A Cohort Study of Thyroid Cancer and Other Thyroid Diseases After the Chornobyl Accident

Pathology Analysis of Thyroid Cancer Cases in Ukraine Detected During the First Screening (1998–2000)

Tetyana I. Bogdanova, PhD[1]
Ludmyla Y. Zurnadzhy, MD[1]
Ellen Greenebaum, MD, MPH[2]
Robert J. McConnell, MD[3]
Jacob Robbins, MD[4]
Ovsiy V. Epstein, MD, PhD[5]
Valery A. Olijnyk, MD, PhD[6]
Maureen Hatch, MD, PhD[7]
Lydia B. Zablotska, MD, PhD[8]
Mykola D. Tronko, MD, PhD[9]

[1] Laboratory of Morphology of Endocrine System, Institute of Endocrinology and Metabolism, Kyiv, Ukraine.

[2] Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York.

[3] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York.

[4] Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

[5] Department of Functional Diseases, Institute of Endocrinology and Metabolism, Kyiv, Ukraine.

[6] Department of General Endocrine Pathology, Institute of Endocrinology and Metabolism, Kyiv, Ukraine.

[7] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

[8] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York.

[9] Department of Pathophysiology of Endocrine System, Institute of Endocrinology and Metabolism, Kyiv, Ukraine.

Supported by The Intramural Research Program of the U.S. National Cancer Institute, the National Institutes of Health, the Department of Health and Human Services, and the Department of Energy.

BACKGROUND. The Ukrainian American Cohort Study evaluated the risk of thyroid disorders in a group of individuals who were younger than age 18 years at the time of the Chornobyl (Chernobyl) accident. In this article, the authors describe the pathology of thyroid carcinomas detected in the first screening.

METHODS. From 1998 to 2000, 13,243 individuals completed the first cycle of screening examinations. Eighty patients underwent surgery between 1998 and 2004. Intraoperative and postoperative pathologic studies were performed at the Institute of Endocrinology and Metabolism, Kyiv.

RESULTS. Pathologic analysis revealed 45 thyroid carcinomas, including 43 papillary thyroid carcinomas (PTCs) (95.6%) and 2 follicular thyroid carcinomas (FTCs) (4.4%). TNM classification (5th edition) of the PTCs included 8 T1 tumors (18.6%), 16 T2 tumors (37.2%), and 19 T4 tumors (44.2%). Fifteen PTCs (34.9%) were N1a,N1b, and 3 PTCs (7.0%) were M1. Among the PTCs, 8 exhibited the classical papillary histologic pattern (18.6%), 14 exhibited a follicular histologic pattern (32.6%), 5 exhibited a solid histologic pattern (11.6%), and 16 exhibited a mixed histologic pattern (37.2%). Both FTCs had a microfollicular-solid structure. Eleven of 20 cohort members who underwent surgery before the first screening had PTCs. Regional metastases (63.6%) and distant metastases (18.2%) were more common in this group.

CONCLUSIONS. Multifocal growth, lymphatic and blood vessel invasion, extrathyroid spread, and regional and distant metastases were more frequent in less differentiated PTCs (>30% solid structure). *Small* carcinomas ($\leq$10 mm) comprised 23.3% of PTCs, and most of those (8 of 10 small carcinomas; 80%) were of the papillary-follicular subtype and therefore were more differentiated. The solid subtype of PTC was associated with shorter latency, especially in individuals who were

The U.S. Nuclear Regulatory Commission provided the initial funds for the purchase of equipment.

We thank the Louise Hamilton Kyiv Data Management Center of the University of Illinois at Chicago (supported in part by the U.S. National Institutes of Health Fogarty International Center) and its head, Oleksandr Zvinchuk, for excellent assistance with cohort database support and data management.

We also acknowledge the confirmation of diagnoses provided by the International Pathology Panel of the Chornobyl Tissue Bank: Dr. A. Abrosimov, Professor T. Bogdanova, Professor M. Ito, Professor V. LiVolsi, Professor J. Rosai, and Professor E. D. Williams. We also thank T. Odnolko and V. Shpak for data base management, Dr. G. M. Terekhova for her clinical role, and Drs. G. Howe and I. Masnyk for their leadership roles.

Address for reprints: Ellen Greenebaum, MD, MPH, Department of Pathology, VC14-215, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032; Fax: (212) 305-2301; E-mail: eg39@columbia.edu

Received July 18, 2006; revision received August 29, 2006; accepted September 18, 2006.

