1. TITLE PAGE

Original Contribution: Characteristics of cribriform morular variant of papillary thyroid carcinoma in post-Chernobyl affected region

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2. ABSTRACT

The aim is to study the characteristics of cribriform morular variant of papillary thyroid carcinoma (CMV-PTC) in patients living in radiation-affected area of Belarus. The clinical and pathological features of 35 patients with CMV-PTC from Belarus were studied and compared with those of conventional papillary thyroid carcinoma diagnosed in the same period. The patients with CMV-PTC were all females and were younger at presentation (mean age = 24) than those with conventional papillary thyroid carcinoma. Familial adenomatous polyposis (FAP) was identified in 20% of the patients with CMV-PTC. The majority of the CMV-PTCs (29/35; 83%) were staged as pT1 and were less advanced than conventional papillary thyroid carcinoma. There was no evidence of lymph node metastases or distant metastases. CMV-PTCs were positive for beta-catenin, APC (adenomatous polyposis coli) and p53 proteins. No psammoma bodies were identified on microscopic examination. Over a median follow-up of 9 years, all the patients were alive, there were no cancer recurrence or mortality related to the thyroid cancer. To conclude, patients with CMV-PTC in radiation-affected region behave in an indolent fashion. They had distinctive features that are different from patients with conventional papillary thyroid carcinoma living in the same region.

KEY WORDS: Cribriform morular variant; papillary thyroid carcinoma; radiation.

3. INTRODUCTION

In 1990, Chan and Loo from Hong Kong reported the first case of cribriform morular variant of papillary thyroid carcinoma (CMV-PTC) in the English literature [1]. This variant of papillary thyroid carcinoma was first accepted as a variant of papillary thyroid carcinoma in the third edition of World Health Classification (WHO) of tumours: tumours of endocrine organs published in 2005 [2]. It was labelled as ‘cribriform carcinoma’. In the current edition of WHO classification of endocrine tumours in 2017, the tumour is called “cribriform-morular” variant of papillary thyroid carcinoma [3, 4]. Belarus is a country highly affected by an accident at the Chernobyl nuclear power plant in Ukraine on April 26, 1986. Radiation is a known predisposing factor for thyroid cancer. Studies have reported that these thyroid cancers in radiation-affected areas affect mainly children, adolescents and young adults and have different characteristics when compared to the thyroid cancers noted in non-radiation affected areas [5, 6].

CMV-PTC is uncommon and affects mainly young adults [3, 4]. Survival data from the literature for patients with CMV-PTC were derived mainly from case reports and small reported series from non-radiation affect areas [7]. The clinical behaviour of the CMV-PTC in radiation-exposed region have not been studied. In this study, we analysed the clinical and pathological features of all the CMV-PTC reported over the past 23 years in Belarus. We also compared the features of them with the conventional papillary thyroid carcinoma diagnosed in the same period. In addition, the features of CMV-PTC noted in the population were compared with CMV-PTC reported in the English literature.

4. SUBJECTS AND METHODS

The clinical presentation, pre-operative ultrasonic examination and fine needle aspiration, surgical treatment, postoperative adjuvant therapy, recurrence and long-term survival data of the patients with CMV-PTC were studied. The Review Board of the Minsk Municipal Clinical Hospital for Oncology in Minsk for Belarus approved the study. The patients with thyroid cancer gave the consents at the time of surgery to share epidemiological, clinical and pathological data for further investigation. The privacy rights was obtained for experimentation with human subjects. The location, size and histological features of the tumours were noted on pathological examination. The Tumour–Lymph nodes–Metastasis (TNM) staging was determined according to the eight edition of AJCC (American Joint Committee on Cancer) Cancer staging manual [8].

