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Papillary Thyroid Cancer in Childhood and Adolescence with Specific Consideration of Patients After Radiation Exposure

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1. Introduction

Papillary thyroid carcinoma (PTC) in children and adolescents is a medical problem that attracts attention of investigators and clinicians primarily because of the high incidence of this malignancy in individuals exposed to radioactive isotopes of iodine in case of nuclear reactor emergencies. New facts uncovered by various research groups make it possible to see the clinical and pathological peculiarities of these tumours in a new light and suggest that the aetiology can modify the biological behaviour of PTC. In particular, relative monomorphism of the structure of post-Chernobyl cancers was detected and morphology varies depending on the patients' age and the time of radiation exposure (LiVolsi et al., 2011).

For 25 years now child and adolescent thyroid cancer patients with and without a history of radiation exposure were concentrated in the Republican Thyroid Cancer Centre in Minsk where they undergo diagnostics, treatment and follow-up (Demidchik et al., 2006). This presents a unique opportunity to compare cases depending on the presumed cancer aetiology and to analyze similarities and differences in the molecular-genetic background of carcinogenesis, morphological structure and extension of these tumours.

The purpose of this study was to look into PTC in childhood and adolescence. We analyzed children between 1 and 14 years of age and adolescents between 15 and 18 years of age who were not exposed to known carcinogenic risks such as irradiation and did not have any indications of hereditary thyroid cancers (e.g. specifically cribriform-morular architecture). The second group consisted of patients of the same age in whom second primary papillary cancers of thyroid developed during the surveillance for primary malignancies in other organs or systems that were treated with external irradiation and/or chemotherapy. The third group, containing the largest number of PTC cases, consisted of children and

adolescents with the history of exposure to radioactive isotopes of iodine in the framework of the Chernobyl Reactor Accident in 1986.

1.1 Epidemiology

Thyroid cancer is uncommon in childhood and adolescence. The incidence of all thyroid cancer types in children and adolescents varies from 0.04-0.17 per 100 000 in Ukraine, Germany, and Russia up to 0.54 in the USA (Hogan et al., 2009; Machens et al., 2010; Romanchishen et al., 2008; Tronko et al., 1999). The age-specific rates differ in paediatric age subgroups, for example, in Canada it is 0.2 per 100 000 children at the age of 5-9 years and 0.4 at the age of 10-14 years (O'Gorman et al., 2009), in USA 0.09 and 0.44 correspondingly (Hogan et al., 2009).

In Belarus, the incidence of thyroid carcinoma in children has been increasing since 1990 and a case-control study established a connection between this raise and the effect of the radioiodine that was released as a result of the Chernobyl accident (Astakhova et al., 1998; Kazakov et al., 1992; E.P. Demidchik et al., 1994, 2002; Yu.E. Demidchik et al., 2007). The highest rate of paediatric thyroid cancer was registered in 1995 at 3.29 per 100 000 for the whole country and 10.5 per 100 000 in southern regions of Belarus (e.g. Gomel). This was followed later by a marked decline of the age-standardized rate and was 0.14 per 100,000 (Savva et al., 2008). The proportion of PTC amid thyroid malignancies in the childhood population of Belarus was 87% in 1989-1997 (Steliarova-Foucher et al., 2006). It need to be clarified that after the demise of follicular carcinoma (major revision was done as the criteria that were used in soviet pathology practice since 1960es were abandoned after the training under supervision of leading westerner thyropathologists at the beginning of 1990es) the real numbers of PTC is close to 100%.

However, even more recently (2005-2008) the thyroid carcinoma incidence rate (IR) in patients under 18 in Belarus amounts to 1.29 per 100 000. Thus, paediatric thyroid cancer incidence is still high in Belarus among radiation-exposed and unexposed patients (Fig.1).

The majority of studies addressing the clinical and pathological characteristics of childhood thyroid carcinoma have reported on less than 100 cases, even if all types of thyroid cancer (sporadic, radiogenic and genetically determined) were included (Dinauer et al., 1998; Grigsby et al., 2002; Machens et al., 2010; O'Gorman et al., 2010). Moreover, some studies extended the patients' age to 19 and 20 (Dinauer et al., 1998; Romanchishen et al., 2008) and thus only partially meet the criteria of childhood thyroid cancer.

2. Diagnostics

In Belarus, mass screening using mobile teams and prophylactic examinations in schools and outpatient clinics was started in 1987. Prior to 1987 the diagnosis of thyroid disease was based primarily on clinical evaluation with particular attention to risk factors, which clinicians took into account: the history of radiation exposure, genetic predisposition, age, gender, lymph nodes status, tracheal or vascular pressure symptoms, recurrent nerve palsy and thyroid nodule features (size, consistency and fixation). Currently in Belarus, thyroid carcinomas in the exposed population are frequently diagnosed using screening by ultrasound and fine needle aspiration biopsy. This method allows detection of small thyroid

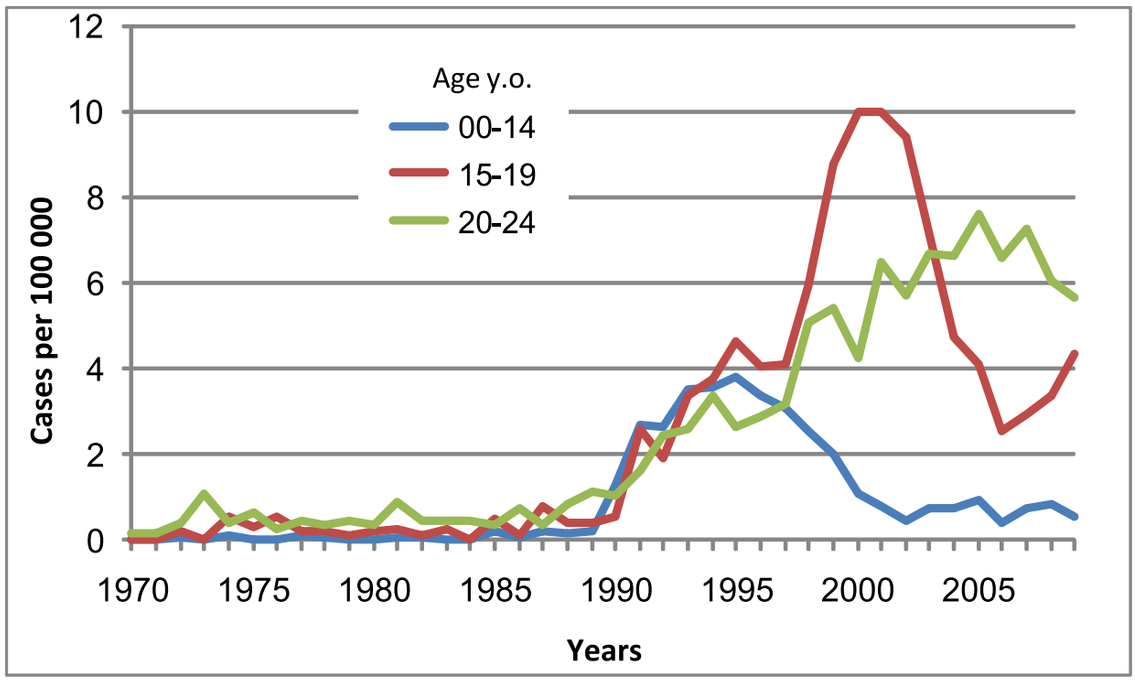


Fig. 1. Annual incidence (per 100 000) of thyroid cancer in Belarus

nodules, including microcarcinomas. Reported sensitivity, accuracy and specificity of this approach are equal to 90-100%, 80-95% and 80-100% respectively in cases of papillary carcinomas. Follicular carcinomas can rarely be diagnosed outright by ultrasound-guided fine needle aspiration biopsy as even positive data are reliable in less than 10% of cases (Chang et al., 2006; Sangalli et al., 2006; Florentine et al., 2006)

The evaluation of patients with thyroid nodules included determining possible predisposing factors, evaluation of present complaints, clinical findings, thyroid function tests, thyroglobulin (Tg) levels, anti-TPO, anti-microsomal and anti-Tg antibodies, imaging procedures (cervical ultrasound scan, chest radiograph, computed tomography scan), and the cytological findings yielded with fine needle aspiration cytology. One diagnostic problem was determining the presence of thyroid cancer in the presence of coexisting multinodular goiter. These patients usually received TSH suppressive therapy with levothyroxine. Dynamic ultrasound examination permitted recognizing structural changes such as enlargement of thyroid nodules or enlarged neck lymph nodes. These signs were suspicious of malignancy. Symptomatic patients usually complained of a neck mass (12.3%). Less commonly (2.8%) there were signs of hypothyroidism. In only 0.5% of cases were symptoms of advanced carcinoma (as e.g. hoarseness or problems with swallowing) recorded.

Preoperative work-up of patients suspected to have thyroid cancer included staging by computed tomography, MRI, thyroid scintigraphy with ^{131}I and serum thyroglobulin measurements. Typically, intraoperative frozen sections made it possible to diagnose the majority of papillary carcinomas.

PTC got its name because of its peculiarity to build papillary structures like cauliflower vegetations, connective tissue stalks which have small blood and lymphatic vessels. There is also frequent connection of classic papillary formations with zones of follicular and solid structures, besides there are some carcinomas in which there are no papillas at all.

Classification of PTC is made up taking into consideration various principles. Due to the peculiarities of tumour architecture investigators point out papillary, follicular, solid (solid-alveolar) and combined variants of structure. If we delved deeply from tissue to cell level, PTC can be classified according to the ability of cytoplasm stained by hematoxylin and eosin (common, clear and oxyphilic variants) and according to nuclear - cytoplasmic correlation (tall and columnar cell variants). At last, PTC can be divided according to the size (microcarcinoma) and growth essentials (solitary, multifocal and diffuse forms).

Many investigators tried to correlate clinical and morphological signs taking into consideration variants of PTC according to the WHO histological classification. For instance, the thyroid tumours that were discovered after the Chernobyl nuclear accident were virtually all of the papillary type (95%). Within the papillary group several subtypes were noted including classical or usual type, follicular and solid variants and mixed patterns. Diffuse sclerosing distribution, cribriform/morular type and Warthin-like variant were rare. No tall cell or columnar cell forms were identified (LiVolsi, 2011). To our opinion a potential bias of this conclusion lays in interobserver variability and lack of distinct borders for designation of this or that PTC variant. Thus, before comparing different forms of thyroid cancer in children and adolescents, it is necessary to dwell on definitions which were used in reports and subsequent analysis of the material.