Published 2006 by the American Cancer Society*
DOI 10.1002/cncr.22321
Published online 2 November 2006 in Wiley InterScience (www.interscience.wiley.com).

diagnosed before the first screening. The histology of post-Chornobyl cancers is changing with time. ***Cancer* 2006;107:2559–66.** *Published 2006 by the American Cancer Society.**

KEYWORDS: Chornobyl accident, Chernobyl, thyroid cancer, pathology, papillary carcinoma, radiation, latency.

An increased prevalence of thyroid cancer in children and adolescents was observed in Ukraine, Belarus, and certain regions of Russia as early as 4 years after the April 26, 1986 Chornobyl (Chernobyl) accident.[1–5] This phenomenon was attributed to radiation, mainly radioactive iodine exposure because of the consumption of contaminated milk. Papillary thyroid carcinoma (PTC), which is the most frequently detected thyroid cancer in the exposed populations,[2,4,6–11] has a known association with both external and internal irradiation.[12–14]

Most post-Chornobyl papillary carcinomas in children aged 14 years or younger at the time of surgery have been characterized by solid and solid-follicular structure.[2,4,6–11] These subtypes also have been observed in nonexposed children, but at a younger age and in a much lower percentage of children.[15,16] It has been suggested that solid and solid-follicular variants of papillary carcinoma, as well as the RET/PTC3 rearrangement typical of these variants, are a consequence of radiation exposure after the Chornobyl accident.[2,6,7,9–11]

More recent studies have associated the presence of the solid variant of PTC and aggressive behavior of tumors in Chornobyl-exposed children with latency (the time between the accident and surgery) rather than with the children's age at the time of exposure.[17] A marked solid component and more aggressive behavior characterize tumors with a shorter latency to detection,[17] whereas longer latency is associated with a higher percentage of typical papillary carcinomas.[4,17] Because the ratio of histologic subtypes of papillary carcinoma is changing with longer latency, there is no unique morphologic signature of post-Chornobyl PTC.

The Ukrainian American Cohort Study was established to evaluate the risk of thyroid disorders in a well-defined group of individuals younger than age 18 years at the time of the accident and who had thyroid radioactivity measurements within the next few weeks.[18–20] Cohort members are examined at least every 2 years, and individuals who have nodules identified that are suspicious for cancer are sent to surgery. In this report, we provide a detailed characterization of the pathology of the thyroid cancers detected as a result of the first cycle of screening (from 1998 to 2000) and an analysis of their pathology related to tumor latency.

MATERIALS AND METHODS

In 1998, screening examinations of cohort members began in accordance with the Ukrainian-American *Scientific Protocol for the Study of Thyroid Cancer and Other Thyroid Diseases in Ukraine Following the Chornobyl Accident.* Members were drawn from the most heavily contaminated areas of the Kyiv, Chernihiv, and Zhytomyr Oblasts and must have been younger than age 18 years at the time of the accident. An oblast is an administrative district similar in size to a state or province. Members of the cohort under study had direct measurements of thyroid radioactivity in May to June 1986, allowing calculation of their individual thyroid doses of ^{131}I.[18–20]

From 1998 through 2000, 13,243 participants underwent the first cycle of screening, which included examination by an endocrinologist, an ultrasound examination, determination of thyroid-stimulating hormone level, urinary iodine, and, if indicated, fine-needle aspiration (FNA) biopsy.[18,19] Ultrasound examinations using a 7.5-megahertz probe routinely targeted the thyroid gland and perithyroid regions, including the jugular (lateral) lymph nodes. FNA biopsy was undergone by all patients who had focal thyroid lesions that measured $\geq$10 mm in greatest dimension detected either on palpation or on ultrasound and by all patients who had sonographically suspicious lesions (based on hypoechogenicity, irregular shape/contour, microcalcifications, extension through thyroid capsule, interval growth, abnormal adenopathy) that measured from 5 mm to 10 mm in greatest dimension. All patients were referred for surgery if cytology was diagnostic or suspicious for malignancy in either a nodule or a lymph node or for a follicular neoplasm in a nodule.

Subsequent to the first round of screening, 80 of the 13,243 cohort members underwent surgery between 1998 and 2004 (76 at the Institute of Endocrinology and Metabolism, Academy of Medical Science of Ukraine in Kyiv [IEM], 2 at Chernihiv Regional Hospital, 1 at Kyiv Regional Hospital, and 1 at Zhytomyr Regional Hospital). All 80 histologic specimens were diagnosed (4 specimens were rediagnosed) at the IEM. In all patients who had a nodule identified, intraoperative study of frozen sections was performed. When the frozen-section diagnosis was carcinoma, the patient underwent a total or near total

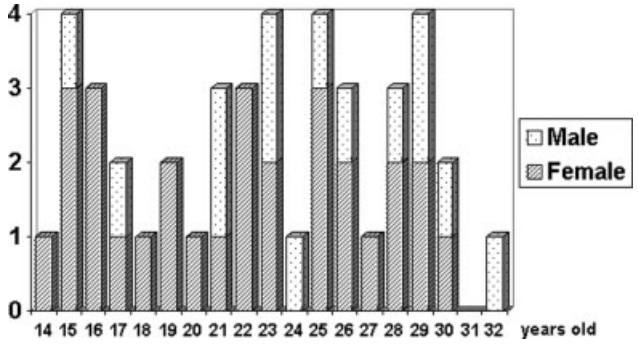

FIGURE 1. Patients' ages at the time of surgery.

