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HISTOPATHOLOGICAL CHARACTERISTICS AND POST-OPERATIVE FOLLOW-UP OF PATIENTS WITH POTENTIALLY RADIOGENIC PAPILLARY THYROID CARCINOMA DEPENDING ON ONCOCYTIC CHANGES AVAILABILITY IN THE TUMOR CELLS

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***Aim*: To compare the frequency of main histopathological characteristics, ^{131}I thyroid radiation doses, invasive properties and post-operative follow-up of patients of different age groups with potentially radiogenic papillary thyroid carcinoma (PTC) with the presence and absence of oncocytic changes in tumor cells. *Materials and Methods:* PTC removed in 483 patients from high risk age-group for radiogenic thyroid cancer development (children and adolescents at the time of Chornobyl accident who lived in the northern regions of Ukraine: Kyiv, Zhytomyr, and Chernihiv regions) have been studied microscopically. *Results:* The frequency of PTC with the presence of oncocytic changes (OCh) in tumor cells increased significantly with increasing of patients' age at the time of surgery: from 8.3% in children 4–14 years old to 54.3% in adults 39–48 years old ($p_{trend} < 0.0001$). The presence of such changes is associated with papillary and solid-trabecular dominant tumor growth pattern in more than 90% of cases in each age group. The mean ^{131}I thyroid dose in the whole series of PTC patients with OCh was significantly lower compared to the same index in PTC patients without OCh (493.7 mGy and 765.8 mGy, respectively, $p < 0.0001$). In addition, regional metastases recurrences were revealed more frequently in patients with OCh in primary PTC compared with patients without OCh in primary tumor (7.2% *vs* 1.5%, $p = 0.0022$). *Conclusions:* Significantly increasing age-trend of OCh in PTC of patients affected by the Chornobyl fallout and operated at age from 4 to 48 years, as well as opposite decreasing linear age-trend of ^{131}I thyroid dose may reflect a gradual increase of sporadic PTCs frequency in the potentially radiogenic series with time elapsed since accident. The frequency of oncocytic insensitive to radioiodine therapy of lymph node metastases recurrences also increased with patients age and OCh availability in primary PTC.**

***Key Words*: papillary thyroid carcinoma, histopathology, Chornobyl accident, oncocytic cell changes, post-operative follow-up.**

To date, it has been conclusively demonstrated that an increase in thyroid cancer incidence among people under the age of 18 at the time of the Chornobyl accident, which is observed in Ukraine up to now [1–3], is a direct medical consequence of the Chornobyl accident. Childhood and adolescents at the time of the accident were classified as a high-risk group for the development of radiation-induced (radiogenic) thyroid cancer. During the 33 years that have passed since the accident, a large number of different studies have been performed on post-Chornobyl thyroid cancer: dosimetric, epidemiological, morphological, and molecular-biological.

The relationship of a sharp increase in thyroid cancer incidence in a specified age cohort with ^{131}I thyroid irradiation due to the Chornobyl accident was demonstrated [4–7]. Many changes have been revealed (linear trends, increasing or decreasing) of structural

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Abbreviations used: DSV – diffuse-sclerosing variant; ETE – extrathyroid extension; IEM – State Institution "V.P. Komisarenko Institute of Endocrinology and Metabolism of National Academy of Medical Sciences of Ukraine"; ITS – intrathyroid spread; OCh – oncocytic changes; PTC – papillary thyroid carcinoma; RI – radioiodine; RIT – radioiodine treatment.

characteristics of papillary thyroid carcinoma (PTC), which is the main type of "post-Chornobyl" thyroid cancer, as well as the changes of PTC's invasive properties [3, 8, 9]. Significant histopathological differences were established also between "radiogenic" (patients born before the accident) and "sporadic" PTCs (patients born after the accident) in age-matched groups of children, adolescents, and young adult at the time of surgery [10–12].

With the increase of the time elapsed since the Chornobyl accident and patients age at the time of surgery, not only the PTC sizes and their "encapsulation", but also the ratio of PTC histological subtypes was changed [3, 8, 9, 11, 13]. More often rare PTC subtypes, such as Warthin-like, Tall cell were registered [3, 9, 11, 13]. In addition, it has been found that in recent years, unlike in previous ones, more pronounced invasive properties have been related to PTCs with a dominant papillary growth pattern. Such tumors are more likely to be characterized by the absence of a tumor capsule and the presence of regional metastases [3, 9]. It is also noted that the dominant papillary structural component coexisted with trabecular, solid, Tall cell and Warthin-like areas, which most commonly showed an oncocytic phenotype.