Classical PTC is characterized by the formation of papillae made up of fibrovascular cores lined by one or two layers of neoplastic cells with a distinctive set of nuclear features which includes enlargement, elongation, clearing, thickened nuclear membranes, intranuclear cytoplasmic pseudoinclusions, nuclear grooves and small nucleoli closely opposed to the nuclear membrane. This pattern was usually mixed with the solid and follicular areas (DeLellies, R.A. & Williams, 2004).

The follicular variant of papillary thyroid carcinoma is almost exclusively arranged in follicles (without papillae formation but small solid areas are not unusual) lined by cells with characteristic PTC nuclei and usually presents as an encapsulated or circumscribed tumour with pushing borders and less commonly as a partially/non-encapsulated infiltrative neoplasm.

The solid variant is recognized by predominantly solid areas or a nested pattern of growth with prominent intratumoural capillary networks. These represent more than 50% of the tumour mass and can be associated with the follicular structures and even classic papillary vegetations.

Tall-cell variant (TCV) of papillary thyroid carcinoma is defined as being composed largely of tall cells with height at least twice the width and eosinophilic cytoplasm as well as basally oriented nuclei (many of them contain large intranuclear cytoplasmic eosinophilic pseudoinclusions). These cells represent 50% or more of the papillary carcinoma cells to make the diagnosis of tall cell variant (Morris et al., 2010). In paediatric cases we have seen predominantly follicular and solid areas composed of tall-cell PTC nuclei.

Diffuse sclerosing variant of PTC (DSV) is characterized by diffuse involvement of one or both lobes, extensive sclerosis, numerous psammoma bodies, typical papillary carcinoma elements, widespread squamous metaplastic changes and dense lymphocytic infiltration. Some cases had dominant tumour mass of conventional papillary carcinoma with prominent fibrosis. We observed formed lymphoid follicles, intensive lymphoplasmacytic infiltration, diffuse scattered psammoma bodies and tumour emboli in lymphatic channels and in surrounding normal-looking thyroid gland. These particular tumours more likely represent the early phase of classical DSV. In our investigation we define such designation as 'beginning'DSV or monofocal PTC with DSV-like intrathyroidal dissemination.

Diagnostic criteria for extrathyroidal extension and multifocal growth are important for staging of the disease. Some pathologists believe that the presence of adipose tissue within the normal thyroid gland and its pseudocapsule implies that thyroid carcinoma complexes within fat tissue cannot be accepted as a criterion of extrathyroidal extension (Mete O. et al., 2010). To skip controversies surrounding diagnostic criteria we divided extrathyroidal extension in tables as in a case of invasion of skeletal muscle and fat tissue as well. The differences in estimation of the prevalence of multifocality across studies may be explained by the conflicting definitions used for multifocality and multicentricity. This inconsistency makes it difficult to analyze the literature on the subject. Some professionals consider tumour emboli in lymphatic channels as 'multifocality'. To our opinion, this phenomenon should be diagnosed only in true multicentric transformation of the follicular epithelium (in case of independent clonal proliferations). Some situations are difficult to interpret without molecular investigation but tumours that differ from each other by anatomical sites and/or morphological structure and accompanied by fibrosis we define as multifocal. On the other hand, glands with a large clinical papillary cancer and multiple small intrathyroidal foci are 'lymphatic spread'.

3. Treatment

Optimal treatment of thyroid cancer in patients of any age includes surgery, radioiodine therapy for ablation of the thyroid remnant or treatment of distant metastases and levothyroxine suppressive therapy (Reiners & Demidchik, 2003; Luster et al., 2007; Reiners et al., 2008, 2009).

Patients with the history of exposure to radiation are considered as a high risk group (Clark, 2005). This point of view is based on the assumption that radionuclides of iodine affect the whole thyroid gland with an increased risk of multifocality. Therefore, the risk of tumour relapse in the thyroid remnant after partial resection is theoretically higher than in patients with sporadic carcinomas. There are many studies about the technique of operative intervention in patients with thyroid cancer. Today, prognostic factors for this disease have been carefully studied and treatment methods have been improved. Total thyroidectomy is considered the procedure of choice in patients with multifocal cancers, large tumour size, extrathyroidal extension and regional or distant metastasis. One important reason for recommending a total thyroidectomy is to faciliatate the ablation of the thyroid remnant and treatment of local or distant metastases with radioiodine (Luster et al., 2007; Reiners, 2009). Survival rates and quality of life of patients after surgical treatment remain high even in those cases when the findings at surgery reveal invasive carcinomas with involvement of

adjacent organs and tissue structures of the neck (Gilliland et al., 1997, Lerch et al., 1997, Schlumberger, 2001, Shaha et al., 1997).

4. Comparative clinical and morphological analysis of sporadic papillary thyroid cancer, PTC as second malignancy and post-Chernobyl PTC

We define cancers as possibly radiation induced that developed in patients exposed to radioiodine in the context of the Chernobyl accident (this process was completed by June 1986). Therefore, for all patients in the sporadic group born after February 1987 (the eldest of which was 18 in 2005), the fall-out from Chernobyl likely did not play a role in thyroid carcinogenesis (LiVolsi et al., 2011). As a third group, we consider patients with second primaries of the thyroid that developed after treatment for another preceding primary malignancy. In the context of thyroid cancer external irradiation and probably the effect of chemotherapeutic agents for the combined therapy of hemoblastosis and other neoplasms in childhood have to be taken into consideration (Acharya et al., 2003; LiVolsi et al., 2011; Naing et al., 2009; Seaberg et al., 2005; Taylor et al., 2009).

4.1 Sporadic cancer

We analyzed 150 children and adolescents who had sporadic PTC (118 girls and 32 boys - 3.7:1 - aged from 4 to 18 years inclusively). Most patients underwent total thyroidectomy (126; 84.0%) or lobectomy (21; 14.0%) with simultaneous lymph node removal (133; 88.7%) on one or both sides of the neck. Lymph node central neck dissection included excision of level VI; bilateral selective or modified radical neck dissection was also performed (levels II – V). The number of removed lymph nodes varied from 1 to 87. In the latter part of the study the majority of patients (83; 55.3%) received radioiodine therapy for thyroid remnant ablation (75; 50.0%) with an average activity of 3.7 (0.31-9.44) GBq. In patients with lung metastases (8; 5.3%) a higher average activity of 7.42 (5.5-12.89) GBq of radioiodine was delivered. In all children and adolescents, TSH suppressive therapy was used as part of the treatment. The average follow-up time for patients in this group was 66.0 months (29.7-303.3).

Clinical and pathologic data on 150 patients with sporadic PTC is presented in Table 1.

The median size of sporadic carcinoma tumour nodules was 12 (1-100) mm both for children and adolescents. Total involvement of thyroid gland was observed among the patients that suffered from diffuse sclerosing PTC and the maximum tumour size made up 100 mm. The tumour dimension surpassed 10 mm in 49 (62.8%) of children and 43 (59.7%) adolescents. Lung metastases (children; 8 cases, 10.3%) and multifocal growth (children and adolescents, 5 cases, 3.3%) were rare.

Classical type of PTC that included pure papillary or mixture of patterns dominated both in children (25; 32.1%) and adolescents (36; 50.0%) followed by follicular and tall cell variants. Extrathyroidal extension took place in one of every three patients (children and adolescents, 49; 32.7%). PTC involved veins (29; 19.3%) and lymph vessels (120; 80.0%) in one of every five children and adolescents (tumour complexes and/or psammoma bodies, 4 of 5 cases).

PTC was more likely to develop in the background of asymptomatic autoimmune thyroiditis that was evenly distributed in all age groups (21 of 78 children, 26.9%; 17 of 72 adolescents, 26.4%).

	Age groups, years at presentation		Total (n=150)
	4-14 years (n=78)	15-18 years (n=72)	
Age at diagnosis, mean± SD	11.8±2.2	16.1±1.0	13.8±2.8
Gender (girls: boys)	2.5:1	6.2:1	3.7:1
girls	56 (71.8%)	62 (86.1%)	118 (78.7%)
boys	22 (28.2%)	10 (13.9%)	32 (21.3%)
Tumour size, mm median (range)	12.0 (1-100)	11.5 (3-58)	12.0 (1-100)
≤10 mm	29 (37.2%)	29 (40.3%)	58 (38.7%)
1-5 mm	5(6.4%)	12 (16.7%)	17 (11.4%)
6-10 mm	24 (30.8%)	17 (23.6%)	41 (27.3%)
≥11 mm	49(62.8%)	43(59.7%)	92(61.3%)
Localization			
Subcapsular	36 (46.2%)	18 (25.0%)	54 (36.0%)
Inside lobe	37 (47.4%)	46 (63.8%)	83 (55.4%)
Isthmus	5 (6.4%)	8 (11.2%)	13 (8.6%)
Local spreading, N0:	19(24.3%)	23 (31.5%)	42 (28.0%)
intrathyroidal	10 (12.8%)	15 (20.8%)	25 (16.7%)
extrathyroidal	4 (5.1%)	4 (5.6%)	8 (5.3%)
not reported, pTx	5 (6.4%)	4 (5.6%)	9 (6.0%)
Regional spreading, N+:	59(75.7%)	49 (68.0%)	108 (72.0%)
N1a	10 (12.8%)	17 (23.6%)	27 (18.0%)
N1b	49 (62.8%)	32 (44.4%)	81 (54.0%)
N1b unilateral	31(39.7%)	28 (38.9%)	59 (39.3%)
N1b bilateral	18(23.1%)	4 (5.6%)	19 (12.7%)
Distant metastases, M1 (lungs)	8 (10.3%)	0	8 (5.3%)
Tumour histology (predominant architecture):			
Papillary	28 (35.9%)	31 (43.0%)	59 (39.3%)
Follicular	29 (37.2%)	28 (38.9%)	57 (38.0%)
Solid	21 (26.9%)	13 (18.1%)	34 (22.7%)
Histological types:			
Classical PTC	25 (32.1%)	36 (50%)	61 (40.7%)
Follicular	16 (20.5%)	15 (20.9%)	31 (20.7%)
Diffuse sclerosing (DSV)	5 (6.4%)	4 (5.5%)	9 (6.0%)
Monofocal with diffuse sclerosing involvement (DSV-like)	10 (12.8%)	2 (2.8%)	12 (8.0%)
Tall cell	11 (14.1%)	8 (11.1%)	19 (12.6%)
Solid	11 (14.1%)	7 (9.7%)	18 (12.0%)
Multifocal growth	3 (3.9%)	2 (2.8%)	5 (3.3%)
Morphological specifications:			
Infiltrative growth	57 (73.1%)	54 (75.0%)	111 (74.0%)
1. Intrathyroidal (pT1-T2)	17 (21.8%)	20 (27.8%)	37 (24.7%)
2. Extrathyroidal extension (pT3)	31 (39.7%)	18 (25.0%)	49 (32.7%)
in fat tissue	29 (37.2%)	16 (22.2%)	45 (30.0%)
in muscle	2 (2.5%)	2 (2.8%)	4 (2.7%)
3. pTx	9 (11.5%)	16 (22.2%)	25 (16.7%)