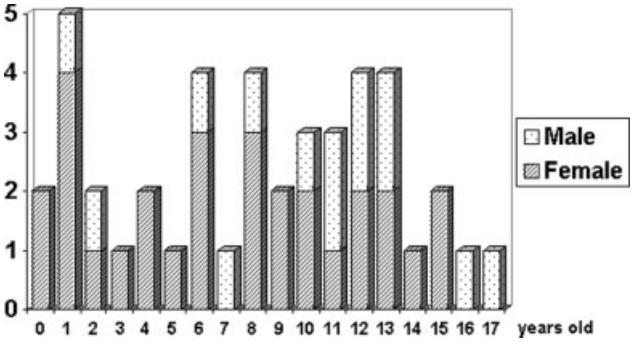

FIGURE 2. Patients' ages at the time of the accident.

thyroidectomy; this was followed by the receipt of postoperative radioactive iodine therapy and subsequent suppressive thyroid hormone therapy. If it was indicated by physical examination and/or ultrasound findings, then the patient also underwent a lymph node dissection. When the frozen-section diagnosis was follicular neoplasm, the patient underwent a hemithyroidectomy, which was followed by a completion thyroidectomy when indicated. Postoperative study of paraffin sections stained with hematoxylin and eosin was performed at the Pathology Laboratory of the IEM in all 80 specimens. The diagnosis was made by 2 of the authors (T.I.B. and L.Y.Z.) according to the World Health Organization histologic classification system.[21] All specimens also were reviewed by 1 of the authors (E.G.). All diagnoses were confirmed by the International Pathology Panel, which was established in the framework of the Tissue Bank Project[22] (available at URL: www. Chornobyltissuebank.com [accessed September 2006]).

PTCs were subdivided into several subtypes or variants, depending on the dominant structural component. PTCs were classified as papillary, follicular, or solid when >80% of the surface of the slides had the corresponding structure, and they were classified as mixed when they were composed of a combination of 2 patterns (papillary-follicular, papillary-solid, solid-follicular) at a ratio of 50%:50%, 50%:40%, or 60%:30%, allowing for up to approximately 10% of the tumor to have a third pattern. PTCs were classified as the papillary-follicular-solid variant when the 3 structural components were present in nearly equal proportions.

Distant metastases to lungs were determined by radioactive iodine scans of all postthyroidectomy patients. We classified tumor stage according to TNM classification system (5th edition). We evaluated the difference between the 5th and 6th editions and chose the 5th to be consistent with the classification system that is used by the Chornobyl Tissue Bank. We believe that the 5th edition of TNM classification system is more suitable for thyroid cancer and that the 6th edition is better for other head and neck cancers.[23]

RESULTS

Forty-three of 45 patients with thyroid carcinoma (95.6%) had PTC, and 2 of those patients (4.4%) had the follicular variant. Thirty-two of 43 PTCs (74.4%) were identified in surgical specimens from young adults aged 19 years to 32 years, 10 PTCs (23.3%) were detected in adolescents aged 15 years to 18 years, and only 1 PTC (2.3%) was detected in a child aged 14 years (Fig. 1). The ratio of women to men among all 43 patients with PTC who underwent surgery was 29:14 (2.1:1).

At the time of the accident, 12 of 43 patients with PTC were children (10 girls and 2 boys) aged birth to 4 years (27.9%); 12 patients were children (9 girls and 3 boys) aged 5 years to 9 years (27.9%); 15 patients were children (8 girls and 7 boys) aged 10 years to 14 years (34.9%), and only 4 patients (2 girls and 2 boys) were adolescents aged 15 years to 18 years (9.3%) (Fig. 2). Thus, most patients were aged 14 years or younger at the time of the accident (39 of 43 patients; 90.7%).

The size of papillary carcinomas ranged from 1 mm to 50 mm, nearly 50% measured from 11 mm to 20 mm, and nearly 25% measured ≤10 mm (*small* carcinomas) (Table 1). In 2 patients (4.7%) who underwent resection of a multinodular, goiterous gland, occult papillary carcinomas that measured 1 mm and 9 mm (both T1N0M0) were detected only by final pathology analysis of paraffin sections.