PTCs with oncocytic changes (OCh) have been the subject of many years of discussion regarding the disease course in individuals with such a tumor. According to some authors, OCh in PTC are combined with the presence of vascular invasion, frequent development of metastases [14, 15], even such extremely rare as distant metastases to the brain [16] and liver [17]. According to other authors, PTC with OCh are characterized by signs of less aggressive behavior compared to PTC without OCh [18, 19]. As for the potentially radiogenic post-Chornobyl PTC, data on a comparative analysis of the histopathological characteristics of tumors with the presence and absence of OCh, to clarify the relationship between OCh and the development of recurrence of the disease, were not found in the available literature.

In view of this, the current study aims to analyze the frequency of OCh in PTC with increasing age of the operated patients and the time elapsed after the Chornobyl accident, to determine the effect of such changes on the invasive properties of tumors and the development of metastatic recurrences, i.e. to find out "place" of oncocytic metaplasia in potentially radiogenic papillary thyroid carcinomas.

MATERIALS AND METHODS

Patients. The study protocol was approved by the ethics committee of the State Institution "V.P. Komisarenko Institute of Endocrinology and Metabolism of NAMS of Ukraine" (IEM). The study included 483 Ukrainian PTC cases selected among 3,938 PTCs operated at IEM between 1990 and 2017, when a significant rise in thyroid cancer incidence was registered in Ukraine. At the time of the Chornobyl accident, these patients were living in the most contaminated by ^{131}I northern regions of the country, namely in Kyiv, Chernihiv and Zhytomyr regions. Additionally, they were distributed by age at the time of surgery for children (4–14 years: 121 cases), adolescents (15–18 years: 66 cases) and adults (19–28: 114 cases; 29–38: 99 cases and 39–48 years: 83 cases).

Dosimetry. Thyroid ^{131}I doses were estimated for every patient using the ecological and dosimetric model that includes iodine ecological transport and iodine biokinetic models. The model was adapted to available information about the patient's residence, and his/her individual direct thyroid measurements in May–June 1986. Estimated thyroid doses due to ^{131}I intake were based on the thyroid dose system used for the Chornobyl Tissue Bank [20, 21].

Histopathology. The biopsy material obtained from the surgical department was examined according to a standard protocol developed for the Chornobyl Tissue Bank [22]. First, the mass and size of the thyroid lobe, the size of the tumor, and the number and size of all removed lymph nodes were determined.

Tumor samples were fixed in 10% neutral formalin solution, further histologically processed in a Leica histoprocessor (Germany), and embedded in paraffin using a LAMB device (United Kingdom). The paraffin block microtomy was performed on a Leica RM2025 microtome (Germany). The paraffin sections were stained with hematoxylin and eosin, studied in Leica, Zeizz (Germany) microscopes, and a final pathological diagnosis was established according to the latest 4th Edition of the WHO Histological Classification [23]. Almost all cases included in the analysis were additionally reviewed by international experts as part of joint projects [24, 25] and by an international pathology panel of the Chornobyl Tissue Bank project [22, 26]. The diagnosis of PTC was confirmed in all cases.

Tumors were further classified according to the dominant histological growth pattern into three categories: papillary, follicular or solid-trabecular (when corresponding structure represented > 50% of a tumor). In addition, PTCs were assigned main histological variants according to the WHO classification [23] as follows: classic papillary, follicular, solid-trabecular, diffuse-sclerosing, Warthin-like and Tall cell variants.

We also evaluated oncocytic (oxyphilic/Hurtle) cell metaplasia in tumor cells. For this, PTCs in each age group were subdivided into two subgroups: i) tumors with the presence of OCh: OCh (+), and ii) tumor with their absence: OCh (–). OCh (+) PTCs included as tumors with focal OCh (1/2 +: up to 50% of cells had such changes), as well as tumors with severe oncocytic metaplasia (3/4 +: more than 50% of cells had OCh). Tumor stage was defined according to the 7th and 8th editions of TNM classification system [27, 28]. Only marked intrathyroid spread of the tumor to the lobe(s) was considered positive, including the diffuse-sclerosing variant (DSV)-like spread. Distant

metastases to the lung were determined by radioactive iodine scans performed following thyroidectomy.