circumscribed/encapsulated growth (pT1, pT2, pTx)	7 (9.0%)	11 (15.3%)	18 (12.0%)
Diffuse involvement (DSV and DSV-like – pT1-pTx)	14 (17.9%)	7 (9.7%)	21 (14.0%)
Intratumoural fibrosis:			
Focal	48 (52.0%)	37 (51.4%)	85 (56.7%)
Septal	6 (8.0%)	13 (18.1%)	19 (12.7%)
Massive (central scarring)	25 (32.0%)	19 (26.4%)	44 (29.3%)
Blood vessels involvement	20 (25.6%)	9 (12.5%)	29 (19.3%)
Lymph vessels involvement	66 (84.6%)	54 (75%)	120 (80%)
Nodular type of mononuclear infiltration	20 (25.6%)	13 (18.0%)	33 (22.0%)
Sparse mononuclear infiltration	35 (44.9%)	39 (54.2%)	74 (49.3%)
Comorbidity:			
Autoimmune thyroiditis	21 (26.9%)	17 (26.4%)	38 (25.3%)
Follicular adenoma	0	3 (4.2%)	3 (2.0 %)
Nodular goitre	0	4 (5.5%)	4 (2.7%)
Treatment:			
Surgical:			
Total thyroidectomy	65 (83.3%)	61 (84.7%)	126 (84.0%)
Lobectomy	13 (16.7%)	8 (11.1%)	21 (14.0%)
Resection	0	3 (4.2%)	3 (2.0%)
Neck dissection	67(85.9%)	66(91.7%)	133(88.7%)
Number of dissected cervical lymph nodes /N+ median (range)	26 (2-87)/4 (1-77)	22 (1-65)/1 (1-18)	24 (1-87)/3 (1-77)
I-131 therapy:			
ablation (GBq)	n=41	n=34	n=75
median (range)	4.0 (0.61-9.44)	3.48 (0.31-6.7)	3.7 (0.31-9.44)
treatment for lung metastases (GBq), median (range)	n=8 7.42 (5.5-12.89)	-	n=8 7.42 (5.5-12.89)
Follow-up, months median (range)	79.35 (29.72-303.25)	57.22 (29.69-102.9)	66.03 (29.69-303.25)

Table 1. Clinical and pathologic features of sporadic PTC

The distribution of TNM tumour stages according to tumour size of sporadic PTC is shown in Table 2.

The most striking feature of this comparison is the high rate of extrathyroidal extension (patients in pT3 stage observed in 40.0%) and lymph node metastases (N1 discovered in 72.0%). However, it is easy to understand that even small tumours within the size of up to 10 mm corresponding to a volume of 0.5 ml which is too large to be harboured in the small thyroid lobe of a young child with a volume of less than 2 ml (Farahati et al., 1999).

The inability to define the T-category (pTx observed in 36 patients. 24.0%) can largely be attributed to surgeons or pathologists sectioning the specimen prior to it being properly processed. This fact draws attention to the necessity to follow strict rules while dealing with thyroid carcinomas and illustrates the need for standardization of sampling: removed parts

pT/tumour size	N0	N1a	N1b	Total	M0	M1
T1a (1-10mm)	14 (9.3%)	10 (6.7%)	9 (6.0%)	33 (22.0%)	33 (22.0%)	0
1-5mm	6 (4.0%)	5 (3.3%)	2 (1.0%)	13 (8.7%)	13 (8.7%)	0
6-10mm	8 (5.3%)	5 (3.3%)	7 (4.7%)	20 (13.3%)	20 (13.3%)	0
pT1b(11-20mm)	9 (6.0%)	2 (1.0%)	8 (5.3%)	19 (13.0%)	19 (13.0%)	0
pT2 (21-40mm)	2 (1.0%)	0	0	2 (1.0%)	2 (1.0%)	0
pT3	8 (5.3%)	8 (5.3%)	44 (29.3%)	60 (40.0%)	52 (34.7%)	8 (5.3%)
1-10mm	3 (2.0%)	5 (3.3%)	9 (6.0%)	17 (11.3%)	16 (10.7%)	1 (0.6%)
≥11 mm	5 (3.3%)	3 (2.0%)	35 (23.3%)	43 (28.7%)	36 (24.0%)	7 (4.7%)
pTx	9 (6.0%)	7 (4.7%)	20 (13.3%)	36 (24.0%)	36 (24.0%)	0
1-10mm	3 (2.0%)	2 (1.0%)	4 (2.7%)	9 (6.0%)	9 (6.0%)	0
≥11 mm	6 (4.0%)	5 (3.3%)	16 (10.7%)	27 (18.0%)	27 (18.0%)	0
n (%)	42 (28.0%)	27 (18.0%)	81 (54.0%)	150 (100%)	142 (94.7%)	8 (5.3%)

Table 2. Tumour size, lymph node and distant metastases in children and adolescence with sporadic PTC (according to AJCC/UICC TNM. 7th edition)

of the thyroid gland should be sectioned by the pathologist only along cephalocaudal axis (from the upper to the lower pole in vertical plane).

4.2 Second primary thyroid cancer

There were 34 patients with the second primary malignant thyroid tumour in the follow-up period from 1995 to 2010, where PTC was detected in 32 individuals (94.1%). One person had medullary carcinoma and the other one suffered from poorly differentiated cancer.

Only 23 from 32 cases of PTC (10 girls and 13 boys) were enrolled into the study because the tumour in the thyroid gland was diagnosed at the age of 8-18 years. In seven cases primary metachronous papillary cancer developed when the patients were aged 19-32 years. Finally, two adolescents underwent treatment for brain neoplasms (astrocytoma and medulloblastoma) at the age of 4-8 and were excluded from the study due to the fact that thyroid tumours had cribriform morular structures (generative mutation of APC-gene, Turcot syndrome, was detected in 1 case).

The first primary malignancy was detected in the patients at a median age of 4.7 years (1-12 years). Median latent period till the second tumour (thyroid cancer) was 9.2 years (4-16 years).

Treatment for the first malignant neoplasm (hemoblastosis, sarcoma, medulloblastoma) was provided in accordance with the standard protocols. External irradiation was used in all the cases (the total absorbed doses for the primary tumour varied from 12 to 54 Gy). Surgical and postoperative treatment of thyroid carcinomas was also standardized: as a rule, total thyroidectomy (21; 91.4%) with bilateral neck dissection (in 21 of 23 patients. 91.3%) was performed. Thirteen patients underwent from 1 to 4 ablative courses of radioiodine therapy (average activity 4.36 GBq, 0.3-7.8 GBq). In one case a patient who was previously treated for Hodgkin's lymphoma at the age of 3.6, five years later the diffuse sclerosing variant of PTC (pT3N1bM1) with distant metastases to lungs was diagnosed and treated with 4 courses of radioiodine therapy (13.6 GBq) after surgery.

Eleven of 23 patients with secondary papillary cancer had been treated previously for malignant lymphoma (9 patients with Hodgkin's disease). In seven patients leukaemia was the primary malignancy (acute myeloblastic leukaemia was diagnosed in one patient who died of sepsis which was in progress while treating the third recurrence of hemoblastosis). Acute lymphoblastic leukemia was diagnosed in six patients. These data are in accordance with the observation that the risk of second primary malignancy in the thyroid is much higher if Hodgkin disease, non-Hodgkins lymphoma or leukemia has been the primary malignancy (Meadows et al., 2009). One patient with medulloblastoma was cured. Three more girls and one boy had soft tissue malignancies of the head, neck and urinary bladder. The last patient was diagnosed with embryonal rhabdomyosarcoma of the urinary bladder which was detected at the age of 1.4. He then developed an astrocytoma of the brainstem 14 years later and PTC was detected two years after brain tumour at the age of 17.

For patients who developed PTC after treatment for lymphoma, the latent period from completion of lymphoma treatment till verification of papillary thyroid cancer was 8.6 years (5 to 13 years). The median period until the development of PTC for the patients with leukemia was 6.9 years (4 to 12 years) and for patients with soft tissue tumours the latency was a median of 14.0 years (10 to 16 years).

As a rule, thyroid malignancies are likely to develop after irradiation of the neck. However, combined treatment was carried out in the case of embryonal rhabdomyosarcoma of urinary bladder (according to the protocol CWS-91), which consisted of irradiation of the suprapubic area with a total absorbed dose of 40 Gy and chemotherapy with vincristine, doxorubicin, cyclophosphamide, actinomycin D and ifosfamide. In 1992 it may have been impossible to provide complete protection of the neck while irradiating a one-year old child, and this may have contributed to the development of papillary thyroid carcinoma after 16 years, though alternative hypotheses must also be considered.

It should be noted that one patient was subjected to unusual aggressive external irradiation. This female was diagnosed to have aggressive fibromatosis involving soft tissues around right scapulae in May 1985 that was removed. Then, from January to March 1986, the patient was treated for tumour relapse (three lumps 5x4, 6x6 and 4x3cm) which required removal of the medial part and lower corner of the right scapular bone, right sided VI-VIII ribs and adjacent soft tissues. In addition, postoperative irradiation was carried out with 40 Gy at the right scapula and 16 Gy at the left supraclavicular area (February-March 1986). In April 1986, new nodule of irregular shape in soft tissues of lumbar spine was detected with the size of 8x1.5 cm. After radiation therapy with the dose of 60 Gy (15/04-19/05 1986) the tumour became 5x3.5 cm. In July of the same year besides a paravertebral tumour located in soft tissues at level D10-D11 another tumour 6x5.5 cm appeared in the area of medial side of the left scapula. The patient was exposed to irradiation again with the dose of 46 Gy. In November 1996, a tumour in the right lobe of thyroid gland was detected and lobectomy with isthmus resection was carried out (follicular thyroid cancer with minimal invasion of the capsule was diagnosed; later it was reclassified as a follicular variant of PTC).