According to the TNM classification system, only 18% of all PTCs detected were T1, including 80% of our cohort's first-screening small PTCs. The remaining 2 small PTCs, which measured 9 mm and 10 mm, had signs of extrathyroid spread and were classified as T4. In total, 19 PTCs (44.2%) were T4, 16 PTCs (37.2%) were T2, and no PTCs were T3. Fifteen PTCs (34.9%) had regional metastases identified by pathology exam-

TABLE 1
Papillary Carcinoma: Size and TNM Classification (5th Edition)

			T1		T2		T4		N1a		N1a, N1b		M1	
Size, mm	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
≤10	10	23.3	8	80			2	20	1	10	1	10		
11–20	21	48.8			11	52.4	10	47.6	4	19	1	4.5		
21–30	7	16.3			3	42.9	4	57.1	4	57.1				
31–40	4	9.3			2	50	2	50	2	50	1		2	50
41–50	1	2.3					1		1				1	
Total	43		8	18.6	16	37.2	19	44.2	12	27.9	3	7	3	7.0

TABLE 2
The Presence of Tumor Capsule and Invasive Properties of Papillary Carcinomas Depending on Histologic Structure

	Capsule presence						Invasion							
	Complete		Partial		Absence		Intrathyroid		Lymphatic		Blood vessels		Extrathyroid	
Histologic variant*	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
PV (8)	1	12.5	4	50	3	37.5	6	75	2	25	—	—	3	37.5
FV (14)	5	35.7	1	7.1	8	57.1	8	57.1	4	28.6	2	14.3	3	21.4
SV (5)	1	20	2	40	2	40	5	100	4	80	4	80	4	80
MiV (16)	—	—	3	18.8	13	81.3	12	75	12	75	6	37.5	10	62.5
PFV (6)	—	—	1	16.7	5	83.3	4	66.7	3	50	1	16.7	3	50
PSV (4)	—	—	—	—	4	100	3	75	3	75	2	50	4	100
SFV (4)	—	—	—	—	4	100	4	100	4	100	3	75	2	50
PFSV (2)	—	—	2		—	—	1		2		—	—	1	
Total (43)	7	16.3	10	23.3	26	60.5	31	72.1	22	51.2	12	27.9	20	46.5

PV indicates typical papillary variant; FV, follicular variant; SV, solid variant; MiV, mixed variant; PFV, papillary-follicular variant; PSV, papillary-solid variant; SFV, solid-follicular variant; PFSV, papillary-follicular-solid variant.

* The number of patients with each histologic variant and the total number of patients are indicated in parenthesis.

ination, including 12 unilateral (N1a) PTCs (27.9%) and 3 bilateral (N1a, N1b) PTCs (7.0%). Postoperative radioiodine scans detected lung metastases in 3 patients (7.0%) and unilateral regional micrometastasis (8-mm primary tumor) in 1 patient (2.3%). Although a greater proportion of larger PTCs had regional and distant metastases, the small size of a PTC (≤10 mm) did not preclude extrathyroid spread and regional metastases.

Papillary carcinomas were classified according to their histologic structural patterns into the following 4 subtypes or variants: papillary, follicular, solid, and mixed. The mixed subtype also was subdivided into papillary-follicular, papillary-solid, solid-follicular, and papillary-follicular-solid variants (Table 2).

Table 2 shows that the most frequent variant of PTC was mixed (16 tumors; 37.2%), and 10 of 16 tumors (62.5%) were characterized by the presence of a solid component. In addition, 18.6% of PTC variants had typical papillary structure, 32.6% had primarily follicular structure, and 11.6% had primarily solid structure.

We also analyzed each of the variants for the presence of a capsule and according to their invasive properties (Table 2). Completely encapsulated tumors were found most often among the follicular variant of papillary carcinoma (35.7% of tumors) and most rarely among the papillary and solid variants (only 1 of each variant). No completely encapsulated tumors with mixed structure were identified in any of the patients. The highest percentage of partly encapsulated tumors was noted for the typical papillary variant; however, as a whole, nonencapsulated tumors were dominant (60.5%).

Most PTCs, irrespective of their histologic structure, invaded the tumor capsule if it was present (all 5 papillary variants, 4 of 6 follicular variants, 2 of 3 solid variants, and all 3 mixed variants). Most PTCs displayed intrathyroid spread (all solid variants and solid-follicular variants and 57% of follicular variants). Lymphatic and extrathyroid invasion were more frequent in solid and mixed variants, and blood vessel invasion was more frequent in solid variants (see Table 2).