The authors have reviewed and confirmed the diagnosis of CMV-PTC diagnosed in the Department of Pathology of Minsk Municipal Clinical Hospital for Oncology in Belarus between the years 1993 to 2015 using the criteria of the WHO Classification of Tumours of Endocrine Organs [3, 4]. The laboratory in the Department of Pathology was set up in the year 1995. The same team of pathologists diagnosed all the thyroid carcinomas in Belarus. Amongst these, patients with papillary thyroid carcinomas having the features of CMV-PTC were identified for further clinical and pathological studies. After the histological review, a block from each patient with representative CMV-PTC morphology was selected for immunohistochemical analysis. The antibodies used were against beta catenin (Thermo Fisher Scientific), APC (adenomatous polyposis coli) (Thermo Fisher Scientific), p53 (Dako) and Ki-67 (Thermo Fisher Scientific). The antibodies used were pre-diluted. The deparaffinised sections were treated with buffer and stained according to the protocols recommended by the companies. Blocks of colonic adenoma and colonic adenocarcinoma from patients with polyposis coli were used as positive controls for staining of beta catenin and APC. A block of anaplastic thyroid carcinoma was used as positive control for Ki-67 and p53. In addition, a block of

conventional papillary thyroid carcinoma was used to compare the staining of CMV-PTC in beta catenin and APC staining.

The data of the patients with CMV-PTC and conventional PTC diagnosed in the same Belarus hospital were entered in a database for statistical analysis. Statistical analysis was made with the Statistical Package for Social Sciences for Windows (version 24.0, IBM, New York, NY, USA). Significance level was taken at $p < 0.05$.

We have previously reviewed the 129 cases of CMV-PTC in the literature [7]. No evidence was present that these patients were from areas affected by post-Chernobyl radiation or previously treated with external irradiation. In this study, we compared the features of the CMV-PTC in radiation-affected areas with those of the 129 reported cases in the literature.

RESULTS

There were 35 patients with CMV-PTC noted (Table 1). In the same period, there were 21,355 papillary thyroid carcinomas noted in the same institution. Thus, the variant accounted for 0.16% of papillary thyroid carcinomas diagnosed over the 23-years study period in the country of Belarus. In addition, in the same period, there were 14,353 patients with conventional papillary thyroid carcinoma and 7,002 patients with follicular, diffuse sclerosing, tall cell and other variants.

All the patients with CMV-PTC were females. On the other hand, the female to male ratio of conventional papillary thyroid carcinoma was 4.9 to 1. The difference in gender distribution between the CMV-PTC and conventional papillary thyroid carcinoma was significant ($p=0.0001$). The mean and median age of patients with CMV-PTC at presentation was 24 years and 21 years respectively (range = 15-52 years). The patients with CMV-PTC most often presented in the second decade of life (age = 10-19; $n=15$). Seventy-four percent ($n=26$) of the patients were under the age of 30 years at presentation. In contrast, the mean and median age of patients with conventional papillary thyroid carcinoma was 46 years and 48 years respectively (range= 5 to 93). Only 15% of the conventional papillary thyroid carcinoma were younger than 30 years at presentation. The difference in age distribution between the two variants of papillary thyroid carcinoma was significant in this population ($p=0.0001$).

All the patients with CMV-PTC were asymptomatic. The thyroid nodules in these patients were detected during the check-up by general practitioners. They were often diagnosed as benign lesions by ultrasonic examination; with 86% (30/35) being reported as benign thyroid nodules. The remaining 14% ($n=5$) of patients were reported as suspicious of cancers.

Of the 35 patients with CMV-PTC, 20% ($n=7$) had familial adenomatous polyposis (FAP) or FAP-associated syndromes. All but one had T1 thyroid cancers. Five of these 7 patients had single or multiple colonic polyps revealed during 1 to 185 months after the detection of the thyroid cancer and three had colonic cancers. One of these three patients also had frontal sinus osteoma. The patient was

diagnosed on clinical ground to have follicular adenoma and had a right lobectomy. Six years later, she had multiple foci of CMV-PTC detected in the left thyroid. The original slides of the right lobe were reviewed and the follicular adenoma was reclassified as CMV-PTC. The osteoma was detected one year after the resection of the thyroid cancer. She also had two colonic cancers (one in transverse colon and one in sigmoid colon) resected 10 years and 11 years after the operation for the thyroid cancer. The other patient with Gardner syndrome was operated for an osteoma of mandible detected by radiological examination sixteen years before the diagnosis of thyroid cancer, but she had no colonic polyposis.