A few relapses of desmoid tumour still took place: nodules in gluteus on the right and left sides (removed and irradiated with a dose of 60 Gy), a lump in the right thigh treated with

hyper fractionated external beam therapy with a total absorbed dose of 25 Gy. The area of the right thigh and iliac nodes additionally were irradiated with 60 Gy. The patient then got chemotherapy with cyclophosphamide (1500 mg) and cisplatin (120 mg) from October 1998 to March 1999 (4 courses). The treatment failed to stabilize the progress, and there were further relapses in 2001 and 2006 that led to surgical excision of the long head of the right side biceps (nodule 7.5x6.0x2.8 cm) and consecutive radiotherapy with 40 Gy again. At present, there is no progression of both tumours and the patient gets substitutive hormonal treatment for thyroid carcinoma.

Clinical and pathologic data for the 23 patients with PTC as a second primary malignancy are presented in Table 3.

Characteristics	Age groups, years at presentation		Total (n=23)
	4-14 years (n=10)	15-18 years (n=13)	
Age at diagnosis.			
mean± SD	11.0±2.0	16.3±1.2	14.0±3.1
Sex (girls: boys)	1:1	1:1.6	1:1.3
girls	5 (50%)	5 (38.5%)	10 (43.5%)
boys	5 (50%)	8 (61.5%)	13 (56.5%)
Tumour size, mm			
median (range)	10 (8-50)	10 (3-45)	10 (3-50)
≤10 mm	6 (60%)	8 (61.5%)	14 (60.9%)
1-5 mm	0	2 (15.4%)	2 (8.7%)
6-10 mm	6 (60%)	6 (46.1%)	12 (52.2%)
≥11 mm	4 (40%)	5 (38.5%)	9 (39.1%)
Localization:			
Subcapsular	6 (60%)	8 (61.5%)	14 (60.9%)
Inside lobe	2 (20%)	5 (38.5%)	7 (30.4%)
Isthmus	2 (20%)	0	2 (8.7%)
Local spreading, N0:	1 (10%)	5 (38.5%)	6 (26.1%)
intrathyroidal	1 (10%)	3 (23.1%)	4 (17.4%)
extrathyroidal	0	2 (15.4%)	2 (8.7%)
not-reported, pTx	0	0	0
Regional spreading, N+:	9 (90%)	8 (61.5%)	17 (73.9%)
N1a	5 (50%)	5 (38.5%)	10 (43.5%)
N1b	4 (40%)	3 (23.1%)	7 (30.4%)
N1b unilateral	3 (30%)	3 (23.1%)	6 (26.1%)
N1b bilateral	1 (10%)	0	1 (4.3%)
Distant metastases, M1 (lungs)	1 (10%)	0	1 (4.3%)
Tumour histology (predominant architecture):			
Papillary	3 (30%)	6 (46.2%)	9 (39.1%)
Follicular	5 (50%)	6 (46.2%)	11 (47.8%)
Solid	2 (20%)	1 (7.7%)	3 (13.1%)
Histological types:			
Classical PTC	4 (40%)	4 (30.8%)	8 (34.8%)
Follicular	2 (20%)	3 (23.1%)	5 (21.7%)
Diffuse sclerosing (DSV)	1 (10%)	1 (7.7%)	2 (8.6%)
Monofocal with diffuse sclerosing involvement	1 (10%)	1 (7.7%)	2 (8.6%)

Characteristics	Age groups, years at presentation		Total (n=23)
	4-14 years (n=10)	15-18 years (n=13)	
(DSV-like)			
Tall cell	0	3 (23.1%)	3 (13%)
Solid	2 (20%)	1 (7.7%)	3 (13%)
Multifocal growth	0	0	0
Morphological specifications:			
Infiltrative growth	8 (80%)	8 (61.5%)	16 (69.8%)
1. Intrathyroidal (pT1-T2)	2 (20%) 6 (60%)	1 (7.7%) 7 (53.9%)	3 (13%) 13 (56.8%)
2. extrathyroidal extension (pT3)	6 (60%)	7 (53.9%)	13 (56.8%)
in fat tissue	0	0	0
in muscle			
circumscribed/encapsulated growth	0	3 (23.1%)	3 (13%)
Diffuse involvement (DSV and DSV-like)	2 (20%)	2 (15.4%)	4 (17.2%)
Intratumoural fibrosis:			
Focal	4 (40%)	7 (53.9%)	11 (47.8%)
Septal	3 (30%)	3 (23.1%)	6 (26.1%)
Massive (central scarring)	3 (30%)	1 (7.7%)	4 (17.2%)
Blood vessel involvement	5 (50%)	3 (23.1%)	8 (34.8%)
Lymph vessel involvement	9 (90%)	9 (69.3%)	18 (78.3%)
Nodular type of mononuclear infiltration	2 (20%)	2 (15.4%)	4 (17.2%)
Sparse mononuclear infiltration	6 (60%)	11 (84.7%)	17 (73.9%)
Comorbidity:			
Autoimmune thyroiditis	0	0	0
Follicular adenoma	0	0	0
Nodular goitre	0	1 (7.7%)	1 (4.3%)
Treatment			
Surgical:			
Total thyroidectomy	10 (100%)	11 (84.7%)	21 (91.4%)
Lobectomy	0	1 (7.7%)	1 (4.3%)
Resection	0	1 (7.7%)	1 (4.3%)
neck dissection	10 (100%)	10 (77%)	20 (87%)
number of dissected cervical lymph nodes /N+ median (range)	21 (6-64)/5 (1-18)	13 (3-39)/1 (1-18)	19 (3-64)/3 (1-18)
Ablation (GBq) median (range)	n=7 4.36 (2.1-7.805)	n=6 4.59 (0.307-7.696)	n=13 4.36 (0.307-7.805)
Treatment for lung metastases (GBq), median (range)	13.352±NA	-	13.352±NA
Follow-up, months from the end of treatment for PTC median (range)	104.99 (84.2-171.85)	68.38 (18.15-186.64)	99.35 (18.15-186.54)

Table 3. Clinical and pathologic features of PTC as second primary malignancy

In sporadic cases of PTC (Table 1) the gender rate was different between children and adolescents with an increasing preponderance of females (from 2.5:1 to 6.2:1 accordingly). However, in second primary malignancies (females) these differences were not detected (1:1 in children, 1:1.6 in adolescents). Another divergence with sporadic PTC was the complete absence of autoimmune thyroiditis in second primary thyroid cancers. With respect to the other characteristics, PTC as a second primary malignancy presented very similar to sporadic PTC.

The distribution of TNM tumour stages according to tumour size of PTC as second primary malignancy is shown in Table 4.

pT/tumour size	N0	N1a	N1b	Total	M0	M1
T1a (1-10mm)	1 (4.3%)	2 (8.7%)	0	3 (13.0%)	3 (13.0%)	0
1-5mm	1 (4.3%)	1 (4.3%)	0	2 (8.7%)	2 (8.7%)	0
6-10mm	0	1 (4.3%)	0	1 (4.3%)	1 (4.3%)	0
pT1b (11-20mm)	3 (13.0%)	0	0	3 (13.0%)	3 (13.0%)	0
pT2 (21-40mm)	0	0	0	0	0	0
pT3	2 (8.7%)	8 (34.7%)	7 (30.4%)	17 (73.9%)	16 (69.6%)	1 (4.3%)
1-10mm	1 (4.3%)	6 (26.0%)	4 (17.4%)	11 (47.8%)	11 (47.8%)	0
≥11 mm	1 (4.3%)	2 (8.7%)	3 (13.0%)	6 (26.1%)	5 (21.7%)	1 (4.3%)
Total (%)	6 (26.0%)	10 (43.6%)	7 (30.4%)	23 (100.0%)	22 (95.7%)	1 (4.3%)

Table 4. Tumour size, lymph nodes and distant metastases in children and adolescents with PTC as second primary malignancy according to AJCC/UICC TNM. 7th edition

When comparing the extension of tumour disease in two groups (table 2 and 4) it should be noted that the majority of patients (74%) operated for sporadic PTC showed minimal extrathyroidal extension. The rate of local metastases was similar in both groups (72% vs. 74%). Organ metastases were only observed in cases with extracapsular spread of thyroid carcinoma.

4.3 Post-Chernobyl PTC

The victims of the Chernobyl disaster represent a quite homogenous cohort. There is a general agreement now that the minimal latent period for the development of radiation-induced thyroid cancer is approximately 4 years. The incidence of radiogenic thyroid carcinoma is higher in females (1.6:1). European findings also indicate that the number of cases of thyroid carcinoma in males is lower than in females (Farahati et al., 1997). The vast majority of radiation-associated thyroid cancers are PTC with a high incidence of extrathyroidal extension and lymph node metastases (49.1% and 64.6%, respectively). (Pacini et al., 1997; Williams et al., 2004; Williams et al.; 2008; Reiners et al. 2008).

Clinical and pathologic data of 908 patients with post-Chernobyl PTC are presented in Table 5.

As in the two previous groups, post-Chernobyl PTC cases are characterized by infiltrative growth (82.6%), a high rate of extrathyroidal extension (37.0%) and nodal metastases (74.4%). Multifocal growth was detected much more frequently (6.2%) than in children and adolescents with sporadic (3.3%) or second primary (0) carcinomas.

