Morphological and clinical presentation of papillary thyroid carcinoma in children and adolescents of Belarus: the influence of radiation exposure and the source of irradiation

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Summary

Objective: The aims were to analyse the features of papillary thyroid carcinoma in a large cohort of children and adolescents in Belarus and to study the influence of radiation exposure as well as the source of irradiation on the morphological and clinical presentations of the tumours.

Design and patients: The clinical and pathological features of 1086 young patients (age range =4 to 18 inclusive, followed up for ≥18 years) with papillary thyroid carcinoma diagnosed during the years 1990 to 2010 were reviewed. The patients were divided into three groups: “external radiation-related”, “post-Chernobyl” (internal irradiation-related) and “sporadic”. Besides, patients from “post-Chernobyl” cohort (n=936) were further divided into the three equal subgroups according to the dates of surgery, which were corresponding to the early (4-9 years), intermediate (10-12 years) and long (14-18 years) latency periods.

Results: Patients in the “external radiation-related” group often showed extra-thyroidal extension in tumours sized ≤10 mm (p = 0.002). Distant metastases were more frequently (p=0.006) discovered in patients with papillary thyroid carcinoma in post-Chernobyl group (104 of 936, 11.1%) when compared to juveniles from other two groups. Lateral nodal disease and distant metastases were often noted in post-Chernobyl patients operated during the early and intermediate latency periods only.

Conclusion: Young patients in Belarus with papillary thyroid carcinoma in the “post-Chernobyl” group differed in many clinical and pathological parameters from those in the “sporadic” group. “External radiation related” papillary thyroid carcinomas were distinguished from other two groups of carcinoma in more advanced local spread and more aggressive behaviour of micro-carcinomas.
Introduction

Epidemiological surveys have shown that exposure to ionizing radiation (in particular intake of I\textsuperscript{131}) in childhood or adolescence is a strong environmental risk factor for development of papillary thyroid carcinoma [1, 2].

Belarus is a country affected by an accident at the Chernobyl nuclear power plant in Ukraine on April, 26 1986. Thus, a comparative analysis of clinical and pathological characteristics of papillary thyroid carcinoma in Belarus provide a unique opportunity to identify the key features of papillary thyroid carcinoma associated with internal irradiation in comparison to cases related to external irradiation as non-radiogenic carcinoma. The purpose of the study was to carry out a retrospective clinical and pathological analysis of papillary thyroid carcinomas in aetiologically divergent groups of patients in Belarus.
Material and Methods

Study cohort and terms

The study subjects were children and adolescents (373 males and 713 females) suffered from papillary thyroid carcinoma in the age range of 4 to 18 inclusive at surgery. The details of the patients’ presentations, radiation exposure history, surgical and pathological findings as well as outcome were obtained from hospital papers and electronic medical records. Patients considered as having positive history of radiation exposure were identified according to medico-geographical data.

The patients were divided into three groups in the assessment. Among them, patients with papillary thyroid carcinoma attributed to externally irradiation were labelled “external radiation-related” (after therapeutic radiation for malignancies during childhood). In total, 23 patients surgically treated during the period 1995 to 2010 were identified to belong to this group.

In cases of “external radiation-related” papillary thyroid carcinoma, the first primary malignancy was detected in the patients at a median age of 4.7 years (range, 1–12 years). For patients who developed papillary thyroid carcinoma after the treatment for lymphoma, the average latent period from completion of lymphoma management until the verification of papillary thyroid carcinoma was 8.6 years (range, 5 to 13 years). The median latent period for the development of papillary thyroid carcinoma in patients with leukaemia was 6.9 years (range, 4 to 12 years). Also, the median latent period for occurrence of papillary thyroid carcinoma in patients with sarcomas was 14.0 years (range, 10 to 16 years). The treatments for the primary malignant neoplasms (lymphoma/leukaemia, sarcoma and medulloblastoma) were in accordance with the standard protocols (including cytotoxic therapies). External irradiation was used in all the cases. The total absorbed radiation doses for the primary
cancer varied from 12 to 54 Gy. As a rule, the thyroid gland was in or close to the treatment field. However, in two of the three patients in the sarcoma subgroup, the primary tumour was far away from the thyroid.