The remaining patient was diagnosed to have Grade 4 medulloblastoma with the involvement of the cerebellar vermis, the roof of the 4th ventricle and C1-C2 spinal cord at the age of 7. She was treated with post-operative radiotherapy. During the post-treatment follow-up, she was diagnosed with thyroid tumor at the age of 16. 3920 T>A mutation in *APC* gene was detected by polymerase chain reaction. The patient had no colonic polyps. The patient was diagnosed to be a type 2 Turcot syndrome.

Of the 35 patients with CMV-PTC, five were the members of the specific epidemiological cohort that includes 11,664 individuals who were aged ≤ 18 years at the time of the Chernobyl accident on April 26, 1986. In this cohort all study participants had thyroid radioactivity measurements taken in Belarus within 2 months after the accident and were screened for the first time during 1997 to 2000. The cohort was screened two more times during 2002 to 2004 and 2004 to 2006, and final follow-up was extended to the end of September 2008 to account for patients who were referred for additional biopsies and surgeries [9]. Besides, two patients had intra-uterine exposure and 17 patients were children (1-14 years old at exposure) at the time of the Chernobyl accident and more likely their papillary thyroid carcinoma was associated with internal irradiation with radioactive iodine [10]. Therefore, 2/3 (24 of 35) of our patients more likely were exposed to post-Chernobyl irradiation.

Ten patients were born long after the full decomposition of ^{131}I or were adults at the time of exposure and have no/very low risk to develop post-Chernobyl papillary thyroid carcinoma. One

patient was a child at the time of the Chernobyl accident but lived in an unpolluted area. The patient was operated for the first time for a 16-mm CMV-PTC in the year 2007 at the age of 35 years old. Next year she was diagnosed with multiple colonic polyps and colorectal carcinoma. She died of this second primary malignancy in the year 2011.

Overall, four of seven patients with familial adenomatous polyposis and associated syndromes had no direct connection to post-Chernobyl ^{131}I exposure. Although limited information on residential history and consumption available, it is possible to conclude that their thyroid doses due to I-131 intake range from a few milliGray to around 6 Gray (Vladimir Drozdovitch, personal communication, Minsk, Belarus, December 2017).

All the patients had fine needle aspiration done before surgery for the thyroid cancers. On fine needle aspiration, the diagnosis of 80% (28/35) of the lesions were either consistent or suspicious of papillary thyroid carcinoma. The other patients were diagnosed to have benign lesions (n=4) or follicular neoplasms (n=3).

Surgical treatment included total thyroidectomy plus lymph node dissection in 77% (n=27) and lobectomy in 23% (n=8) of the cases. The carcinomas were at the right lobe in 40% (n=14), the left lobe in 31% (n=11), both lobes in 26% (n=9) and the isthmus in 3% (n=1) at presentation. The mean diameter of the CMV-PTCs was 35 mm (range, 15 to 60 mm). Approximately two third (63%; n = 22) of the carcinomas are less than 10 mm in maximum dimension. Multi-focal thyroid carcinomas were detected in 31% (n=11) of the cases. Multi-focal thyroid carcinomas were noted in 6 of 7 patients (85.7%) having CMV-PTC with FAP. On the other hand, only 18% (5/28) patients having CMV-PTC without FAP had multi-focal thyroid carcinomas. The difference are statistically significant (p=0.002).

On macroscopic examination, CMV-PTC was often well demarcated (Figure 1). On microscopic examination, the thyroid cancers showed nuclear features of papillary thyroid carcinoma well as typical cribriform and morular areas in different proportions. There were no psammoma bodies identified (Figure 2). Many CMV-PTCs showed lymphovascular invasion (noted in 37%; 13/35). In

two patients, the CMV-PTCs were associated with separate papillary carcinoma with different morphology. One patient had a 60 mm follicular variant of papillary thyroid carcinoma. The other had a 5 mm conventional papillary thyroid carcinoma with metastatic focus of carcinoma in lymph node having morphology of conventional papillary thyroid carcinoma.