Statistical analysis. Statistical analysis of the data obtained was performed using the GraphPad InState package computer program (GraphPad software, Inc., La Jolla, CA, USA). The likelihood of difference for the categorical data was estimated using the Fisher's Exact Test and for the continuous data using Mann-Whitney nonparametric test. We assessed changes in histopathological characteristics of PTCs across age groups using the chi-square test for trend. The difference between the indexes was considered significant at $p < 0.05$.

RESULTS

Descriptive characteristics of PTC in different age group. Five groups of patients with PTC were analyzed: aged 4–14, 15–18, 19–28, 29–38 and 39–48 years at the time of surgery. In all groups women were predominant, but the percentage of men in the childhood group was higher than in all other groups, and it was statistically significant compared to adults. All patients by age at the time of the Chornobyl accident did not exceed 14 years, that is, they were exposed to childhood, but in the group of the most adult patients (39–48 years at the time of surgery) the age of patients at the time of exposure was significantly higher than in all other groups. ^{131}I thyroid dose was the highest in the groups of children and adolescents and the lowest in the group of the most adult patients 39–48 years at the time of surgery. OCh in tumor cells significantly increased with age of the operated patients (Table 1).

Histopathological characteristics and OCh in PTC. The distribution of PTC in each age group into two subgroups was as follows: with the presence of OCh: OCh (+) and with the absence of such ones: OCh (–) showed that PTC with OCh (+) is more often nonencapsulated tumors compared to PTC without OCh (OR <1 for all corresponded subgroups). The presence of OCh did not significantly affect the mean PTC size and frequency of micro-PTC sized up to 10 mm, except for the mean size of childhood PTC with OCh (+), the size of which significantly exceeded the PTC size without OCh (Table 2).

Analysis of the histological structure showed that PTC with OCh (+) in almost all cases was associated with papillary or solid-trabecular dominant growth pattern (Fig. 1 *a, b*), whereas PTC with follicular dominant structure had OCh less than in 10% of cases, mainly in the presence of solid or papillary areas (see Table 2).

In our previous studies [3, 10] we have noted that the dominant growth pattern most often reflects the histologic subtype / variant of PTC or the largest structural component in tumors with mixed structure. Rare PTC subtypes, such as DSV, Warthin-like and Tall cell variants, have been detected in a small number of cases and had always been associated with OCh (+).

Thus, DSV was observed in 7 out of 10 cases (70.0%) in children, in one out of 4 (25.0%) in adolescents and in one out of 23 cases (4.3%) in adults aged 19–28 years. In all cases tumors with DSV were represented by oncocytic cell solid loci diffuse spreaded in both thyroid lobes. Warthin-like and Tall cell variants were found exclusively in the older age groups, that is, in patients aged from 29 to 48 years with the presence of OCh in the PTC cells. Thus, Warthin-like variant was observed in 7 out of 102 PTC with OCh availability (6.9%) and combined with papillary-solid structure (Fig. 2, *a*). Tall cell variant was registered

Table 1. Main characteristics of patients of different ages at the time of surgery with potentially radiogenic papillary thyroid carcinoma

Characteristics	Children	Adolescents	Adults	Adults	Adults
	4–14 years old (n=121)	15–18 years old (n=66)	19–28 years old (n=114)	29–38 years old (n=99)	39–48 years old (n=83)
	n (%) or mean (SD)[1]	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Female	72 (59.5)	44 (66.7)	86 (75.4)	78 (78.8)	60 (72.3)
Male	49 (40.5)	22 (33.3)	28** (24.6)	21** (21.2)	23* (27.7)
Age at exposure, years	1.9 (1.2)	1.6 (1.1)	2.0 (1.3)	4.4$^{\&}$ (2.6)	13.9$^{@}$ (2.5)
Age at surgery, years	11.5 (2.4)	16.7 (1.1)	23.9 (3.1)	33.9 (2.5)	43.5 (2.6)
^{131}I thyroid dose, mGy	984.0 (2113.3)	1333.3 (3438.4)	667.5 (1409.2)	157.7 (1536.1)	45.0$^{@}$ (54.8)
Oncocytic changes	10 (8.3)	4 (6.1)	23$^{\&}$ (20.2)	57$^{\&\$}$ (57.6)	45$^{\&\$}$ (54.3)

Note: [1]% – for count data; SD – for age and ^{131}I thyroid dose; *$p < 0.05$; **$p < 0.01$ compared with childhood group; $^{\&}p < 0.001$ compared with childhood and adolescents groups; $^{\$}p < 0.001$ compared with adults group aged 19–28 years; $^{@}p < 0.001$ compared with all previos groups.