The second group was named “post-Chernobyl” and included 936 patients affected by internal radiation under various circumstances and to various amounts of $^{131}$I who were operated in the years 1990 – 2005 (post-Chernobyl period). The identification of these cases and the assessment of radiation exposure have been thoroughly discussed [3, 4]. In brief, according to the exposure conditions at the time of the accident, four groups of patients were noted. 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 have been 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.

To reflect the duration of latency (from the April, 26 1986 to the age at surgery) and address clinical and morphological trends that were observed in the course of papillary thyroid carcinoma during these years, all cases were divided into three equal subgroups according to the time: operated for the period of January, 1990 to December, 1995; January, 1996 to May, 1999; and June, 1999 to September, 2005.

The “sporadic” group comprised 127 juveniles who were born during the years 1987-1992 (from April 1, 1987 to December 31, 1992) and having been operated for papillary thyroid carcinomas during the period of 1991–2010. There is no epidemiological evidence of radiation exposure in this group of patients. These patients were born long after the $^{131}$I full decomposition (April, 26 1986 – July, 28 1986). They were not exposed to the internal irradiation and had no history of external therapeutic irradiation as well.
Pathological parameters

All the available histological slides were re-evaluated 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 [5]. 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 [6].

Statistical analysis

The difference between the frequencies of each feature represented by categorical variable was established using Chi-square test or Fisher-Freeman-Halton exact test. The difference between values of each feature represented by continuous variable was compared using Kruskal–Wallis test. P-value of < 0.05 was considered statistically significant.

For an analysis of clinical and morphological features of patients with aetiologically different papillary thyroid carcinoma, we used multivariate logistic regression with nominal variable with five category: (1) patients with “sporadic” papillary thyroid carcinoma; (2) patients with “external radiation-related” papillary thyroid carcinomas; (3) patients from post-Chernobyl group operated for the period of January, 1990 to December, 1995, (4) patients operated for the period January, 1996 to May, 1999, (5) patients operated for the period June, 1999 to September, 2005. Age at presentation and gender of the patients with papillary thyroid carcinoma were included as two confounders in multivariate logistic regression. Patients with “sporadic” papillary thyroid carcinoma were considered as the baseline
(reference group). The odds ratio (OR) with respect to baseline was calculated as exponential transformation of respective parameters and their 95% confidence intervals (CI). Analyses were conducted using R version 3.1.1 software (R Project for Statistical Computing, http://www.r-project.org).
Results

i) Papillary thyroid carcinomas in children and adolescents: age- and gender-related associations

The clinical and pathological features of patients with papillary thyroid carcinoma were listed in the Table 1. There were significant differences in age and gender distribution. According to the results of multivariate analysis (table 2), younger patients with papillary thyroid carcinoma are likely to have lateral (N1b) cervical lymph nodes metastases (OR = 0.92 [95% CI OR = 0.87-0.97]; p = 0.002) and distant metastases (OR = 0.83 [95% CI OR = 0.76-0.90]; p < 0.001).

Gender-connected differences in the characteristics of the whole group of young patients with papillary thyroid carcinomas were also noted (table 2). Papillary thyroid carcinoma in boys was associated with higher frequency of distant metastases when compared with papillary thyroid carcinoma in girls (OR = 2.11 [95% CI OR = 1.41-3.21]); p < 0.001). On the contrary, papillary thyroid carcinomas in boys are less frequently associated with co-existing pathologies (OR = 0.38 [95% CI OR = 0.25-0.56]; p < 0.001).

ii) Descriptive characteristics of aetiologically different groups of papillary thyroid carcinoma in children and adolescents

On pathological examination (table 1), many patients within the “external radiation-related” group revealed tumours in more advanced local spread (pT3-T4): (17 of 23, 73.9%, p<0.001). The frequency of papillary micro-carcinoma in patients of all aetiologically different groups has distinguished significantly (p=0.025). However, the prevalence of extrathyroidal extension in tumours sized ≤10 mm apparently characterized patients within the “external radiation-related” group (p = 0.004).
Distant metastases were more frequently (p = 0.006) revealed in patients with post-Chernobyl papillary thyroid carcinoma (104 of 936, 11.1%) when compared to juveniles from “external radiation-related” (4.3%) and “sporadic” papillary thyroid carcinoma groups (2.4%). On the other hand, frequency of distant metastases gradually increased in patients suffered from post-Chernobyl papillary thyroid carcinoma (2.6-4.8-11.9% according to the periods in which patients were operated).