The majority of the CMV-PTCs (29/35; 83%) were staged as pT1. There were five (14%; 5/35) pT2 cancers. Only one patient (3%) had pT3a cancer with size of 47 mm. There was no case with extra-thyroidal invasion invading to the muscles. In patients with conventional papillary thyroid carcinoma, 53% (n=7681) was classified as T1, 14% as T2 (n=2047), 27% as T3 (n=3816) and as 6% T4 (n=809). The difference in T staging between the CMV-PTC and conventional papillary thyroid carcinoma was significant ($p=0.001$).

Apart from the patient with a separate papillary micro-carcinoma mentioned above, all the patients with CMV-PTC showed no evidence of lymph node metastases. On the other hand, 39% (5539 of 14,353) of conventional papillary thyroid carcinoma had lymph node metastases. The difference in prevalence of lymph node metastases between CMV-PTC and conventional papillary thyroid carcinoma was significant ($p=0.0001$). In addition, no evidence of distant metastasis was present in patients with CMV-PTC. It is worth noting that 0.88% (127 of 14,353) of conventional papillary thyroid carcinoma showed distant metastases. The difference was not statistically significant.

Immunohistochemical staining showed that the CMV-PTC were strongly positive for beta-catenin (both cytoplasmic and nuclear positivity). The pattern of expression in CMV-PTC was different from conventional papillary thyroid carcinoma and non-neoplastic thyroid follicles (Figure 3). Nuclear staining of APC protein was noted in CMV-PTC including carcinomas from patients with FAP (Figure 4A). P53 nuclear staining was noted too (Figure 4B). On the other hand, Ki-67 index (nuclear positivity) was low in all cases (less than 5%) (Figure 4C).

No patient with CMV-PTC has received radioactive iodine therapy after surgery. On the other hand, 23% (3,300 of 14,353) patients with conventional papillary thyroid carcinoma had received radioactive iodine therapy after surgery. The difference was significant ($p=0.0001$).

The mean and median follow-up period for patients with CMV-PTC was 9.6 years and 8.9 years respectively. Approximately half of the patients ($n=17$; 49%) had more than 10 years' follow-up. All the patients were alive without evidence of thyroid cancer during last follow-up. There were no cancer recurrence or mortality related to the thyroid cancer. On the other hand, there were two deaths reported in the patients with FAP. These patients died of adenocarcinoma of colon.

6. DISCUSSION

In the literature, there were 129 well-documented CMV-PTC [7]. These patients were not reported in areas affected intensively by radiation and could be considered as having sporadic thyroid cancer. In 2015, Mitsutake and colleagues have mentioned four CMV-PTC in the settings of FAP [11]. These four patients were found amongst the thyroid cancers from the young population in Fukushima of Japan (affected recently by accident at the Fukushima Daiichi nuclear power plant). No pathological or clinical details of the CMV-PTCs were documented in the study. The current series of 35 patients with CMV-PTC is the only group showing the characteristics of CMV-PTC in region affected by Chernobyl accident (Table 1).

The largest series of CMV-PTC comprised 32 CMV-PTCs from Japan [12]. However, no detailed information or prevalence of the disease was noted. Researchers from the same hospital have documented the prevalence of CMV-PTC in papillary thyroid carcinoma was 0.22% (18 of 8583) [13]. The other large series of CMV-PTC was reported in USA and have documented a prevalence of CMV-PTC as 0.16% of papillary thyroid carcinoma [14]. In the present series, we have selected the period that the patients with thyroid cancer were born or were very young during the time of radiation exposure. The present analysis showed that the prevalence of the CMV-PTC in papillary thyroid carcinoma in Belarus (0.16% of papillary thyroid carcinoma) was similar to the radiation unaffected regions.

Table 2 showed the features of CMV-PTC documented in the literature versus those in the current series [7]. In the literature, CMV-PTC occurred almost exclusively in females (female to male = 31 to 1). In this series with 35 patients of CMV-PTCs from radiation-affected region, all the patients were females. Papillary thyroid carcinomas often occur in the fifth decade of life [15]. In papillary thyroid carcinoma, diffuse sclerosing variant of PTC and CMV-PTC are often noted in young patients [7, 16, 17]. In the literature, patients with CMV-PTC presented younger than those with diffuse sclerosing variant of PTC. In the current series, CMV-PTCs were noted in the third decade of life and

mean age at presentation of the patients was 24. The mean age at presentation for patients with CMV-PTC in Belarus was similar to that of CMV-PTC noted in regions not affected by radiation [7].