Characteristics	Age groups, years at presentation		Total (n=908)
	4-14 years (n=508)	15-18 years (n=400)	
Demographics Age at diagnosis, mean± SD	12.0±2.4	16.8±1.1	14.1±3.1
Gender (girls: boys)	1.6:1	2.0:1	1.88:1
girls	314 (61.8%)	266 (66.5%)	580 (63.9%)
boys	194 (38.2%)	134 (33.5%)	328 (36.1%)
Tumour size. mm median (range)	12 (1-85)	12 (1-124)	12 (1-124)
≤10 mm	199 (39.2%)	178 (44.5%)	377 (41.5%)
1-5 mm	16 (3.2%)	43 (10.7%)	59 (6.5%)
6-10 mm	183 (36.0%)	135 (33.8%)	318 (35.0%)
≥11 mm	309 (60.8%)	222 (55.5%)	531 (58.5%)
Localization:			
Subcapsular	245 (48.2%)	198 (49.5%)	443 (48.8%)
Inside lobe	239 (47.0%)	177 (44.3%)	416 (45.8%)
Isthmus	24 (4.8%)	25 (6.2%)	49 (5.4%)
Local spreading, N0:	124 (24.4%)	109 (27.2%)	233 (25.7%)
intrathyroidal	53 (10.4%)	73 (18.3%)	126 (13.9%)
extrathyroidal	22 (4.3%)	15 (3.7%)	37 (4.1%)
non-detected pTx	49 (9.6%)	21 (5.2%)	70 (7.7%)
Regional spreading. N+:	384 (75.6%)	291 (72.8%)	675 (74.4%)
N1a	217 (42.7%)	104 (26.0%)	321 (35.3%)
N1b	167 (32.9%)	187 (46.8%)	354 (39.1%)
N1b unilateral	137 (27.0%)	158 (39.5%)	295 (32.5%)
N1b bilateral	30 (5.9%)	29 (7.3%)	59 (6.5%)
Distant metastases, M1 (lungs)	75 (14.8%)	28 (7.0%)	103 (11.3%)
Tumour histology (predominant architecture):			
Papillary	138 (27.2%)	154 (38.5%)	292 (32.2%)
Follicular	253 (49.8%)	191 (47.8%)	444 (48.9%)
Solid	117 (23.0%)	55 (13.7%)	172 (18.9%)
Histological types:			
Classical PTC	200 (39.4%)	151 (37.8%)	351 (38.7%)
Follicular	158 (31.1%)	126 (31.5%)	284 (31.3%)
Diffuse sclerosing (DSV)	13 (2.6%)	13 (3.3%)	26 (2.9%)
Monofocal with diffuse sclerosing involvement (DSV-like)	26 (5.1%)	18 (4.5%)	44 (4.8%)
Tall cell	23 (4.5%)	45 (11.3%)	68 (7.5%)
Solid	88 (17.3%)	40 (10.0%)	128 (14.1%)
Clear cell	0	2 (0.5%)	2 (0.2%)
Oncocytic	0	5 (1.1%)	5 (0.6%)
Multifocal growth	22 (4.3%)	34 (8.5%)	56 (6.2%)

Characteristics	Age groups, years at presentation		Total (n=908)
	4-14 years (n=508)	15-18 years (n=400)	
Morphological specifications:			
Infiltrative growth	440 (86.6%)	310 (77.5%)	750 (82.6%)
1. Intrathyroidal (pT1-T2)	91 (17.9%)	106 (26.5%)	197 (21.7%)
2. extrathyroidal extension (pT3)	195 (38.4%)	141 (35.3%)	336 (37.0%)
in fat tissue	173 (34.1%)	136 (34.0%)	309 (34.0%)
in muscle	22 (4.3%)	5 (1.3%)	27 (3.0%)
3. pTx	154 (30.3%)	62 (15.5%)	216 (23.8%)
4. pT4	0	1 (0.2%)	1 (0.1%)
circumscribed/encapsulated growth (pT1, pT2, pTx)	29 (5.7%)	59 (14.8%)	88 (9.7%)
Diffuse involvement DSV and DSV-like (pT1-pTx)	39 (7.7%)	31 (7.7%)	70 (7.7%)
Intratumoural fibrosis:			
Focal	217 (42.7%)	188 (47.0%)	405 (44.6%)
Septal	86 (16.9%)	69 (17.3%)	155 (17.1%)
Massive (central scarring)	190 (37.4%)	128 (32.0%)	318 (35.0%)
Blood vessel involvement	105 (20.7%)	62 (15.5%)	167 (18.4%)
Lymph vessel involvement	442 (87.0%)	316 (79.0%)	758 (83.5%)
Nodular type of mononuclear infiltration	76 (15.0%)	63 (15.8%)	139 (15.3%)
Sparse mononuclear infiltration	394 (77.6%)	286 (71.5%)	680 (74.9%)
Comorbidity:			
Autoimmune thyroiditis	25 (4.9%)	43 (10.8%)	68 (7.5%)
Follicular adenoma	9 (1.8%)	10 (2.5%)	19 (2.1%)
Nodular goitre	16 (3.1%)	32 (8.0%)	48 (5.3%)
Surgical treatment:			
Total thyroidectomy	306 (60.2%)	315 (78.8%)	621 (68.4%)
Lobectomy	182 (35.9%)	76 (19.0%)	258 (28.4%)
Resection	20 (3.9%)	9 (2.3)	29 (3.2%)
Neck dissection	435 (85.6%)	349 (87.3%)	784 (86.3%)
Number of dissected cervical lymph nodes/N+ median	8 (1-61)/3 (1-44)	19 (1-95)/3 (1-46)	12 (1-95)/ 5 (1-46)
Ablation (GBq) median (range)	n=259 5.2 (0.4-28.1)	n=228 4.9 (0.3-40.4)	n=487 5.1 (0.3-40.4)
Treatment for lung metastases (GBq), median (range)	n=95 16.3 (1.2-52.9)	n=33 21.9 (2.4-60.5)	n=128 17.2 (1.2-60.5)
Follow-up, months median (range)	184.8 (122.5-270.0)	131.6 (68.1-253.9)	165.4 (68.1-270.0)

Table 5. Clinical and pathologic features of post-Chernobyl PTC

The distribution of TNM tumour stage according to tumour size of post-Chernobyl PTC is shown in the table 6.

pT/tumour size	N0	N1a	N1b	Total	M0	M1
T1a (1-10mm)	99 (10.9%)	46 (5.1%)	34 (3.8%)	179 (19.7)	178 (19.6%)	1 (0.1%)
1-5mm	47 (5.2%)	11 (1.2%)	5 (0.6%)	63 (6.9%)	63 (6.9%)	0
6-10mm 116	52 (5.7%)	35 (3.9%)	29 (3.2%)	116 (12.8%)	115 (12.7%)	1 (0.1%)
pT1b (11-20mm)	27 (3.0%)	30 (3.3%)	29 (3.2%)	86 (9.5%)	86 (9.5%)	0
pT2 (21-40mm)	1 (0.1%)	2 (0.2%)	3 (0.3%)	6 (0.7%)	6 (0.7%)	0
pT3-4	39 (4.3%)	136 (15.0%)	205 (22.6%)	380 (40.9%)	303 (33.3%)	77 (8.5%)
1-10mm	23 (2.5%)	48 (5.3%)	37 (4.1%)	108 (11.9%)	101 (11.1%)	7 (0.8%)
≥11 mm	16 (1.8%)	88 (9.7%)	168 (18.5%)	272 (29.0%)	202 (22.2%)	70 (7.7%)
pTx	67 (7.4%)	107 (11.8%)	83 (9.1%)	257 (28.3%)	232 (25.6%)	25 (2.8%)
1-10mm	36 (4.0%)	32 (3.5%)	22 (2.4%)	90 (9.9%)	85 (9.4%)	5 (0.6%)
≥11 mm	31 (3.4%)	75 (8.3%)	61 (6.7%)	167 (18.4%)	147(16.2%)	20 (2.2%)
n (%)	233 (25.7%)	321 (35.4%)	354 (39.0%)	908 (100%)	805 (88.7%)	103 (11.3%)

Table 6. Tumour size, lymph nodes and distant metastases in children and adolescents with post-Chernobyl PTC according to AJCC/UICC TNM. 7th edition

According to our data, 22.6% of our patients with post-Chernobyl PTC were treated in stage pT3N1b and nearly all cases with associated distant metastases belonged to this group.

4.4 Comparison of sporadic PTC, PTC as second primary cancer and post-chernobyl PTC

We analyzed pathologic peculiarities, associated with local carcinoma spread (Table 7) and metastases in lymph nodes (Table 8).

Thus, high risk of extrathyroidal extension in patients with sporadic PTC is associated with several morphological peculiarities:

1. Tumour size≥11 mm
2. Subcapsular localization
3. Diffuse sclerosing variant (classical)
4. Massive intratumoural fibrosis (central scarring)
5. Blood or/and lymph vessel involvement

In PTC as second primary malignancy, only lymph vessel involvement seems to be a predictor of the risk for extrathyroidal extension (however, we must bear in mind the small number of patients in this group). On the other hand, for post-Chernobyl PTC, extrathyroidal extension is correlated to many features:

1. Tumour size≥11 mm
2. Subcapsular or isthmus localization
3. Predominance of follicular structures
4. Diffuse sclerosing variant and monofocal papillary carcinoma with diffuse sclerosing involvement of the thyroid gland (DSV-like) as well
5. Infiltrative growth and/or diffuse involvement (DSV and DSV-like)
6. Massive intratumoural fibrosis (central scarring)

Pathology	**sporadic PTC**			**second primary PTC**			**post-Chernobyl PTC**		
	pT-stage			pT-stage			pT-stage		
	T1&T2 (n=54)	T3&T4 (n=60)	P value	T1&T2 (n=6)	T3&T4 (n=17)	P value	T1&T2 (n=271)	T3&T4 (n=380)	P value
Tumour size:									
≥11 mm	22 (40.7%)	43 (71.7%)	0.0012	3 (50.0%)	6 (35.3%)	NS	92 (33.9%)	272 (71.6%)	< 0.0001
Localization (dominant):									
Subcapsular	11 (20.4%)	31 (51.7%)	0.0008	3 (50.0%)	11 (64.7%)	NS	74 (27.3%)	270 (71.1%)	< 0.0001
Inside lobe	40 (74.1%)	21 (35.0%)	< 0.0001	3 (50.0%)	4 (23.4%)	NS	188 (69.4%)	82 (21.5%)	< 0.0001
Isthmus	3 (5.5%)	8 (13.3%)	NS	0	2 (11.8%)	NS	9 (3.3%)	28 (7.4%)	0.0380
Tumour histology, dominate architecture:									
Papillary	25 (46.3%)	20 (33.3%)	NS	3 (50.0%)	6 (35.3%)	NS	109 (40.2%)	102 (26.8%)	0.0004
Follicular	22 (40.7%)	25 (41.7%)	NS	3 (50.0%)	8 (47.0%)	NS	121 (44.7%)	204 (53.7%)	0.0260
Solid	7 (13.0%)	15 (25.0%)	NS	0	3 (17.7%)	NS	41 (15.1%)	74 (19.5%)	NS
Histological types:									
Classical	27 (50.0%)	20 (33.3%)	NS	3 (50.0%)	5 (29.2%)	NS	110 (40.6%)	127 (33.4%)	NS
Follicular	13 (24.1%)	12 (20.0%)	NS	3 (50.0%)	2 (11.8%)	NS	91 (33.6%)	127 (33.4%)	NS
Diffuse sclerosing(DSV)	0	9 (15.0%)	0.0030	0	2 (11.8%)	NS	0	18 (4.7%)	< 0.0001
Monofocal with diffuse sclerosing involvement (DSV-like)	3 (5.5%)	2 (3.4%)	NS	0	2 (11.8%)	NS	5 (1.8%)	20 (5.3%)	0.0365
Tall cell	6 (11.1%)	9 (15.0%)	NS	0	3 (17.7%)	NS	30 (11.1%)	27 (7.1%)	NS
Solid	5 (9.3%)	8 (13.3%)	NS	0	3 (17.7%)	NS	33 (12.2%)	59 (15.5%)	NS
Oncocytic	0	0	NS	0	0		2 (0.7%)	1 (0.3%)	NS
Clear cell	0	0	NS	0	0		0	1 (0.3%)	NS
Pathological specifications:									
Infiltrative growth	37 (68.5%)	49 (81.7%)	NS	3 (50.0%)	13 (76.5%)	NS	197 (72.7%)	337 (88.7%)	< 0.0001
circumscribed/ encapsulated growth	14 (26.0%)	0	< 0.0001	3 (50.0%)	0	0.0113	69 (25.5%)	5 (1.3%)	< 0.0001

