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Characteristics of young adults of Belarus with post-Chernobyl papillary thyroid carcinoma: a long-term follow-up of patients with early exposure to radiation at the 30th anniversary of the accident.

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Summary

Objectives: Studies of thyroid cancer related to the Chernobyl accident have focused on children as they are the most vulnerable group with the highest risk of developing radiation-associated cancer. In contrast, our research aimed to look at the clinical and pathological features of patients with post-Chernobyl papillary thyroid carcinoma that were 2 years old or less at the time of the Chernobyl accident.

Design: The study subjects were patients (n = 359) aged 0 to 2 at the time of the Chernobyl accident and aged ≥19 years at presentation / surgery who were treated in Belarus for papillary thyroid carcinoma during the period 2003–2013.

Results: In conventional or oncocytic variant of papillary thyroid carcinoma, the prevalence of extra-thyroidal extension, nodal disease, infiltrative growth or lymphatic vessel invasion was above 50%. These features were less pronounced when compared to tall cell or diffuse sclerosing variants of papillary thyroid carcinoma. The highest frequency of central lymph node metastases was found in patients aged 1-2 years at exposure ($p = 0.004$). Subjects exposed in utero were characterized by absent / insignificant lymphocytic infiltration around the carcinoma ($p = 0.025$), predominance of conventional papillary architecture and an association with lymphocytic thyroiditis.

Conclusions: A number of features were associated with this group of patients that were very young at the time of radiation exposure. In addition, the incidence and basic characteristics of adult papillary thyroid carcinoma varied depending on the types of exposure conditions.

1. **Introduction**

In a number of publications dedicated to the next anniversaries of the Chernobyl accident, political and weather conditions that resulted in pollution of large areas of Belarus as well as the actions of local authorities that worsened the effects of internal irradiation were recognized [1-3]. For a long time, studies in thyroid cancer related to the Chernobyl accident have focused on children, as they are the most vulnerable group with the highest risk of developing cancer [4]. Environmental exposure to I^{131} during childhood carries an increased risk of thyroid cancer and the risk is radiation-dose dependent. Also, the risk is greatest in those who were youngest at exposure (0-4 years of age) [5].

Our findings on the initial presentation and treatment of post-Chernobyl papillary thyroid carcinoma in children and adolescents (≤18 years old at presentation) of Belarus who were operated during the years 1990 to 2005, revealed that 73.8% had lymph node involvement and 11.1% had distant metastases. Despite the aggressive onset of disease, the overall survival rates were good [6]. In addition, young patients in Belarus with papillary thyroid carcinoma in the "childhood post-Chernobyl" group differed in many clinical and pathological parameters from those in the "sporadic" group (we defined this group of childhood papillary thyroid carcinomas as being from patients in the absence of the ''Chernobyl radioactive iodine factor" or in patients who had no contact with external irradiation (or multimodal treatment) for other non-thyroid primary malignancies) [7].

Previously, follow-up information regarding the Belarus population aged 0-2 years at the time of the Chernobyl accident was lacking. The difference between the current study and previous publications is the shift in focus of our current investigation from children and adolescents to a cohort of young adults. In other words, we aimed to look into the peculiarities of clinical presentation and pathological features of post-Chernobyl papillary

thyroid carcinoma in patients aged ≥19 years at presentation in Belarus who were exposed to internal irradiation at the age of 0-2 years.

2. **Material and methods**

2.1. *Patients*

This retrospective study was approved by the Republican Centre for Thyroid Tumors institutional board and recruited all consecutive cases of any form of thyroid cancer in patients born between January 1 1984 and March 31 1987 (age 0 to 2 at the time of the Chernobyl accident), age ≥19 years at surgery and treated in Belarus during the years 2003-2013.

According to the Belarusian Cancer-Registry (RSPC of Oncology and Medical Radiology named after NN Alexandrov, Belarus), there were 389 patients treated for thyroid carcinoma in the years 2003 to 2013. Of these, 7 were follicular thyroid carcinomas, 6 were medullary thyroid carcinoma (four with sporadic medullary carcinoma, one also having a phaeochromocytoma [MEN 2a] and one associated with papillary thyroid carcinoma), 2 were poorly differentiated thyroid carcinoma (one had synchronous multi-focal papillary thyroid carcinoma). Fifteen patients were misdiagnosed as carcinoma after pathological review (having goitre or adenoma). Therefore, all cases of non-papillary malignancies including patients with co-existing papillary thyroid carcinoma (n=15) and 15 patients with benign thyroid disease were excluded from the investigation. Overall, 359 with papillary thyroid carcinoma were noted.