Table 2. Main histopathological characteristics and ^{131}I thyroid doses in patients of different ages at the time of surgery with potentially radiogenic papillary thyroid carcinoma depending on presence or absence of oncocytic changes in the tumor's cells

Characteristics	Patients age at surgery (years)									
	4–14		15–18		19–28		29–38		39–48	
	OCh[1] (+) (n=10)	OCh (–) (n=111)	OCh (+) (n=4)	OCh (–) (n=62)	OCh (+) (n=23)	OCh (–) (n=91)	OCh (+) (n=57)	OCh (–) (n=42)	OCh (+) (n=45)	OCh (–) (n=38)
^{131}I thyroid dose, mGy	1695.7* (1947.0)	919.9 (2124.0[2])	478.0 (528.4)	1388.5 (3540.2)	719.9 (996.5)	354.2 (1499.9)	550.2 (1930.5)	332.1 (722.2)	40.9$^{\#\#}$ (47.9)	46.6$^{\&\&}$ (41.9)
Complete capsule	0 (–)	6 (5.4[2])	0 (-)	10 (16.1)	6 (26.1)	28 (30.8)	9 (15.8)	11 (26.2)	5 (11.1)	7 (18.4)
Tumor size (mm)	42.0** (19.8)	22.4 (13.0[2])	12.0 (2.8)	19.5 (12.1)	16.5 (10.4)	19.3 (12.1)	16.7 (12.1)	16.1 (9.3)	13.1 (7.8)	15.7 (11.5)
Tumor size ⩽ 10 mm	0 (–)	7 (6.3)	1 (25.0)	13 (21.0)	10 (43.5)	26 (28.5)	17 (29.8)	10 (23.8)	21 (46.7)	18 (47.4)
Dominant growth pattern										
Papillary	0 (–)	16 (5.4)	2 (50.0)	10 (16.1)	11 (47.8)	26 (28.6)	25 (43.9)	18 (42.9)	23 (51.1)	15 (39.5)
Follicular	0 (–)	16 (14.4)	0 (–)	14 (22.6)	2*** (8.7)	44 (48.4)	5** (8.8)	12 (28.6)	3*** (6.7)	14 (36.8)
Solid-trabecular	10*** (100)	61 (55.0)	2 (50.0)	23 (37.1)	10* (43.5)	21 (23.1)	27* (47.4)	12 (28.6)	19* (42.2)	9 (23.7)

Note: [1]OCh – oncocytic changes; [2]% for count data; SD for ^{131}I thyroid doses and mean tumor size; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ compared with OCh (–) in the corresponding age group; $^{\#\#}p < 0.01$ compared with OCh (+) or OCh (–) in all previous age groups.