TABLE 3
Invasive Properties of Papillary Carcinomas According to Histologic Structure

	Intrathyroid spreading		Multifocal growth		Lymphatic invasion		Blood Vessel invasion		Extrathyroid spreading		Regional metastases		Distant metastases	
Histologic structure*	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
PV + FV + PFV (28)	18	64.3	2	7.1	9	32.1	3	10.7	9	32.1	7	28.6	1	3.6
SV + PSV + SFV + PFSV (15)	13	86.7	5	33.3	13	86.7	8	53.3	10	88.7	8	53.3	2	12.5
Total (43)	31	72.1	7	16.3	22	51.2	11	25.6	19	44.2	15	37.2	3	7.0

PV indicates typical papillary variant; FV, follicular variant; SV, solid variant; PFV, papillary-follicular variant; PSV, papillary-solid variant; SFV, solid-follicular variant; PFSV, papillary-follicular-solid variant.
* The number of patients in each subgroup and the total number of patients are indicated in parentheses.

Marked oxyphilic-cell (Hurthle cell) metaplasia was present in 3 tumors (7.0%), including 1 each of the follicular, solid, and papillary-follicular variants. Squamous cell metaplasia was present in 5 tumors (11.6%), including 3 typical papillary variants, 1 follicular variant, and 1 solid variant. Severe fibrous-sclerotic changes in the tumor were present in 18 tumors (41.9%) with various histologic structures but were present most frequently in typical papillary variants (4 of 8 tumors; 50%), papillary-solid variants (2 of 4 tumors; 50%), and follicular variants (5 of 14 tumors; 35.7%).

In addition, we examined the invasive properties separately for the subgroup of tumors with typical papillary, follicular, or mixed papillary-follicular structure (65.1% of all tumors) and for the subgroup of tumors with $\geq$30% solid component (34.9% of all tumors) (Table 3). According to a previously published study,[17] the first subgroup includes well-differentiated papillary carcinomas, and the second subgroup includes less well-differentiated tumors.

Tumor spread of PTCs to adjacent thyroid tissue, as noted above, was observed irrespective of tumor variant. However, multifocal tumor growth, lymphatic and blood vessel invasion, extrathyroid tumor spread, the presence of regional lymph node metastases, and distant metastases to lungs were much more frequent in the subgroups of PTCs that had a markedly solid component. It is also noteworthy that, in PTCs of mixed variant, the invasive growth areas generally had a solid structure.

Thirty-six of the 43 papillary carcinomas (83.7%) were present as solitary tumors. In 3 patients (7.0%), an additional single nodule was present that measured 3 mm, 10 mm, and 15 mm, respectively, was present. One was an adenomatous nodule of microfollicular structure, 1 was a cystic nodule, and the third was a heterogeneous micronormomacrofollicular nodule. In 2 patients (4.7%), 2 additional nodules were reported: One patient had both a follicular adenoma of 6 mm with microfollicular-solid structure and an adenomatous nodule that measured 11 mm with normofollicular-papillary structure, and the other patient had a follicular adenoma that measured 9 mm with solid structure and a nodule that measured 5 mm with normomacrofollicular structure.

Lymphoid infiltration (lymphocytic thyroiditis) was classified as predominantly intratumoral, peritumoral, or extratumoral. Peritumoral thyroiditis was present in 21 patients (48.8%), but no thyroiditis was predominantly intratumoral. The presence of signs of focal thyroiditis (12 tumors; 27.9%) and diffuse thyroiditis (4 patients; 9.3%) in extratumoral thyroid tissue was observed.

Of the 2 follicular carcinomas, 1 measured 8 mm and had invasion through the tumor capsule only (ie, it was minimally invasive; T1N0M0), and the other measured 14 mm and had signs of capsular blood vessel invasion (T2N0M0). Both follicular carcinomas had a microfollicular-solid structure. The patient who had minimally invasive carcinoma was a man aged 29 years at surgery who was aged 16 years at the time of the accident. The patient with capsular blood vessel invasion was a woman aged 23 years at surgery who was aged 13 years at the time of the accident.

Thyroid carcinoma was diagnosed in 45 of 80 members of the cohort (56.3%). The nonmalignant tumors included 23 follicular adenomas, 7 uninodular goiters, 3 multinodular goiters, 1 simple diffuse goiter, and 1 toxic diffuse goiter.