2.2. *Study cohort*

There were 81 males and 278 females (male to female ratio = 1 to 3.4). Details of the patients' presentations, radiation exposure history, surgical and pathological findings as well

as survival outcome were obtained from the hospital's papers and electronic medical records. Patients considered as having a positive history of radiation exposure were identified according to medico-geographical data. Thus, due to the exposure conditions at the time of the accident, four groups of patients were identified. There were (1) subjects aged one year or more (exposed because of food/milk consumption); (2) subjects aged less than one year (exposed because of breast feeding); (3) subjects born in May–June 1986 who were exposed partly in utero, and partly as a result of breast feeding, and (4) subjects born within the time period from July 1986 to March 1987, exposed in utero.

2.3. *Clinicopathological variables*

All the available histological slides of the studied population were re-evaluated by the authors (MF and AKL) and the clinical records were reviewed. The Tumour–Lymph nodes–Metastasis (TNM) staging was determined according to the seventh edition of American Joint Committee on Cancer Classification [8]. The dimensions of the papillary thyroid carcinoma were based on direct measurements of the resected thyroid specimens during macroscopic examination. Extra-thyroidal extension, infiltrative versus circumscribed growth, co-existing pathologies (autoimmune thyroiditis, nodular goitre or follicular adenoma), histological architecture and dominant histological component in every case of papillary thyroid carcinoma were recorded as well. The histological variants were named after the World Health Organization (WHO) criteria [9].

2.4. *Statistical analysis*

The statistical package R version 3.1.3 was used to perform statistical computing [10]. The difference between the frequencies of each feature represented by categorical variable was compared using Fisher-Freeman-Halton exact test for R x C tables or Chi-square test

when expected frequencies in the R x C tables were > 5 for 80% of cells. The difference between values of each feature represented by continuous variable was compared using Kruskal–Wallis test. p-values < 0.05 were considered statistically significant.

3. **Results**

In our group, papillary thyroid carcinoma was the most common form of post-Chernobyl thyroid malignancy, representing 96% of all cases of primary thyroid carcinoma in persons aged 19 to 29 years at surgery. The crude incidence rate ranged from 25 cases per million people aged 20-24 years to 26 cases per million in persons aged 25-29 years. According to data from Belarusian Cancer-Registry, this incidence rate is 1.7 times higher than the crude incidence rate (14.5 per million) in the 19 to 24 year age group of patients born during the period of January 1 1988 to March 31 1991.

Of the 359 papillary thyroid carcinomas, 349 had information available for a comprehensive analysis (Table 1). There were significant associations noted between extra-thyroidal extension and a number of characteristics. These included lymph node ($p<0.001$) and distant metastases ($p=0.015$), histological variant of tumour (prevalence of diffuse sclerosing and tall cell variants, $p<0.001$), occurrence of solid architecture, subcapsular localization in the thyroid, extensive intratumoural fibrosis ($p<0.001$), vascular invasion (lymphatic or blood vessels) and presence of abundant psammoma bodies ($p<0.001$). In addition, in patients with extra-thyroidal invasion, extensive mononuclear infiltration and associated background pathologies of the thyroid were characteristic ($p<0.001$). On the other hand, intra-thyroidal, small sized carcinomas (pT1a) as a rule were located inside the thyroid lobe (64.7%), and showed conventional histological patterns (mixtures of the papillary and follicular architecture). In addition, follicular adenomas (6.5%) and nodular hyperplasia of the thyroid (22.5%) were present as comorbidities. Nevertheless, intra-thyroid carcinomas frequently metastasized to lymph nodes (35.3 and 37% in pT1a and pT1b/pT2 stages correspondingly).

A number of morphological and clinical characteristics were associated with the histological variants of papillary thyroid carcinoma (Table 2, all patients without exclusion, n

= 359). For example, in conventional or oncocytic variants of papillary thyroid carcinoma, the prevalence of extra-thyroidal extension, nodal disease, infiltrative growth or lymphatic invasion was more than 50%; yet, it was less pronounced when compared to tall cell or diffuse sclerosing variants. Also, nearly all patients with distant metastases had diffuse sclerosing variant (Figures 1 & 2).