FAP is an autosomal dominant polyposis syndrome characterized by hundreds of adenomas resulting in large intestinal cancers in early age [18]. Mutation in the *adenomatous polyposis coli* (*APC*) tumour suppressor gene has been implicated in FAP. FAP accounted for 4% of patients with synchronous colorectal carcinoma [19, 20]. In the literature, nearly half of the patients with CMV-PTC presented with FAP. In contrast, only 20% (n=7) of our patients having CMV-PTC had FAP or FAP-related syndromes. All the 35 patients with CMV PTC were screened for FAP/Gardner (Turcot) syndrome with colonoscopy and skull X-ray. Thus, the presence of FAP do not account for an important role in the pathogenesis of majority of patients with CMV-PTC in radiation-affected region. The effect of irradiation may favour the pathogenesis of formation of CMV-PTC over other genetic mechanisms.

Gardner syndrome is a type of FAP having extra-colonic manifestations such as thyroid cancer, fibromatosis and osteoma [21]. In the literature, patients with CMV-PTC sometimes presented with fibromatosis [7]. One patient with CMV-PTC had co-existing osteoma [22]. In the current series, two had osteomas and were diagnosed with Gardner syndrome. Type 2 Turcot's syndrome is a type of FAP with brain tumours – most often medulloblastoma [23]. Fenton and colleagues reported a patient having both CMV-PTC and medulloblastoma [24]. In this series, another case of type 2 Turcot's syndrome with CMV-PTC and medulloblastoma was noted. In the literature, around half of the patients with CMV-PTC had the thyroid cancer as first presentation of the disease [7]. In contrast, in the present series, all patients had thyroid cancer as the first presentation and with colonic cancer being detected later.

It is likely the earlier detection of the thyroid cancer before that of colonic cancer or polyposis in patients with FAP in this setting is due to active screening of thyroid cancer in this region. In Belarus, mass screening using mobile teams and prophylactic examinations in schools and outpatient clinics

started in the year 1987. A dynamic monitoring system is constantly in operation with annual medical examinations of population in the risk group of having post-Chernobyl malignancies. Thus, 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 nodules, including papillary micro carcinomas.

Microscopically, CMV-PTC could be multifocal, showing lymphovascular permeation as well lacking psammoma bodies [7]. In the current series of CMV-PTC, the tumours showed similar histological features to those CMV-PTs reported in the literature. In addition, none of the cases revealed the presence of psammoma bodies. In the absence of psammoma body, the nuclear features of papillary thyroid carcinoma as well as the cribriform and morular areas architecture are the key to identify this variant of papillary thyroid carcinoma.

APC and β -catenin are key members of the Wnt signalling pathway that is important in the pathogenesis of many cancers [25]. Mutations in the *APC* gene leads to the synthesis of truncated APC proteins with loss of expression in the tumour cells. As a result, β -catenin accumulates in the cytoplasm and translocates to the nucleus. Characteristically, CMV-PTC showed strong positivity to β -catenin [8]. APC protein often lost in the sporadic or FAP related colonic cancer [26]. In the present series, all the cases showed strong positivity to β -catenin. However, there was no loss of APC protein in all the cases with CMV-PTC in the present series (both FAP and non-FAP associated cases). Thus, the nuclear β -catenin accumulation is not related to APC mutation but may be explained by other mechanisms. In addition, there is a functional cross talk between p53 and Wnt signalling pathway [27]. P53 could lead to degradation of β -catenin. In the literature, two cases were reported to be negative for p53 [28]. On the other hand, a case showed p53 nuclear positivity in the solid area of CMV-PTC [29]. In the present series, all the CMV-PTC were weakly positive for p53 protein. It may suggest that *TP53* mutation may have a role in the pathogenesis of CMV-PTC.