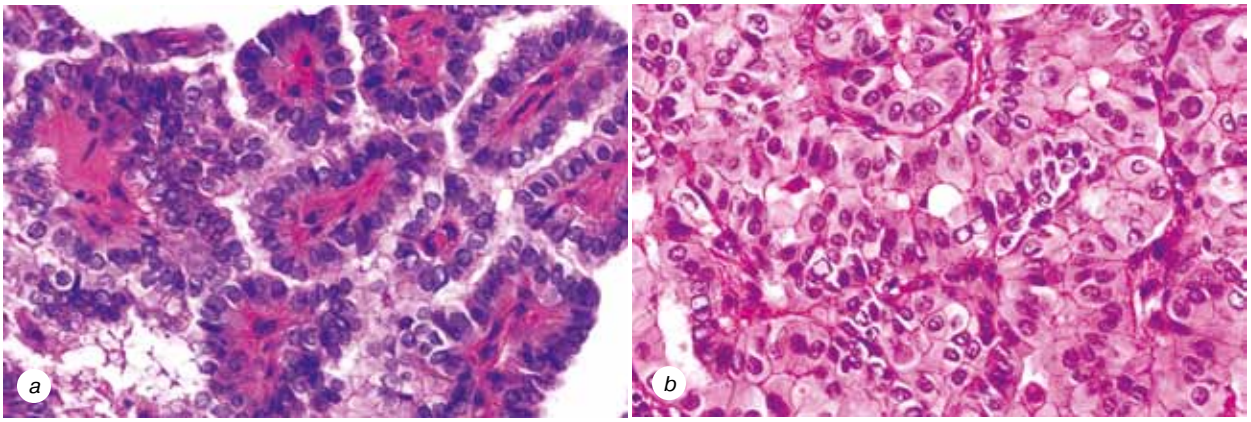

Fig. 1. Oncocytic changes in papillary thyroid carcinomas with dominant papillary growth pattern (*a*) and solid-trabecular growth pattern (*b*). Hematoxylin and eosin, original magnification. ×200

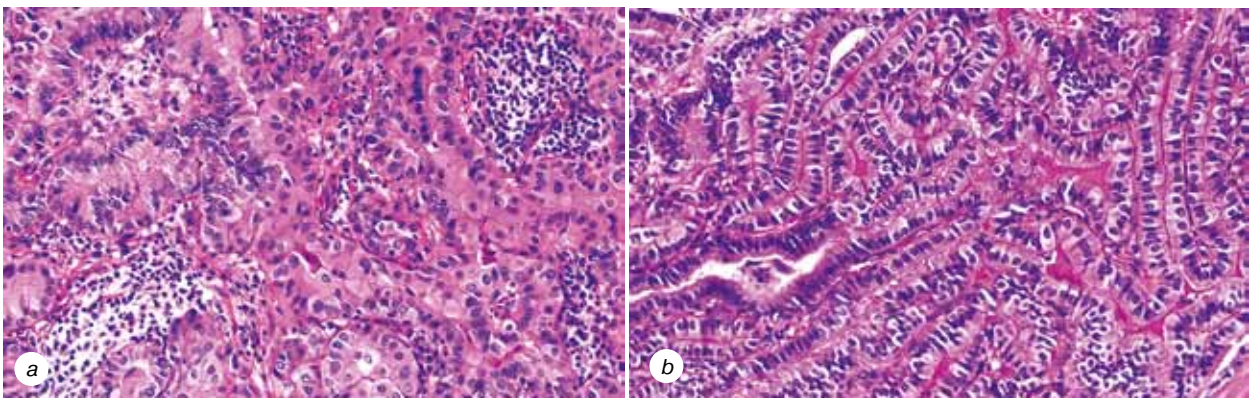

Fig. 2. Oncocytic changes in papillary thyroid carcinomas with Warthin-like (*a*) and Tall cell (*b*) histological PTC's variants. Hematoxylin and eosin, original magnification. ×200

in 9 out of 102 cases (8.8%) with dominant trabecular growth pattern (Fig. 2, *b*).

A comparative analysis of the invasive properties of PTC with presence and absence of OCh revealed no significant differences in the majority of indicators, except for the significantly higher frequency of multifocality in PTC with OCh (+) in adults aged 19–28 years (Table 3). Also attention was paid to the fact that such an important invasiveness' indicator as extrathyroidal extension to muscle tissue, which was isolated by the 8th edition of the TNM classification [28] into a separate category (T3b), in patients aged up to 28 years, was consistently lower in PTC with OCh (+) than in PTC without OCh (OR <1 in all corresponding subgroups), but in patients aged from 29 to 48 years, this indicator for PTC with OCh presence was twice as high than in PTC without OCh (OR = 2.0).

Among the concomitant thyroid pathology associated with the presence of OCh in PTC (Table 4), attention should be paid to concomitant chronic thyroiditis, the incidence of which is higher than that of PTC without OCh (OR > 1 in all relevant subgroups). Concomitant thyroid and non-thyroid cancers were extremely rare in the series studied and apparently not related to OCh in PTC (see Table 4).