Prescreening Cohort Members

Twenty cohort members underwent surgery prior to screening examination, including 11 patients (55.0%) who had thyroid carcinoma (Table 4). All 11 patients had PTC, although 1 patient also had a medullary carcinoma. Among 9 patients who underwent surgery for benign thyroid pathology before the screening started, there were 2 patients with follicular adenoma, 1 patient with multinodular goiter, 3 patients with nodular goiter, 2 patients with diffuse toxic goiter, and 1

TABLE 4
Distribution of Papillary Carcinomas into Histologic Variants and Latency According to Means of Discovery

	Prescreening patients			Screened patients			Total		
Histologic variant	No.	%	Minimum-maximum latency, years	No.	%	Minimum-maximum latency, years	No.	%	Average latency, years
PV	1	9.1	8.1	8	18.6	13.0–16.3	9	16.7	13.8
FV	2	18.2	12.2–13.3	14	32.6	13.0–17.8	16	29.6	14.4
SV	2	18.2	3.8–4.5	5	11.6	12.5–14.7	7	13.0	10.6
MiV	5	45.4	6.3–11.7	16	37.2	12.8–16.9	21	38.9	13.6
PFV	2	18.2	10.8–11.1	6	13.9	13.5–15.6	8	14.8	13.7
PSV	—	—	—	4	9.3	14.8–16.5	4	7.4	15.4
SFV	3	27.2	6.3–11.7	4	9.3	12.8–16.9	7	13.0	12.3
PFSV	—	—	—	2	4.7	13.6–14.2	2	3.7	13.9
DSV	1	9.1	6.3	—	—	—	1	1.8	6.3
Total	11		3.8–13.3	43		12.5–17.8	54		13.3

PV indicates typical papillary variant; FV, follicular variant; SV, solid variant; MiV, mixed variant; PFV, papillary-follicular variant; PSV, papillary-solid variant; SFV, solid-follicular variant; PFSV, papillary-follicular-solid variant; DSV, diffuse sclerotic variant.

patient with mixed goiter. All diagnoses were confirmed by the International Pathology Panel.

Compared with screened cohort members, most of the prescreening cohort members were ages 7 to 14 years at the time of surgery (8 of 11 patients; 72.7%; 5 girls and 3 boys; ratio, 1.7:1). Only 1 patient was an adolescent, a boy aged 15 years, and 2 patients were adult women ages 20 years and 27 years. At the time of the Chornobyl accident, most cohort members were children aged 4 years or younger (9 of 11 patients; 81.8%; 6 girls and 3 boys; ratio, 2:1); the 2 older cohort members were girls aged 14 years and 16 years.

The size of papillary carcinomas ranged from 13 mm to 40 mm, with most measuring from 13 mm to 20 mm (81.8%), similar to the sizes found during the first screening, but no small carcinomas ($\leq$10 mm) were reported. TNM classification of prescreening PTCs into the T4 category was similar to that of the screened PTCs (4 of 11 tumors; 36.4%), but tumors that were identified had a higher percentage of regional metastases (7 of 11 tumors; 63.6%) and distant metastases (2 of 11 tumors; 18.2%) compared with tumors that were identified during screening.

Nearly 50% of the prescreening PTCs were of the mixed variant (45.4%), which was slightly more than the percentage found after screening (37.2%), whereas fewer papillary and follicular variants were found prescreening rather than during screening. One patient who had a diffuse sclerosing variant was identified among the prescreening cohort members only (Table 4).

We compared PTC histology and latency in prescreening and screened cohort members (Table 4). Papillary carcinomas that occurred before the first screening were characterized by shorter latency (average, 8.9 years) compared with carcinomas that were detected during the first screening (average, 14.5 years). PTCs of the solid variant had the shortest latency in the prescreening cohort members (average, 4.2 years) and had somewhat shorter latency in the first-screening cohort members (average, 13.1 years) compared with the other variants. Solid-variant PTCs in the prescreening and screened cohort members combined had shorter latency (average, 10.6 years) than typical papillary (average, 13.8 years), follicular (average, 13.8 years), and mixed (13.6 years) variants.

DISCUSSION

Among patients from iodine-replete regions that were not exposed to radiation, thyroid cancer is found most frequently in individuals age 50 years and older,[12–14] and it is very rare in children.[15,16] The pre-Chornobyl incidence of thyroid cancer in Ukrainian children also was very low (0.5 per 1,000,000 children). After the Chornobyl accident, the incidence of thyroid cancer increased in exposed children and adolescents, mostly in the highly contaminated northern regions.[1,2,4,5] Increased radiation exposure also has been correlated with the papillary histologic subtype of thyroid carcinomas,[12–14] as reported here and in previously published observations.[2,4,7] Our current results also confirm that active screening for thyroid cancer increases the possibility of finding more cases and finding them earlier compared with no screening, especially small tumors. During the first screening, 23.3% of papillary carcinomas measured <10 mm compared with 11.8% of papillary carcinomas that were measured from 1996 to 2001 in all of Ukraine.[4]