To investigate epidemiological characteristics of the population, adult patients with papillary thyroid carcinoma were compared with the group of 497 children and adolescents who were born during the matching period and operated due to the same type of radiogenic post-Chernobyl tumour. These patients were chosen from the recently analyzed cohort of 936 subjects [6, 7]. All childhood and adult papillary thyroid carcinoma cases were subdivided according to the exposure conditions and age at presentation (Figure 3). Therefore, albeit differences in the types of exposure conditions, all groups of patients demonstrated a similar pattern according to age at surgery: comparatively small number of pre-pubertal children (aged $\leq$ 10 years old), peri-pubertal children (11-14 years old) and adolescents (15-18 years old) with the majority of the patients being young adults ($\geq$19 years old). These patients had papillary thyroid carcinoma because of radioactivity-contaminated milk/food consumption (aged one year-two year at the time of the Chernobyl accident, n = 429) or exposure due to breastfeeding (aged less than one year, n = 347). Also, lesser number of patients had been exposed partly in utero / partly as a result of breastfeeding (n = 20) or irradiation in utero (n = 60).

The types of exposure conditions (Table 3) influenced many morphological and clinical features of papillary thyroid carcinoma. The highest frequency of central lymph node metastases was revealed in patients aged 1-2 year at exposure ($p = 0.004$). In these patients, follicular variant of papillary thyroid carcinoma and carcinomas with small vein invasion occurred more often ($p = 0.031$ and $p = 0.011$ accordingly). In addition, carcinomas with

prominent solid architecture predominated in subjects aged less than one year at exposure ($p = 0.02$). Besides, patients in the group exposed in utero were characterized by absent / insignificant mononuclear peritumoural infiltration ($p = 0.025$), predominance of conventional papillary architecture (18.8% versus 9.8% and 11.2%) and an association with lymphocytic thyroiditis.

4. **Discussion**

In this study, for the first time, we present the results of clinical and morphological analysis of a unique cohort of patients who were very young children at the time of the Chernobyl accident and were exposed (most probably) to the highest thyroid doses.

Important observations could be identified when comparing (albeit indirectly) the characteristics of post-Chernobyl papillary thyroid carcinoma in the groups of children-adolescents and young adults. Papillary thyroid carcinoma in a cohort of young adults was much more common in females (male to female ratio = 3.4/1), similar to the gender distribution in a non-radiogenic group of children-adolescents (male to female ratio = 4.3/1). However, the gender distribution was different from a cohort of post-Chernobyl papillary thyroid carcinoma in children (male to female ratio =1.6/1) and adolescents (male to female ratio =2.0/1) or cases of papillary thyroid carcinoma due to therapeutic radiation for a prior malignancy (male to female ratio =1/1.3). Besides, patients in their 19-29 year old at presentation developed less extensive papillary thyroid carcinoma (lower rate of nodal disease and distant metastases) when compared to patients who were very young at the exposure.. Thus, distant metastases were exceptional with only 3.2% (Table 1) of all young adults with carcinoma and were noted only in those carcinomas of stage pT3N1b. Besides, young adults with post-Chernobyl papillary thyroid carcinoma had a lower prevalence of lymph node metastases (59.3%) than children-adolescents (73.8%).

In young adults with intra-thyroid papillary thyroid carcinoma, the incidence of lymph node metastases (35.3 or 37% accordingly, Table 1) were almost identical regardless of the tumour size (pT1a or pT1b). In our population, close surveillance was done to detect carcinoma at the earliest stage in individuals with the greatest risk per Gy of developing thyroid cancer (our population who were aged 0-2 years at exposure). In fact, the findings reflected that close surveillance did not affect the extent of their disease at presentation as

intra-thyroid small carcinomas were revealed in less than one third of the patients (29.2%, Table 1).

It was shown during long-term observation that papillary thyroid carcinoma in internally irradiated persons aged 4-18 years at operation was represented by a variety of subtypes, and there have been changes in their relative frequencies with time. For instance, many of the earliest cases were of the solid or solid/follicular variants but later a decline in the proportion of the solid subtype and an increase in the proportion of conventional (or classic) variants was documented. The changes correlated with both increasing age and increasing latency [6, 7].