^{131}I thyroid dose and OCh in PTC. With regard to ^{131}I thyroid doses, significant difference between them in tumor with OCh (+) and tumor with OCh (–) was found only in childhood group, where mean ^{131}I thyroid dose was significantly higher in PTC with OCh (+). In the oldest age group (39–48 years at the time

Table 3. Main invasive characteristics of potentially radiogenic papillary thyroid carcinoma in patients of different ages at the time of surgery with depending on presence or absence of oncocytic changes in the tumor's cells

Characteristics	Patients age at surgery (years)									
	4–14		15–18		19–28		29–38		39–48	
	OCh[1] (+) (n=10)	OCh (–) (n=111)	OCh (+) (n=4)	OCh (–) (n=62)	OCh (+) (n=23)	OCh (–) (n=91)	OCh (+) (n=57)	OCh (–) (n=42)	OCh (+) (n=45)	OCh (–) (n=38)
ITS	9 (90.0)[2]	80 (72.1)	1 (25.0)	19 (30.6)	8 (34.8)	23 (25.3)	14 (24.6)	8 (19.0)	12 (26.7)	9 (23.7)
ETE (T3: 7-th TNM ed)	8 (80.0)	75 (67.6)	1 (25.0)	29 (46.8)	3 (13.0)	32 (35.2)	20 (35.1)	13 (31.0)	11 (24.4)	7 (18.4)
ETE (T3b: 8-th TNM ed)	2 (20.0)	25(22.5)	0 (–)	6 (9.7)	0 (–)	4 (4.4)	3 (5.3)	1 (2.4)	2 (4.4)	1 (2.6)
Multifocality	0 (–)	7 (6.3)	1 (25.0)	6 (9.7)	10* (43.5)	12 (13.2)	14 (24.6)	15 (35.7)	15 (33.3)	8 (21.1)
Lymphatic/vascular invasion	9 (90.0)	94 (84.7)	2 (50.0)	42 (67.7)	7 (30.4)	38 (41.8)	26 (45.6)	15 (35.7)	17 (37.8)	12 (31.6)
Lymph node metastases	7 (70.0)	76 (68.5)	2 (50.0)	33 (53.2)	9 (39.1)	31 (34.1)	21 (36.8)	15 (35.7)	12 (26.7)	11 (28.4)
Distant lung metastases	4 (40.0)	26 (23.4)	0 (–)	9 (14.5)	1 (4.3)	3 (3.3)	2 (3.5)	2 (4.8)	0 (–)	0 (–)

Note: [1]OCh – oncocytic changes; ITS – intrathyroid spreading; ETE – extrathyroid extension; [2]% for count data; *$p < 0.01$ compared with OCh (–) in the corresponding age group.

Table 4. Concomitant pathology and nodal disease recurrences in patients with potentially radiogenic papillary thyroid carcinoma of different ages at the time of surgery with depending on presence or absence of oncocytic changes in the tumor's cells

Characteristics	Patients age at surgery (years)									
	4–14		15–18		19–28		29–38		39–48	
	OCh[1] (+) (n=10)	OCh (–) (n=111)	OCh (+) (n=4)	OCh (–) (n=62)	OCh (+) (n=23)	OCh (–) (n=91)	OCh (+) (n=57)	OCh (–) (n=42)	OCh (+) (n=45)	OCh (–) (n=38)
Other thyroid carcinoma	0 (–)	1 (0.9)	1 (25.0)	0 (–)	0 (–)	0 (–)	0 (–)	1 (2.4)	1 (2.2)	0 (–)
Bening thyroid nodular pathology	0 (–)	2 (1.8)	0 (–)	9 (14.5)	5 (21.7)	10 (11.0)	14 (24.6)	10 (23.8)	22 (48.9)	10 (26.3)
Chronic thyroiditis	6* (60.0)	9 (8.1)	0 (–)	5 (8.1)	6 (26.1)	14 (15.4)	21 (36.8)	8 (19.0)	19 (42.2)	9 (23.7)
Recurrences of regional metastases	1 (10.0)	1 (0.9)	0 (–)	2 (3.2)	1 (4.3)	2 (2.2)	3 (5.3)	0 (–)	5 (11.1)	0 (–)
Additional non-thyroid cancer	2 (20.0)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	1 (2.6)

Note: [1]OCh – oncocytic changes; *$p < 0.001$ compared with OCh (–) in the corresponding age group.

of surgery), in contrast, a significant decrease in thyroid doses was observed in both subgroups: with presence and absence of OCh (see Table 2). Overall, the mean ^{131}I thyroid dose among 139 PTC patients with OCh (493.7 mGy) was significantly lower compared to the same indicator in 344 PTC patients without OCh (765.8 mGy, $p < 0.0001$).