The histologic pattern of ultrasound-detected, post-Chornobyl thyroid cancers is changing with time. Nearly all of the tumors that were detected during the first screening cycle of the current study were of the papillary type (95.6%). The predominant subtypes were mixed or follicular, and only 34.9% of tumors had a significantly solid component. In a previous study of exposed Ukrainian children who underwent surgery from 1990 to 1995,[7] the largely solid-follicular variant made up 79% of the all thyroid tumors.[7] The relatively smaller percentages of the solid variant and the mixed variant with a marked solid component in our study were not surprising, because the solid variant has been associated more typically with shorter post-Chornobyl latency ($\leq$10 years).[4,17] Since screening began in 1998, 12 years after the accident, most patients were adolescents or young adults at the time of surgery, and the latency was from 12 years to 18 years. Despite the older ages of the screened patients at surgery, the solid variant of PTC had a somewhat shorter latency than the classic papillary or follicular variants, whereas the solid variants that were found before the first screening examinations had a much shorter latency than the follicular and papillary variants.

A potential confounding factor in our analysis is detection bias. Because no screening method is flawless, some tumors may have been overlooked during each screening cycle, and 1 subtype may be detected more easily than another and, thus, may be removed at a disproportionately high rate. Consequently, the proportion of tumors that are more difficult to identify will increase as screening continues.

The dominant histology reflects the degree of tumor differentiation, and the classic papillary, follicular, and mixed papillary-follicular subtypes are more differentiated than the solid subtype. Our current findings have confirmed earlier studies, which indicated that invasive properties and aggressive biologic behavior of PTCs also are associated with a lesser degree of differentiation.[12–14,17]

Thus, the presence of >30% solid component in papillary carcinomas (although patients ranged in age at the time of surgery from 19 years to 32 years, and latency was from 12 years to 18 years) was associated with signs of more aggressive biologic behavior compared with the other PTC variants, and this correlation persisted even in smaller tumors. Among 10 patients who had PTCs that measured $\geq$10 mm in greatest dimension, 8 patients had more differentiated tumors, and 2 patients had less differentiated tumors. Only 1 of the smaller, well differentiated PTCs (10 mm) had signs of extrathyroid spread, and another tumor (8 mm) had a micrometastasis to lymph nodes that was found upon postoperative radioiodine examination. By contrast, both of the PTCs that had a solid component (7 mm and 9 mm) had regional lymph node metastasis, and the larger tumor had also extrathyroid spread in connective tissue. There was no difference in latency between the papillary-follicular *small* PTCs versus the *small* PTCs with solid component. In the first subgroup, latency was 13 years to 15.6 years (average, 14.6 years); and, in the second subgroup, latency was 14.9 years to 16.9 years (average, 15.9 years). Our data regarding the correlation between papillary carcinoma and lymphocytic thyroiditis confirm findings reported in a previous study[24] that the dominant location of lymphoid infiltration associated with papillary carcinoma is in a peritumoral distribution rather than an extratumoral distribution.

In conclusion, among the exposed individuals who underwent surgery from 12 years to 18 years after the Chornobyl accident, pathologic analysis revealed 45 thyroid carcinomas. Forty three of those tumors (95.6%) were PTCs, predominantly of the mixed and follicular subtypes; and 2 tumors (4.4%) were FTCs.

Tumors that contained a >30% solid component made up 34.9% of all tumors and were much more likely to exhibit multifocal growth, lymphatic and blood vessel invasion, extrathyroid spread, and regional and distant metastases compared with typical papillary cancers. *Small* PTCs (tumors that measured $\leq$10 mm) comprised 23.3% of our PTCs, and most of those (8 of 10 tumors; 80%) had a more differentiated papillary-follicular structure.

The solid subtype of PTC was associated with shorter latency, especially in tumors that were found before the first screening, compared with typical papillary and follicular subtypes of PTC. Regional and distant metastases were more frequent among the 11 patients who had PTC diagnosed before the first screening (63.6% and 18.2%, respectively, vs. 34.9% and 7.0%, respectively, among 43 patients who had PTC detected during the first screening).

The histology of post-Chornobyl PTC detected predominantly by ultrasound screening is changing with longer latency, suggesting that there is no unique histologic signature for these carcinomas. Both follicular carcinomas in the current study had a microfollicular-solid structure; 1 was minimally invasive, and the other had significant capsular blood vessel invasion.

REFERENCES

1. Likhtarev IA, Sobolev BG, Kairo IA, et al. Thyroid cancer in the Ukraine [letter]. *Nature*. 1995;375:365.
2. Tronko MD, Bogdanova TI, Komissarenko IV, et al. Thyroid carcinoma in children and adolescents in Ukraine after the Chornobyl accident: statistical data and clinicomorphologic characteristics. *Cancer*. 1999;86:149–156.

