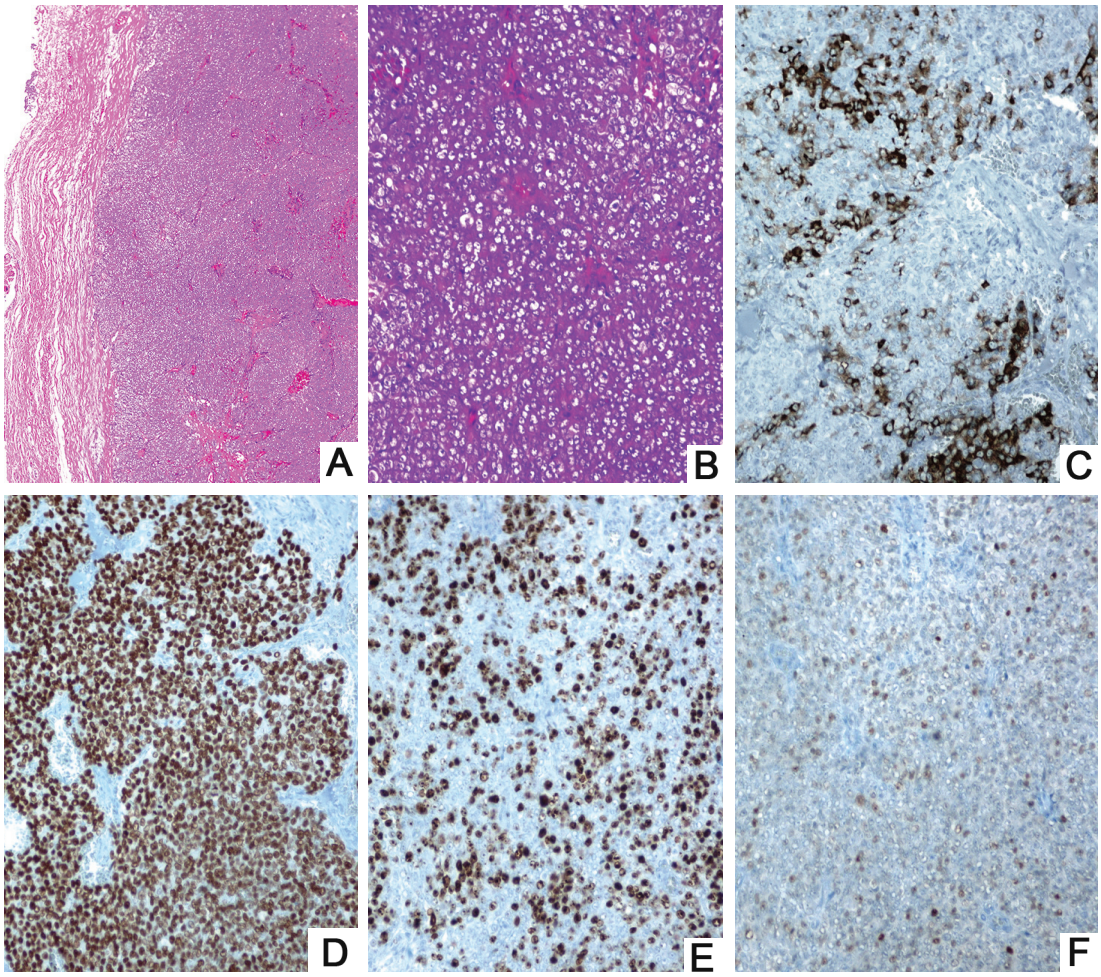

Figure 4.21. Lymph node metastasis of poorly differentiated thyroid carcinoma. (A) Metastasis of PDTC with the solid growth pattern completely replacing lymph node. Haematoxylin and eosin, original magnification x10-panoramic. (B) High-power image of the same section. Numerous nuclei with prominent nucleoli similar to those observed in the primary tumor. Haematoxylin and eosin, original magnification x100. (C) Focal immunostaining for thyroglobulin, original magnification x100. (D) Diffuse strong nuclear reactivity for TTF-1, original magnification x100. (E) Diffuse strong nuclear reactivity for Ki67. Original magnification x100. (F) Focal nuclear reactivity for TP53 showing labeling of 5% of the nuclei, original magnification x100.

As an attempt to at least partly answer this question, a comparative analysis of morphological characteristics of PTCs detected in age-matched groups of patients born before Chernobyl (radiogenic PTCs) and after Chernobyl (sporadic, non-radiogenic PTCs) will be performed. The next chapter describes the results of such analysis.

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