Compared to conventional papillary thyroid carcinoma, CMV-PTC had a relative lower biological aggressiveness and better prognosis in terms of lower frequency of lymph node and distant metastases as well as low recurrence rates and cancer related mortality [7]. In the current series of CMV-PTC noted in radiation-affected region, there was absence of lymph node and distant metastases in all the cases. In addition, with a median follow-up of 9.6 year, no cancer recurrence or mortality due to thyroid cancer noted in these patients. It appears that patients with CMV-PTC in radiation-affected region have better prognosis when compared to those in non-radiation affected regions. It is worth noting nearly all the cancers detected in the present series were of low stages (either T1 or T2) and of smaller size when compared to CMV-PTC noted in non-radiation affected areas. In addition, Ki-67 proliferative index was low in all the cases. The reason of the relative indolent nature of CMV-PTC in Belarus could be related to their early detection because of active screening of thyroid cancer in the region too.

In summary, the present series represents the largest series of CMV-PTC in noted in the English literature. In addition, the characteristic features of CMV-PTC noted in the radiation-affected region was presented for the first the time. CMV-PTC identified in Belarus had distinctive features that are different from the conventional papillary thyroid carcinoma. Furthermore, some of the features of CMV-PTC detected in this radiation-affected region differs from CMV-PTC noted in the literature.

DECLARATION OF INTEREST

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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AUTHOR CONTRIBUTIONS

Alfred King-yin Lam – reviewed the pathology; data analysis and wrote the manuscript

Mikhail Fridman – data collection, reviewed the pathology and edited the manuscript.

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12. FIGURE LEGENDS

Figure 1. Macroscopic appearance of cribriform papillary thyroid carcinomas. On gross examination, the carcinomas are fleshy and well demarcated. There is not much difference between cribriform papillary thyroid carcinoma and the benign lesions such as follicular adenoma or multinodular goiter. The carcinoma in 1A shows areas of necrosis and hemorrhage related to fine needle aspiration. The carcinoma in 1B shows degenerative changes including fibrosis, cysts and mucous degeneration.

Figure 2. Microscopic appearance of cribriform papillary thyroid carcinoma.

A: Low magnification showing the cribriform pattern (haematoxylin & eosin x 40)

B: High magnification showing morular pattern with clear nuclei (haematoxylin & eosin x 100)

C: A focus of lymphovascular invasion is present (haematoxylin & eosin x 200).

Figure 3. Staining for beta-catenin. A: strong nuclear and mild cytoplasmic staining for beta-catenin in cribriform papillary thyroid carcinoma (x200). B: weak membranous staining for beta-catenin in conventional papillary thyroid carcinoma (x200). C: Weak membranous of beta-catenin in non-neoplastic thyroid follicles (x 100). D: Difference in staining pattern noted between cribriform papillary thyroid carcinoma and the adjacent non-neoplastic thyroid follicles (x100).

Figure 4. Staining for other proteins

Figure 4A. Nuclear staining for APC protein in cribriform papillary thyroid carcinoma (x200).

Figure 4B. A. p53 nuclear staining was noted in the cribriform papillary thyroid carcinoma (x 400);

Figure 4C. Low proliferative activity as documented by focal nuclear staining of Ki-67 in cribriform papillary thyroid carcinoma (x400).

Figure 1

Figure 2

Figure 3

Figure 4

Table 1. Characteristics of cribriform morular variant of papillary thyroid carcinoma