In large series, conventional, papillary micro-carcinoma and follicular variant accounted for 90% of the papillary thyroid carcinoma [11]. In radiation affected areas, the distribution of different variants of papillary thyroid carcinoma varies between young adults and children-adolescents groups. Despite the fact that conventional variant of papillary thyroid carcinoma predominated in both cohorts, the follicular, solid and diffuse sclerosing variants of papillary thyroid carcinoma were more common in patients aged ≤18 years at presentation. It is worth noting that diffuse sclerosing variant of papillary thyroid carcinoma is reported to be of higher prevalence in paediatric patients and in patients affected by irradiation [12, 13].

The oncocytic variant of papillary thyroid carcinoma was the second most common in young adults. This result may be linked to the associated lymphocytic thyroiditis (54.8%, Table 2) the frequency of which was dissimilar in the two groups (15.2% in young adults (Table 1) versus 7.7% in a children-adolescents cohort). In addition, the proportion of conventional variant of papillary thyroid carcinoma was 72.5%, which is much higher than 48.8% of “sporadic”, 34.9% of external irradiated, and 38.5% of post-Chernobyl children and adolescents [7]. Besides, the number of cases with background thyroid pathology in young

adults in comparison to children-adolescents was nearly double (34.4 and 15.8% [6] correspondingly).

In our previous study, the most influential factors for extra-thyroidal extension in children-adolescents with post-Chernobyl papillary thyroid carcinoma were infiltrative growth or diffuse intra-thyroidal spread, sub-capsular localization, extensive intra-tumoural desmoid-like fibrosis, and capillary and/ or lymphatic invasion [6]. All these features distinguished young adults with pT3 extension of papillary thyroid carcinoma. In addition, predominance of papillary architecture, extensive mononuclear infiltration, peritumoral / intraglandular psammoma bodies' dissemination and absence of other thyroid pathology were characteristic for young adults with post-Chernobyl PTC with extra-thyroidal extension.

Patients having papillary thyroid carcinoma due to contact with radioiodine in utero have significant differences in many characteristics when compared to their matching pairs with dissimilar types of exposure albeit lower frequency of carcinoma. In our group, patients born 1-2 year before the Chernobyl accident had the highest incidence of papillary thyroid carcinoma and a number of clinical and morphological peculiarities. Comparing the incidence of papillary thyroid carcinoma in the same cohort of patients with reference to the type of exposure, those exposed in utero were better protected from internal irradiation. These findings need further investigation and support the prolongation of studies that will allow conclusions on the consequences to human health of the Chernobyl accident.

5. **Conclusion**

To the best of our knowledge, there are no publications dedicated to the clinical and morphological characteristics of post-Chernobyl papillary thyroid carcinoma in young adults. Additionally, our study has analysed patients according to the types of exposure conditions and age at presentation. As a result, we demonstrated a number of features that were associated with the variants of papillary thyroid carcinoma and tumour extension in this group of patients. Besides, the incidence and basic characteristics of childhood and adult thyroid carcinoma varied depending on the types of exposure conditions.

It is also worth noting that post-Chernobyl thyroid cancers may continue to evolve in biological behaviour and in clinical and morphological presentation as well. In future, investigations need to clarify whether the prognosis of these patients (in terms of cancer morbidity / mortality) differ from their sporadic counterparts. In addition, studies should be done on the choices of treatment in young adults.

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Figure Legends:

Figure 1: Macroscopic features of papillary thyroid carcinoma, diffuse sclerosing variant. The gross features: papillary thyroid carcinoma with clinically evident disease (the large primary and metastatic nodules in the neck – (a, b).
In cases of diffuse sclerosing papillary thyroid carcinoma widespread involvement of one (c) or both lobes (d) is the characteristic. The fibrosing features are evident in every case of this variant of papillary thyroid carcinoma but extensive dense sclerosis in both lobes is rare (e). In a number of cases a dominant nodule is seen (arrow) accompanied by widespread lymphatic permeation (f).

Figure 2: Microscopic features of papillary thyroid carcinoma, diffuse sclerosing variant:
a - numerous psammoma bodies intermixed with islands of papillary carcinoma and dense mononuclear infiltration are shown. Slides stained with haematoxylin and eosin, x40.
b – interstitial broad fibrotic bands. Slides stained with haematoxylin and eosin, x40.
c – cancer cells seen within dilated lymphatic vessels visualized with D2-40 antibody, x200
d - extensive squamous metaplasia. Slides stained with haematoxylin and eosin, x200

Figure 3: Childhood and adult papillary thyroid carcinoma cases subdivided according to the exposure conditions and age at presentation.