Postoperative follow-up data. In total, 475 out of 483 patients (98.3%) underwent postoperative follow-up at the IEM for 0.01 to 28.0 years (average 7.9 ± 7.2 years). 325 out of 475 (68.4%) patients received after radioiodine treatment (RIT) also at the IEM and underwent from one to 10 courses of RIT: the average number of courses was 1.7 ± 1.4, the average cumulative dose of radioiodine was 5565.1 ± 5352.2 MBq. No significant difference was observed between the number of RIT courses or the average cumulative dose of radioiodine in patients with PTC with or without OCh. 73 out of 475 patients (15.4%) who underwent postoperative follow-up at the IEM received RIT at other hospitals of Ukraine but provided information on the RIT results to IEM at the current examination.

The number of recurrent metastases requiring reoperation was small, accounting for a total of 15 out of 475 cases (3.1%). The recurrence-free period lasted from one to 9 years.

In patients in whom primary PTC was characterized by OCh, recurrences of regional metastases occurred more likely than in patients without OCh in the primary tumor (10/139 cases, 7.2% *vs* 5/344, 1.5%, $p = 0.0022$, OR = 5.3). In addition, patients aged 29–48 years in whom primary PTC was without OCh (first surgery during 2015 — 2017) have no recurrence of lymph node metastases to date (see Table 4). In patients aged 29–48 years with OCh in the primary tumor, 6 among 8 recurrences of regional metastases (75.0%) were insensitive to RIT, while among 7 recurrences of regional metastases in patients 4–28 years there was no case of radioiodine-insensitive metastases ($p = 0.007$). It should be noted that, regardless of the age of patients and the presence of OCh in the primary tumor, among 15 cases of recurrent regional metastases, oncocytic cell metastases with trabecular-solid or papillary-trabecular-solid dominant growth pattern prevailed (13/15, 86.7%).

Age-related trends of histopathological characteristics of PTC with presence and absence of OCh. Statistically significant age-related linear trends in histopathological characteristics associated with potentially radiogenic PTC were more pronounced in tumors without OCh (Table 5). The histopathologic characteristics of PTC with the presence of OCh either did not show linear age-related trends, or such trends did not differ in direction ("up" or "down" trends) and were less statistically significant. An exception is the much higher significance of a trend toward a decrease in ^{131}I thyroid dose in PTC patients with the presence of OCh (see Table 5).

DISCUSSION

Our previous studies have found that the frequency of OCh in children, adolescents, and young adults aged up to 28 years at the surgery with radiogenic PTC was significantly lower compared to sporadic PTC (more than 2-fold) in all age-matched groups [12]. The age at surgery in the mentioned study was limited by 28 years, because there were no older sporadic non-irradiated by Chornobyl ^{131}I PTC cases (patients born after the Chornobyl accident) when the study was performed.

At the same time, the age of patients from a high-risk group of developing radiogenic thyroid cancer (children and adolescents at the time of the Chor-

Table 5. Age-related trends for different characteristics of potentially radiogenic papillary thyroid carcinoma depending on presence or absence of oncocytic changes in the tumor's cells

Characteristics	Patients age at surgery (from 4 to 48 years)	
	OCh[1] (+)	OCh (–)
	p_{trend}	p_{trend}
Oncocytic cell changes		
Oncocytic cell changes	< 0.0001↑	-
^{131}I thyroid dose		
^{131}I thyroid dose	0.0092↓	0.0482↓
Histopathology		
Complete tumor capsule	0.777	0.0006↑
Tumor size ⩽ 10 mm	0.085	< 0.0001↑
Dominant growth pattern:		
papillary	0.021↑	< 0.0001↑
follicular	0.526	0.443
Solid-trabecular	0.009↓	< 0.0001↓
Concomitant bening thyroid pathology	0.0003↑	< 0.0001↑
Chronic thyroiditis	0.877	0.013↑
Invasive features		
Intrathyroid spread	0.001↓	< 0.0001↓
Extrathyroid extension (any)	0.031↓	< 0.0001↓
Extrathyroid extension (muscle: T3b)	0.266	< 0.0001↓
Multifocality (Tm)	0.201	< 0.0001↑
Lymphatic/vascular invasion	0.063	< 0.0001↓
Lymph node metastases (N1)	0.011↓	< 0.0001↓
Distant lung metastases (M1)	< 0.0001↓	< 0.0001↓
Recurrences of regional metastases	0.525	0.345