Pathology	**sporadic PTC**			**second primary PTC**			**post-Chernobyl PTC**		
	pT-stage			pT-stage			pT-stage		
	T1&T2 (n=54)	T3&T4 (n=60)	P value	T1&T2 (n=6)	T3&T4 (n=17)	P value	T1&T2 (n=271)	T3&T4 (n=380)	P value
diffuse involvement (DSV and DSV-like)	3 (5.5%)	11 (18.3%)	NS	0	4 (23.5%)	NS	5 (1.8%)	38 (10.0%)	< 0.0001
Fibrosis									
focal intratumoural fibrosis	34 (63.0%)	27 (45.0%)	NS	1 (16.7%)	10 (58.8%)	NS	152 (56.1%)	145 (38.2%)	< 0.0001
septal	10 (18.5%)	3 (5.0%)	0.0365	2 (33.3%)	4 (23.5%)	NS	58 (21.4%)	54 (14.2%)	0.0203
massive (central scarring)	9 (16.7%)	29 (48.3%)	0.0004	1 (16.7%)	3 (17.7%)	NS	41 (15.1%)	173 (45.5%)	< 0.0001
Blood vessel involvement	5 (9.3%)	22 (36.7%)	0.0008	2 (33.3%)	6 (35.3%)	NS	22 (8.1%)	114 (30.0%)	< 0.0001
Lymph vessel involvement	31 (57.4%)	60 (100%)	< 0.0001	2 (33.3%)	16 (94.1%)	0.0078	169 (62.4%)	359 (94.5%)	< 0.0001
Mononuclear infiltration									
nodular type	9 (16.7%)	15 (25.0%)	NS	0	4 (23.5%)	NS	22 (8.1%)	76 (20.0%)	< 0.0001
sparse	32 (59.3%)	32 (53.3%)	NS	5 (83.3%)	12 (70.6%)	NS	213 (78.6%)	268 (70.5%)	0.0223
Autoimmune thyroiditis comorbidity	12 (22.2%)	10 (16.7%)	NS	0	0		26 (9.6%)	23 (6.1%)	NS

Table 7. The relationship between characteristics of the primary tumour and spread of sporadic, second-primary and post-Chernobyl PTC beyond the thyroid gland capsule (Note: N.S. – not significant)

7. Blood or/and lymph vessel involvement
8. Nodular type of mononuclear infiltration

In our opinion, the most intriguing finding is the association between radiogenic PTC and a predominantly follicular architecture with extrathyroidal extension. It should be mentioned that tumours with pure follicular, papillary or solid pattern had no preponderance for local spread beyond the thyroid gland but carcinomas of mixed structure did ($p<0.001$). In addition, if any follicular or solid formation was identified in the post-Chernobyl PTCs, it was also commonly associated with extrathyroidal extension ($p<0.001$ if solid structures appeared and $p=0.03$ for whichever size of follicular pattern). These differences may be explained by the molecular features of PTC in children and adolescents, as well as by peculiarities of tumour growth in young individuals.

High risk of metastases in regional lymph nodes in patients with sporadic PTC is associated with several morphological peculiarities:

1. Largely subcapsular localization
2. Diffuse sclerosing variant (classical)

Pathology	**sporadic PTC**			**second-primary PTC**			**post-Chernobyl PTC**		
	pN-stage		P value	pN-stage		P value	pN-stage		P value
	N0 (n=42)	N1 (n=108)		N0 (n=6)	N1 (n=17)		N0 (n=233)	N1 (n=675)	
Tumour size:									
≥11 mm	22 (52.4%)	70 (64.8%)	NS	4 (66.7%)	5 (29.4%)	NS	75 (32.2%)	456 (67.6%)	< 0.0001
Localization (dominant):									
Subcapsular	10 (23.8%)	44 (40.7%)	0.0008	3 (50.0%)	11 (64.7%)	NS	79 (33.9%)	364 (53.9%)	< 0.0001
Inside lobe	31 (73.8%)	52 (48.1%)	< 0.0001	3 (50.0%)	4 (23.4%)	NS	146 (62.7%)	270 (40.0%)	< 0.0001
Isthmus	1 (2.4%)	12 (11.2%)	NS	0	2 (11.8%)	NS	8 (3.4%)	41 (6.1%)	0.0380
Tumour histology/ dominate architecture:									
Papillary	9 (21.4%)	50 (46.3%)	NS	3 (50.0%)	6 (35.3%)	NS	52 (22.3%)	240 (35.5%)	0.0004
Follicular	24 (57.2%)	33 (30.6%)	NS	3 (50.0%)	8 (47.0%)	NS	137 (58.8%)	307 (45.5%)	0.0260
Solid	9 (21.4%)	25 (23.1%)	NS	0	3 (17.7%)	NS	44 (18.9%)	128 (19.0%)	NS
Histological types:									
Classical	13 (31.0%)	48 (44.4%)	NS	3 (50.0%)	5 (29.2%)	NS	73 (31.3%)	278 (41.2%)	NS
Follicular	16 (38.1%)	15 (13.9%)	NS	3 (50.0%)	2 (11.8%)	NS	104 (44.6%)	180 (26.7%)	NS
Diffuse sclerosing (DSV)	0	9 (8.3%)	0.0030	0	2 (11.8%)	NS	0	26 (3.9%)	< 0.0001
Monofocal with diffuse sclerosing involvement (DSV-like)	1 (2.4%)	11 (10.2%)	NS	0	2 (11.8%)	NS	3 (1.3%)	41 (6.1%)	0.0365
Tall cell	7 (16.7%)	12 (11.1%)	NS	0	3 (17.7%)	NS	14 (6.0%)	54 (8.0%)	NS
Solid	5 (11.8%)	13 (12.1%)	NS	0	3 (17.7%)	NS	36 (15.5%)	92 (13.6%)	NS
Oncocytic	0	0	NS	0	0		2 (0.9%)	3 (0.4%)	NS
Clear cell	0	0	NS	0	0		1 (0.4%)	1 (0.1%)	NS
Morphological specifications:									
Infiltrative growth	25 (59.5%)	86 (79.6%)	NS	3 (50.0%)	13 (76.5%)	NS	158 (67.8%)	592 (87.7%)	< 0.0001
circumscribed/ encapsulated growth	16 (38.1%)	2 (1.9%)	< 0.0001	3 (50.0%)	0	0.0113	72 (30.9%)	16 (2.4%)	< 0.0001

Pathology	sporadic PTC			second-primary PTC			post-Chernobyl PTC		
	pN-stage		P value	pN-stage		P value	pN-stage		P value
	N0 (n=42)	N1 (n=108)		N0 (n=6)	N1 (n=17)		N0 (n=233)	N1 (n=675)	
Diffuse involvement (DSV and DSV-like)	1 (2.4%)	20 (18.5%)	NS	0	4 (23.5%)	NS	5 (1.8%)	67 (9.9%)	< 0.0001
Fibrosis									
Focal	26	59	NS	1	10	NS	111	296	NS
Septal	(61.9%)	(54.6%)	NS	(16.7%)	(58.8%)	NS	(47.6%)	(43.8%)	0.0005
	5	14		2	4		57	96	
	(11.9%)	(13.0%)		(33.3%)	(23.5%)		(24.5%)	(14.2%)	
Massive (central scarring)	11 (26.3%)	33 (30.6%)	NS	1 (16.7%)	3 (17.7%)	NS	45 (19.7%)	269 (39.9%)	< 0.0001
Blood vessels involvement	3 (7.1%)	26 (24.1%)	0.0206	2 (33.3%)	6 (35.3%)	NS	26 (11.2%)	146 (21.6%)	< 0.0001
Lymph vessels involvement	14 (33.3%)	106 (98.1%)	< 0.0001	2 (33.3)	16 (94.1)	0.0078	104 (44.6)	649 (96.2)	< 0.0001
Mononuclear infiltration									
Nodular type	1	32	< 0.0001	0	4	NS	15	123	< 0.0001
	(2.4%)	(29.6%)			(23.5%)		(6.4%)	(18.2%)	
Sparse	26	48	NS	5	12	NS	184	489	0.0223
	(61.9%)	(44.4%)		(83.3%)	(70.6%)		(79.0%)	(72.4%)	
Autoimmune thyroiditis comorbidity	13 (30.9%)	25 (23.1%)	NS	0	0		18 (7.7%)	49 (7.3%)	NS

Table 8. The relationship between tumour characteristics and nodal involvement of sporadic, second-primary and post-Chernobyl PTC (Note: N.S. – not significant)

3. Blood or/and lymph vessel involvement
4. Nodular type of mononuclear infiltration

High risk of nodal disease in patients with PTC as second primary malignancy ("iatrogenic") is associated with only morphological detail: lymph vessel involvement. As for post-Chernobyl PTC it has the same characteristics for N1 as in a case of extrathyroidal spread excluding predominance of follicular architecture:

1. Tumour size≥11 mm
2. Subcapsular or isthmus localization
3. Predominance of papillary structures
4. Diffuse sclerosing variant and monofocal PTC with diffuse sclerosing involvement of the thyroid gland (DSV-like) as well
5. Infiltrative growth and/or diffuse involvement (DSV and DSV-like)
6. Massive intratumoural fibrosis (central scarring)
7. Blood or/and lymph vessel involvement
8. Nodular type of mononuclear infiltration

Comparing morphological specifications which are rather important for nodal disease and extrathyroidal spread it should be noted that many features are intermixed. Association of the nodular type of productive inflammation with increased risk of expansion of metastases in lymph nodes ($p<0.001$) may have several explanations. First, cytokines and chemokines produced by mononuclear cells promote the survival of tumors, especially clones that developed as a result of activation of the RET proto-oncogene (e.g. mainly observed in the papillary phenotype). Variants of papillary carcinoma with remarkable ability for invasion of lymphatic vessels and metastatic dissemination can appear as a result of such clone selection (lymphogenous, intrathyroidal and regional). Secondly, extended antigen stimulation by autoimmune thyroiditis (Hashimoto thyroiditis) may lead to emergence of papillary carcinoma through activation of ERK-kinase in epithelial cells (Guarino V. et al., 2010).