3. Tsyb AF, Shakhtarin VV, Lushnikov EF, et al. Development of cancer and non-cancer thyroid diseases in children and adolescents after the Chornobyl accident. In: Thomas G, Karaoglou A, Williams ED, editors. Radiation and Thyroid Cancer. Singapore: World Scientific, Inc; 1999:79–87.
4. Tronko ND, Bogdanova TI. Thyroid cancer in children and adolescents. In: Vozianov A, Bebeshko V, Bazyka D, editors. Health Effects of Chornobyl Accident. Kyiv: DIA LTD Inc; 2003:60–68.
5. Jacob P, Goulko G, Heidenreich WF, et al. Thyroid cancer risk to children calculated. *Nature*. 1998;392:31–32.
6. Nikiforov Y, Gnepp DR. Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991–1992) from the republic of Belarus. *Cancer*. 1994;74: 748–766.
7. Bogdanova T, Bragarnik M, Tronko ND, Harach HR, Thomas GA, Williams ED. Childhood thyroid cancer after Chernobyl [abstract]. *J Endocrinol*. 1995;144(suppl OC):25.
8. Bogdanova TI. Pathomorphologic characteristics of malignant thyroid tumors in children. In: Robbins J, editor. Treatment of Thyroid Cancer in Childhood. Bethesda, MD: National Institutes of Health; 1994:51–59.
9. Bogdanova TI, Kozyritskiy VG, Tronko ND. Thyroid Pathology in Children. Atlas [in Russian]. Kyiv: Chornobylinterinform Inc; 2000.
10. Cherstvoy E, Pozharskaya V, Nerovnya A. The pathomorphology of childhood papillary thyroid carcinoma in Belarus in different periods after the Chornobyl accident (1991–997). In: Thomas G, Karaoglou A, Williams ED, editors. Radiation and Thyroid Cancer. Singapore: World Scientific, Inc; 1999:55–60.
11. Thomas GA, Bunnell H, Cook HA, et al. High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post Chernobyl thyroid papillary carcinomas: a strong correlation between RET/PTC3 and the solid/follicular variant. *J Clin Endocrinol Metab*. 1999;84:4232–4238.
12. LiVolsi VA. Surgical Pathology of Thyroid. Philadelphia: WB Saunders Inc; 1990.
13. Rosai J, Cargangiu ML, Delellis RA. Tumors of the Thyroid Gland. Washington, DC: Armed Forces Institute of Pathology; 1992.
14. Rosai J. Ackerman's Surgical Pathology. 8th ed. St. Louis, MO: Mosby Inc; 1996.
15. Peters SB, Chatten J, LiVolsi VA. Pediatric papillary thyroid carcinoma [abstract]. *Mod Pathol*. 1994;7:55A.
16. Harach HR, Williams ED. Childhood thyroid cancer in England and Wales. *Br J Cancer*. 1994;72:777–783.
17. Williams ED, Abrosimov A, Bogdanova TI, et al. Thyroid carcinoma after Chernobyl. Latent period, morphology and aggressiveness. *Br J Cancer*. 2004;90:2219–2224.
18. Tronko M, Bobylyova O, Bogdanova T, et al. Thyroid gland and radiation (Ukrainian-American Thyroid Project). In: Shibata Y, Yamashita S, Watanabe M, Tomonaga M, editors. Radiation and Humankind. Amsterdam: Elsevier Inc, Excerpta Medica International Congress Series; 2003:91–104.
19. Stezhko VA, Buglova EE, Danilova LI, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods. *Radiat Res*. 2004; 161:481–492.
20. Tronko MD, Howe GR, Bogdanova TI, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: thyroid cancers in Ukraine detected during first screening. *J Natl Cancer Inst*. 2006;98:897–903.
21. Hedinger C, Williams ED, Sobin L. World Health Organization Histological Typing of Thyroid Tumours. 2nd ed. Berlin: Springer Inc; 1988.
22. Thomas GA, Williams ED, Becker DV, et al. Thyroid tumor banks [letter]. *Science*. 2000;289:2283.
23. Sobin LH, Wittekind C, editors. TNM Classification of Malignant Tumors. 6th ed. New York: John Wiley & Sons; 2002.
24. Bogdanova T, Zurnadzhy L, Tronko M, Thomas GA, Williams ED. Characterization of lymphoid infiltration in post Chornobyl childhood thyroid carcinoma in Ukraine. In: Thomas G, Karaoglou A, Williams ED, editors. Radiation and Thyroid Cancer. Singapore: World Scientific, Inc; 1999:213–216.