Note: [1]OCh – oncocytic changes; ↑ – an uptrend; ↓ – a downtrend.

nobyl accident) reached 48 years in 2017. Therefore, in the current study, a comparative analysis of the PTC's structural characteristics, their invasive properties, frequency of metastasis recurrences and ^{131}I thyroid doses in the presence and absence of OCh in the primary potentially radiogenic PTC with increasing patient's age at surgery up to 48 years was performed.

It was revealed that the OCh frequencies in the oldest age groups (29–38 and 39–48 years) were the highest (see Table 1), and did not have significant differences not only among themselves, but also in comparison with this indicator in adult PTC patients aged 35–60 years (average 47.8 ± 6.7 years) who were not included in high-risk age group and did not live in ^{131}I contaminated regions of Ukraine [29]. In such patients, OCh have been observed in 58.9% (33 out of 56) cases (p = 0.605 compared with the age group aged 39–48 years in the current study). There was also no significant difference in the OCh frequency in the oldest age group with that reported for patients with PTC of a similar age from North Korea who did not have a history of irradiation [30].

With regard to the histological structure, it is obvious that the presence of OCh is associated with the papillary and solid-trabecular dominant growth pattern. The PTC of the follicular dominant structure had an OCh of less than 10% of cases, mainly in the presence of solid or papillary areas. Comparative analysis of invasive properties of PTC with and without OCh did not reveal significant differences between most invasiveness indicators, that is, PTCs with OCh in patients of the studied age groups were not characterized by morphological signs of higher aggressiveness.

It is important to emphasize that only in childhood group was obsereved significantly higher ^{131}I thyroid dose for PTC with OCh compared with PTC without OCh (see Table 2). It may be due to the fact that in the present series, OCh in children were represented by DSV of PTC in 70.0% of cases, which is apparently associated not only with OCh but also with higher ^{131}I thyroid doses.

The revealed significantly increasing linear age-related trend for OCh may be partly associated with an increase in the frequency with age of PTCs mostly consisting of oncocytic cells, such as Warthin-like and Tall cell variants. Potential somatic mutations underlying these trends remain unclear, including the relationship between OCh and availability of *BRAF* mutations. The possibility of such a relation and the appropriateness of its analysis in further studies are indicated by the fact that *BRAF* mutations (as well as OCh in this study) are more likely to occur in PTC of a classical papillary or trabecular structure), and the frequency of such mutations increases with age [31].

In addition, the significant increase of OCh frequency with increasing patients' age and the time elapsed since the Chornobyl accident simultaneously with a linear decrease in ^{131}I thyroid doses (see Table 5) may be explained by the gradual increase of sporadic PTC cases among patients of potentially radiogenic series. This assumption is supported by a significant decrease in the relative risk (EOR/Gy) of developing radiogenic PTC among members of the Ukrainian-American cohort over time passed after Chornobyl: from 5.25 in 1998–2000 to 1.36 in 2012–2015 [6, 7] and the similarity of OCh rates to those reported in non-irradiated patients aged over 40 years at the time of surgery [29, 30].

It is important to emphasize that, despite the fact that the frequency of regional metastases recurrences was generally low in patients aged 4 to 48 years (15/483, 3.1%), recurrence of nodal disease was significantly higher if primary PTC has OCh. Associations between OCh, age of the operated patients and development of radioiodine-insensitive recurrence of metastases are also traced.

Summarizing the results, it should be concluded that in patients from the high-risk group for the development of radiogenic thyroid cancer, with the increase of their age at the time of surgery, there was a significant linear increase in the frequency of OCh in PTC tumor cells and the opposite direction of the linear decrease in the average thyroid radiation dose. In our opinion, this may reflect a gradual increase of sporadic PTC cases among patients of potentially radiogenic series. An increase in the frequency of OCh in the primary tumor was also associated with more frequent recurrences of regional metastases that were insensitive to radioiodine therapy.

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