Tumour histoarchitectonics probably play an important role in pathological and clinical behaviour of thyroid cancer but our current knowledge does not always permit a full understanding of the observations we have made. For example, why is a high proportion of follicular structures associated with stage pT3? And why is a largely papillary pattern associated with an elevated risk of N1 disease? Additionally, why do carcinomas of "pure" architecture appear less aggressive than PTC with mixed patterns?

5. Conclusion

Early assessment of post-Chernobyl thyroid carcinoma and sporadic thyroid carcinomas indicated that irradiation does not discriminate between genders; the female-to-male ratio was significantly higher in Italy and France (2.5/1), compared to the ratio of patients from post-Chernobyl Belarus (1.6/1). The overwhelming majority of the post-Chernobyl thyroid malignancies were PTC compared to a relatively high percentage of follicular carcinomas that was found in Italy/France (15.2%). This disproportion could be more likely explained by direct radiation-induced double-strand DNA breaks which preferentially lead to deletions and rearrangements. This mechanism is a characteristic for PTC but not for follicular carcinomas (DeLellies R.A. & Williams E.D., 2004), therefore predominance of PTC is non-directly supported radiation as a source for thyroid malignancies.

While comparing the pathology of malignant thyroid tumors of pediatric Belarusian patients with naturally-occurring thyroid carcinomas from patients from Italy and France it was identified that extrathyroidal extension and lymph node metastases were significantly more frequent in thyroid cancers in Belarus (49.1%, 64.6% respectively) compared to thyroid cancers in Italy/France, where it was 24.9% and 53.9%, respectively. It was hypothesized that these differences depend on the age at presentation: mean age at diagnosis in radiation-induced cases was 11 years in children and 15 years in adolescents while naturally-occurring thyroid carcinomas were diagnosed after 14 years of age (Pacini F. et al., 1997). Our research group and others documented that patient age did not have any influence on the tumors' ability to grow beyond the thyroid capsule and /or metastasize to lymph nodes or internal organs (Machens A. et al., 2010). Moreover, based on the rate of thyroid lymphocytic infiltration and circulating antithyroperoxidase antibody it was suggested that thyroid autoimmunity could be an additional consequence of the Chernobyl accident (Pacini F. et al., 1997). However, it is quite normal for us to see full-blown mononuclear infiltration in patients with sporadic PTC as well (autoimmune thyroiditis plays the leading role in the background pathology (n=38, 25.3%)).

It seems to be logical that sporadic PTC in children and adolescents from Belarus show few differences in comparison with the well-known clinical and morphological features of non-radiation induced thyroid cancers in other countries. For example, the female to male ratio is the same as in the rest of the world (3.7:1 in our own material, 4:1 for all histological variants of carcinoma according to long-term USA statistical data (Hogan et al., 2009). The lymph node metastases (72%) are as widespread as extrathyroidal extension (32.7%). In other countries the frequency of lymphatic nodes' involvement in children and adolescents appears to be also at a high level - from 40.7% in Canada up to 84.3% in Germany (Machens et al., 2010; O'Gorman et al., 2010). The data concerning extrathyroidal extent also varies considerably: from 9.6% in Russia up to 67.6% in South Korea (Koo J. et al., 2009, Romanchishen et al., 2008).

There are other nontrivial differences. In the period between 1986 and 2008 there were 150 sporadic papillary carcinoma patients and 42 cases of other malignant tumours composed of follicular cells—well differentiated carcinoma, no other specified (as it was defined by international group of pathologists (LiVolsi et al., 2011) who participated in Chernobyl tissue bank project), n=22, follicular thyroid carcinoma (FTC, n=4), collision carcinomas such as PTC and FTC (n=3), poorly differentiated carcinoma (4) and cribriform morular variant of PTC (n=9). This contradicts the worldwide data that put follicular carcinoma in much significant place after papillary carcinoma (its frequency varies from 6.1% in Russia up to 10-11% in Great Britain, Canada and the USA) (Romanchishen A.F. et al., 2008; Harach H.R. & Williams E.D., 1995; O'Gorman C.S. et al., 2010; Hogan et al., 2009). Besides, in our research primary tumor size (mean 15.8±14.3 mm, median 12 mm) was smaller than in German (median 31 mm) and Canadian (mean 23±15 mm) children and adolescents (Machens A. et al., 2010; O'Gorman C.S. et al., 2010). Moreover, multifocal growth was observed rarely, though other reports indicate that childhood thyroid cancers are typically not multifocal (Grigsby P.W. et al., 2002; DeLellies, R.A. & Williams, 2004). Finally, though prior reports have indicated that PTC in children and adolescents is prone to relapse (Demidchik Y.E. et al., 2006; Grigsby P.W. et al., 2002; Naing S. et al., 2009), with one report indicating a recurrence rate of up to 34% (Grigsby P.W. et al., 2002), here we observed a recurrence in only one case.

A notion prevails that radiogenic and sporadic papillary cancers do not differ in phenotype, but the distribution of variants of papillary carcinoma in both groups are a little different. For example, Ukrainian and Russian reports of post-Chernobyl cancer in children and adolescents indicate that the follicular (follicular-solid) variant occurs much more often than others types (Tronko M.D. et al., 1999; Williams E.D. et al., 2004). On the contrary, carcinoma of classical structure dominates in paediatric sporadic carcinomas (Harach H.R. & Williams E.D., 1995). Some researchers state that DSV appears in children and adolescents more often. However, as shown in tables 1, 3 and 5, regardless of the aetiology, the most frequent variant of carcinoma in children and adolescents in Belarus is the classical variant of papillary carcinoma.

Patients who received treatment for Hodgkin's lymphoma comprised 40.1% of all thyroid cancers that occurred as second primary malignancies. Children fell ill at an average age of 7. Such tumors appear in boys more often than in girls (6 boys and three girls in our own material). Moreover, in both cases of non-Hodgkins lymphoma, male patients were affected. As a result, gender proportion typical for the first cancer determined the ultimate

predominance of boys in the group of patients with second primary cancers. However, in the work of Acharya et al. (2003), out of 33 patients with confirmed history of therapeutic irradiation, 18 were diagnosed with Hodgkin's disease. Ten others had non-Hodgkin's lymphoma and 3 had acute leukemia, but the gender proportion was 2.3:1 girls:boys. The exact age when the first malignant tumour grew is not given (the median is given – 12 years and interval – from 3.7 to 18.3 years) and in the quoted research thyroid cancer appeared in the interval from 6.2 to 30.1 years.

Other features that indicate a difference between the variants of PTC of different aetiology are directly connected with the parameters of pathological aggressiveness. Ability to spread into surrounding tissues (pT3) is to a greater degree characteristic for second-primary carcinoma (73.9% of all observations). High frequency of autoimmune thyroiditis again brings up the question of what comes first: cancer in the background of a chronic inflammatory process or changes observed by the pathologist in surgical material that indicate a tumour-associated immunoreaction. It may also be theorized that long existing inflammatory responses with associated tissue renewal and repair leads to lower degrees of aggressiveness of thyroid carcinoma since it is connected to both upregulation of molecules of major histocompatibility complex (for example, HLA-Dr) or direct cytotoxic action of lymphocytes and macrophages on tumour cells (Guarino V. et al., 2010), with structural reorganization of thyroid gland tissue. Sclerosis, hyalinosis and mechanical compression of lymphatic vessels or compensatory-adaptive node of vascular walls as a response to local anoxia should have considerably impeded tumour cell embolism. Nevertheless, in our research autoimmune thyroiditis was identified in patients from both the sporadic and post-Chernobyl carcinoma groups and did not influence the invasive or metastatic potential.

Ultimately, tumour aetiology has no real impact on the clinical course and on the overall favourable prognosis of thyroid carcinoma, and the age of patients (children as compared to adolescents) is not essential for treatment planning or for disease outcome (Machens et al., 2010). On the other hand, observations show that the exposure to irradiation potentially induces clinicopathological characteristics of high-grade thyroid carcinomas, e.g. potential for multifocal growth, lymphovascular invasion, extrathyroidal spread, regional and distant metastasis, or recurrences (Naing et al., 2009). With the help of various statistical methods our own research discovered some characteristics which indicate clinical courses of papillary carcinomas in patients with the history of irradiation somewhat differ from the one of sporadic carcinomas, but the prognostic significance of this fact is not yet clear in spite of our large cohort of post-Chernobyl cancers. We believe that a more extended observation period and addition of new cases of sporadic and second-primary papillary carcinomas to the cohorts described here will give the possibility to define more precisely the role that aetiology plays for prognosis and treatment planning in children and adolescents.