No. Gender	Age/Year of Birth (AA)	Surgery	T stage	LVI	size (mm)	multi-focal	FAP	FU (months)	Remarks
1. Female	23/1986 (0)	lobectomy	1	0	9	0	0	89	
2. Female	45/1961 (25)	lobectomy	1	0	9	0	0	119	
3. Female	17/1983 (3)	TT+LND	1	0	9	0	0	195	
4. Female	26/1985 (1)	TT+LND	1	0	13	0	0	69	
5. Female	20/1985 (1)	TT+LND	1	0	5	0	0	135	
6. Female	19/1988 (-2)	TT+LND	1	0	9	1	1	108	polyposis
7. Female	18/1991 (-5)	TT+LND	2	0	32	0	0	87	
8. Female	39/1977 (9)	lobectomy	1	0	20	1	1	5	osteoma
9. Female	18/1984 (2)	TT+LND	1	0	12	0	0	168	
10. Female	15/1978 (8)	TT+LND	1	0	12	1	1	281	osteoma, CRC
11. Female	21/1984 (2)	TT+LND	1	0	6	0	0	138	
12. Female	33/1978 (8)	TT+LND	1	0	12	1	0	69	
13. Female	18/1994 (-8)	TT+LND	1	1	14	1	1	57	polyposis
14. Female	20/1981 (5)	TT+LND	3	0	47	0	0	189	
15. Female	47/1967 (19)	TT+LND	1	0	15	1	0	27	
16. Female	16/1982 (4)	lobectomy	1	1	4	0	0	219	
17. Female	16/1985 (1)	TT+LND	1	1	8	1	0	181	
18. Female	34/1980 (6)	TT+LND	1	1	13	0	0	23	with a separate PCA(conventional)
19. Female	52/1962 (24)	TT+LND	1	1	1	6	0	0	34
20. Female	33/1975 (11)	lobectomy	1	1	6	0	0	96	
21. Female	28/1987 (-1)	lobectomy	1	1	20	0	0	20	
22. Female	32 /1981 (4)	TT+LND	2	0	35	1	0	47	with a separate PCA (follicular)
23. Female	15/1989 (-3)	lobectomy	1	0	7	0	0	142	
24. Female	19/1985 (1)	TT+LND	1	0	14	0	0	149	
25. Female	15/1984 (2)	TT+LND	1	0	10	0	0	215	
26. Female	16/1984 (2)	lobectomy	1	1	8	0	0	194	
27. Female	23/1989 (-3)	TT+LND	1	1	16	0	0	53	
28. Female	18/1981 (5)	TT+LND	2	1	30	0	0	208	
29. Female	17/1984 (2)	TT+LND	1	0	7	1	0	189	
30. Female	22/1984 (2)	TT+LND	1	0	10	0	0	120	

31. Female	34/1972 (14)	TT+LND	1	0	16	0	1	120	CRC
32. Female	21/1984 (2)	TT+LND	1	1	8	0	0	145	
33. Female	24/1982 (4)	TT+LND	1	0	15	1	1	123	CRC
34. Female	16/1991 (-5)	TT+LND	1	1	30	1	1	110	medulloblastoma
35. Female	21/1987 (-1)	TT+LND	2	1	28	0	0	110	

AA (age at Chernobyl accident in year, “-“= born after the accident); LVI = lymphovascular permeation by cancer; FU (months): length of follow up in months since surgery; TT+LND = total thyroidectomy and lymph node dissection; CRC = colon cancer

Table 2. Comparison of the features of cribriform morular variant of papillary thyroid carcinoma in different regions

Features	CMV-PTC in non-radiation affected region	CMV-PTC in radiation affected region	p-value
Number	129	35	
Gender distribution	125 females; 4 males	35 females; 0 males	NS
	4 males (31:1)		
Mean age	28	24	NS
FAP	53%	20%	0.0001
Multi-focal lesions	51%	31%	0.05
Mean diameter	30mm	15mm	0.0001
Psammoma bodies	18%	0%	0.019
lymphovascular permeation	14%	37%	0.007
pT stages			
1 & 2	72%	97%	0.0001
3 & 4	28%	3%	
Lymph node positive	12%	0%	0.023
Distant metastases	3%	0%	NS
Cancer recurrence	9%	0%	0.009
Cancer mortality	2%	0%	NS

CMV-PTC = cribriform morular variant of papillary thyroid carcinoma; NS = not significant; FAP: familial adenomatous polyposis; pT stages = pathological T stages

Results:

- The patients with CMV-PTC in radiation-affected region were all young females
- The majority of CMV-PTCs in radiation-affected region was pT1
- CMV-PTCs were positive for beta-catenin, APC and p53 proteins.
- CMV-PTCs had no psammoma bodies noted on microscopic examination.
- Patients with CMV-PTC in radiation-affected region behave in an indolent fashion.

A

B

Figure 1

Figure 2

Figure 3

Figure 4

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Characteristics of cribriform morular variant of papillary thyroid carcinoma in post-Chernobyl affected region

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