6. References

Acharya, S.; Sarafoglou, K.; LaQuaglia, M.; et al. (2003) Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. *Cancer*, 97, 10, 2397–2403, ISSN 0008-543X

Astakhova, L.; Anspaugh, L., Beebe, G.; et al. (1998) Chernobyl-related thyroid cancer in children of Belarus: a case-control study. *Radiat Res,* 150, 349–356, ISSN 0033-7587

Beasley, N.J.; Walfish, P.G.; Witterick, I.; Freeman, J.L. (2001) Cause of death in patients with well-differentiated thyroid carcinoma. *Laryngoscope*, 111, 6, 989-991 ISSN 1531-4995

Chang, S.H., Joo, M., Kim, H. (2006) Fine Needle Aspiration Biopsy of Thyroid Nodules in Children and Adolescents. *J Korean Med Sci,* 21, 469-73, ISSN 1011-8934

Clark, O.H. (2005) Papillary Thyroid Carcinoma: Rationale for Total Thyroidectomy. In: *Textbook of Endocrine Surgery*. Orlo H. Clark, Quang-Yang Duh and Electron Kebebew. Elsevier Saunders, 110-113, ISBN 0-7216-0139-1, Philadelphia, USA

DeLellies, R.A. & Williams E.D. (2004) *World Health organization classification of tumours. Pathology and genetics of tumours of endocrine organs.* Ronald A. DeLellies, Ricardo V. Lloyd, Philipp U. Heitz, Charis Eng. IACR Press, Lyon, France, ISBN 92 832 2416 7

Demidchik, E.P., Demidchik, Yu.E., Gedrevich, Z.E., et al. (2002) Thyroid Cancer in Belarus. In: *Chernobyl: Message for the 21th Century.* Shunichi Yamashita, Yoshisada Shibata, Masaharu Hoshi and Kingo Fujimura, 69-75, Elsevier, ISBN 0-444-50869-4, Amsterdam, The Netherlands

Demidchik, E.P., Kazakov, V.S., Astakhova, L.N., et al. (1994) Thyroid Cancer in Children After the Chernobyl Accident: Clinical and Epidemiological Evaluation of 251 Cases in the Republic of Belarus. In: *Nagasaki Symposium on Chernobyl: Update and Future.* Shigenobu Nagataki, 21-30, Elsevier, ISBN 0-444-81953-3, Amsterdam, The Netherlands

Demidchik, Yu.E., Demidchik, E.P., Saenko, V.A., et al. (2007) Childhood Thyroid Cancer in Belarus. In: *Radiation Risk Perspertives.* Yoshisada Shibata, Hiroyuki Namba, Keiji Suzuki and Masao Tomonaga, 32-38, Elsevier, ISBN 978-0-444-52888-9, Amsterdam, The Netherlands

Demidchik, Yu.E., Saenko, V.A., Yamashita, S.(2007) Childhood Thyroid Cancer in Belarus, Russia, and Ukraine after Chernobyl and at Present, Arq Bras Endocrinol Metab, 51, 5, 748-762, ISSN 0004-2730

Demidchik, Y.E.; Demidchik, E.P.; Reiners, C.; et al. (2006) Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. *Annals of surgery,* 243, 4, 525-532, ISSN 0003-4932

Dinauer, C.A. (1998) Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. *Clinical Endocrinology,* 49, 619–628, ISSN 0300-0664

Farahati, J.; Bucsky, P.; Parlowsky, T.; et al., (1997) Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology. *Cancer*, 80, 11, 2156-2162, ISSN 0008-543X

Farahati, J.; Reiners, C.; Demidchik, E.P.; (1999) Is the UICC/AJCC classification of primary tumor in childhood thyroid carcinoma valid? *J. Nucl. Med.*, 40, 12, 2125, ISSN 0161-5505

Florentine, B.D., Staymates, B., Rabadi, M., et al. (2006) The reliability of fine-needle aspiration biopsy as the initial diagnostic procedure for palpable masses: a 4-year experience of 730 patients from a community hospital-based outpatient aspiration biopsy clinic. *Cancer*, 107, 2, 406-16, ISSN 0008-543X

Harrah, H.R. & Williams, E.D. (1995) Childhood thyroid cancer in England and Wales. *Br J Cancer*, 72, 777-783, ISSN 0007-0920

Hogan, A.R.; Zhuge, Y.; Perez, E.A.; et al. (2009) Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *J Surg Res*, 156, 167-172, ISSN 0022-4804

Gemsenjager, E.; Heitz, P.U.; Martina B. (1997) Selective treatment of differentiated thyroid carcinoma. *World J Surg*., 21,5, 546-51; discussion 551-552, ISSN 0364-2313

Gilliland, F.D.; Hunt, W.C.; Morris D.M.; Key C.R. (1997) Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. *Cancer*, 79, 3, 564-573 ISSN 0008-543X

Gimm, O. & Dralle, H. (2001) The current surgical approach to non-medullary thyroid cancer. *Thyroid cancer.* H.-J.Biersack, F.Grunwald. Springer, 81-89, ISBN 3-540-22309-6

Grigsby, P.W.; Gal-or, A.; Michalski, J.; Doherty, G.M. (2002) Childhood and adolescent thyroid carcinoma. *Cancer,* 95, 724-729, ISSN 0004-2730

Groot, G.; Colquhoun, B.P.; Murphy, F.A. (1992) Unilateral versus bilateral thyroid resection in differentiated thyroid carcinoma. *Can J Surg*, 35, 5, 517-520, ISSN 0008-428X

Guarino, V.; Castellone, M.D.; Avilla, E.; Melillo, R.M. (2010) Thyroid cancer and inflammation. *Molecular and Cellular Endocrinology*, 321, 94–102, ISSN 0303-7207

Kazakov, V.S.; Demidchik, E.P.; Astakhova, L.N. (1992) Thyroid cancer after Chernobyl. *Nature*, 359, 21, ISSN 0028-0836

Koo, J.; Hong, S.; Park, C. (2009) Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. *Thyroid,* 19, 1225-1231, ISSN 1557-9077

Lerch, H.; Schober, O.; Kuwert,T.; Saur, H.B. (1997) Survival of differentiated thyroid carcinoma studied in 500 patients. *J. Clin. Oncol.,* 15, 5, 2067-2075, ISSN 0732-183X

LiVolsi, V.A.; Abrosimov, A.A.; Bogdanova, T.; et al. (2011) The Chernobyl Thyroid Cancer Experience: Pathology. *Clinical Oncology,* 23, 261-267, ISSN 1433-2981

LiVolsi, V.A. (2011) Papillary thyroid carcinoma: an update. *Modern Pathology*, 24, S1–S9, ISSN 0893-3952

Luster, M.; Lassmann, M.; Freudenberg, L.S.; et al. (2007) Thyroid cancer in childhood: management strategy, including dosimetry and long-term results. *Hormones (Athenes)*, 6, 4, 269-278, ISSN 1109-3099

Machens, A.; Lorenz, K.; Nguyen, T.; et al. (2010) Papillary thyroid cancer in children and adolescents does not differ in growth pattern and metastatic behavior. *J Pediatr,* 157, 648-652, ISSN 0022-3476

Meadows, A.T.; Friedman, D.L.; Neglia, J.P.; et al. (2009) Inskip Second Neoplasms in Survivors of Childhood Cancer:

Findings From the Childhood Cancer Survivor Study Cohort. *J Clin Oncol*, 27, 14, 2356-2362, ISSN 0732-183X

Mete, O.; Rotstein, L.; Asa, S.L. (2010) Controversies in thyroid pathology: thyroid capsule invasion and extrathyroidal Extension. *Ann Surg Oncology*, 17, 386–391, ISSN 1068-9265

Morris, L.G.T.; Shaha, A.R.; Tuttle, R.M.; et al. (2010) Tall-Cell Variant of Papillary Thyroid Carcinoma: a matched pair analysis of survival. *Thyroid,* 20, 2, 153-158, ISSN 1557-9077

Naing, S.; Collins, B.J.; Schneider, A.B. (2009) Clinical behavior of radiation-induced thyroid cancer: factors related to recurrence. *Thyroid,* 19, 5, 479-485, ISSN 1557-9077

O'Gorman, C.S.; Hamilton, J.; Rachmiel, M.; et al. (2010) Thyroid cancer in childhood: a retrospective review of childhood course. *Thyroid,* 20, 375-380, ISSN 1050-7256

Pacini, F.; Vorontsova, T.; Demidchik, E.P.; et al. (1997) Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. *J Clin Endocrinol Metab,* 82, 3563- 3569 ISSN 0021-972X

Reiners, C.; Demidchik, Y.E. (2003) Differentiated thyroid cancer in childhood: pathology, diagnosis, therapy. *Pediatr. Endocrinol. Rev.*, 1 suppl. 2, 230-236, ISSN 1565-4753

Reiners, C.; Demidchik, Y.E.; Drozd, V.M.; et al. (2008) Thyroid cancer in infants and adolescents after Chernobyl. *Minerva Endocrinol.*, 33, 4, 381-395, ISSN 0391-1977

Reiners, C.; (2009) Radioactivity and thyroid cancer. *Hormones (Athens),* 8, 3, 185-191, ISSN 1109-3099

Romanchishen, A.F.; Thompson, D.B.; Gostimskiy, A.V. (2008) Surgical and postsurgical treatment for childhood and adolescent thyroid carcinoma. *Vestnik Chirurgii,* 67, 55-58 (in Russian), ISSN 0042-4625 2009

Sangalli, G. Serio, G., Zampatti, C., Bellotti, M., Lomuscio, G.(2006) Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. *Cytopathology*, 17, 245–250, ISSN 1365-2303

Savva, N.N.; Zborovskaya, A.A.; Aleynikova, O.V. (2008) Childhood malignancies in Belarus: incidence, survival, mortality, palliative care. Minsk: RNMB (in Russian), ISBN 978-985-6846-27-7

Seaberg, R.M.; Eski, S.; Freeman J.L. (2009) Influence of previous radiation exposure on pathologic features and clinical outcome in patients with thyroid cancer. Archives of otolaryngology, head & neck surgery, 135, 4, 355-359, ISSN 0886-4470

Shaha, A.R.; Shah, J.P.; Loree, T.R. (1997) Differentiated thyroid cancer presenting initially with distant metastasis. *Am. J. Surg,* 174, 5, 474-476, ISSN 0002-9610

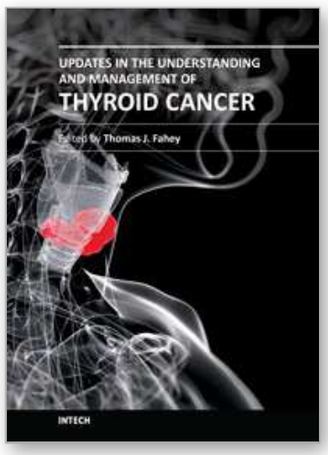
Steliarova-Foucher, E.; Stiller, C.A.; Pukkala, E.; et al. (2006) Thyroid cancer incidence and survival among European children and adolescents (1978-1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer,* 42, 2150-69, ISSN 0959-8049

Taylor, A.J.; Croft, A.P.; Palace, A.M.; et al. (2009) Risk of thyroid cancer in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study, *Int.J.Cancer,* 125, ISSN 1097-0215

Tronko, M.D.; Bogdanova, T.I.; Komissarenko, I.V.; et al. (1999) Thyroid carcinoma in children and adolescents in Ukraine after the Chernobyl nuclear accident: statistical data and clinicomorphologic characteristics. *Cancer* 86, 149-156, ISSN 0008-543X

Williams, E.D.; Abrosimov, A.; Bogdanova, T.; et al., (2004) Thyroid carcinoma after Chernobyl: latent period, morphology and aggressiveness. *Br J Cancer 90*, 2219-2224, ISSN 0007-0920

Williams, E.D.; Abrosimov, A.; Bogdanova, T.; et al. (2008) Morphologic characteristics of Chernobyl-related childhood papillary thyroid carcinomas are independent of radiation exposure but vary with iodine intake. *Thyroid*, 18, 847-852, ISSN1050-7256



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