The histological variants and patterns of papillary thyroid carcinoma showed significant difference between the patients (p < 0.001). In the “sporadic” group, conventional papillary variant comprised the largest portion (48.8%) of carcinomas. In the “post-Chernobyl” group, the incidence rate of conventional and solid variants gradually decreased (42.6-36.9-35.9% and 19.2-13.8-10.6% respectively), whereas the frequency of patients with follicular, tall and oncocyctic variants of papillary thyroid carcinoma slowly increased (26.0-33.7-34.0%, 1.6-9.3-9.9%, 0.3-0.6-2.2% correspondingly). With regard to the tumour architecture, solid pattern was more often noted in papillary thyroid carcinomas in the “post-Chernobyl” group when compared to the other groups (p < 0.001).

Invasion of small blood vessels near a capsule of the thyroid is highly specific (34.8%) for patients operated due to external radiation-related papillary thyroid carcinoma (p=0.017). As for children and adolescents from “post-Chernobyl” group, the prevalence of blood vessel invasion has been decreased (22.4-19.9-14.1 according to the periods). In addition, the frequency of histological features as massive intra-tumour fibrotic deposits, psammoma bodies intra-thyroid dissemination (mild or extensive), and lymphatic vessel invasion makes difference between “post-Chernobyl”, “external radiation-related” and “sporadic”.

The close follow-up of patients after the episode of first primary malignancy makes possible to detect small nodules of papillary thyroid carcinoma associated with external...
irradiation. Therefore, in patients from the “external radiation-related” group with tumour size ≤ 10 mm, many were seen in pT3-T4 stage (78.6%) and N1 (85.7%).

During the years 1990-1995, tumour size in patients from the “post-Chernobyl” group was significantly larger than in the next two periods (p<0.001). Tumours in the first period could be clinically under-diagnosed and discovered due to the screening. Waves of screenings started in Belarus since the year 1990 under the auspicious of Sasakawa Memorial Health Foundation of Japan and the International Project on the Health Effect of the Chernobyl Accident (WHO, project IPHECA) or a number of local screening projects. These interventions resulted in the earlier detection of papillary thyroid carcinoma. Therefore, during the second period, intensive search for thyroid malignancies revealed papillary thyroid carcinomas that were more aggressive (with lung metastases) at presentation and of smaller size (possibly, diagnosed earlier in their natural course). In the third period, mean size of the carcinomas was the smallest, but there were no differences (table 2) in clinical characteristics compared to “sporadic” cases.

iii) Adjusted for age and gender multivariate analysis of “post-Chernobyl” vs “sporadic” papillary thyroid carcinoma according to the periods defined by the time of surgery (table 2)

Patients operated during the period of January, 1990 to December, 1995 were distinguished by their comparatively low frequency of lateral nodal disease (OR = 0.38 [95% CI OR = 0.24 – 0.62]; p < 0.001) and lower rate of lymph node metastases in patients suffered from papillary micro-carcinomas (OR = 0.28 [95% CI OR = 0.12 – 0.63]; p = 0.002). On the other hand, clear tendency for distant metastases (OR = 3.05 [95% CI OR = 1.01 – 13.2]; p = 0.078) was revealed in carcinomas operated this period.

In children and adolescents operated for post-Chernobyl papillary thyroid carcinoma during the period of January, 1996 to May, 1999, there was disproportionately lower frequency of lateral lymph nodes metastases (OR = 0.54 [95% CI OR = 0.35 – 0.83]; p =
0.005) and higher rate of distant dissemination (OR = 4.81 [95% CI OR = 1.68 – 20.3]; p = 0.010).

There was no difference in clinical presentation of patients with papillary thyroid carcinoma of “post-Chernobyl” subgroup operated during the last (third) period compared to their pairs from “sporadic” group matched by age and gender. However, “post-Chernobyl” papillary thyroid carcinomas were distinguished by their higher frequencies of multi-focal growth (OR = 2.85 [95% CI OR = 1.23 – 7.79]; p = 0.024) and follicular variant (OR = 3.07 [95% CI OR = 1.80 – 5.50]; p < 0.001). On the contrary, conventional papillary thyroid carcinoma (OR = 0.58 [95% CI OR = 0.38 – 0.89]; p = 0.012) and psammoma bodies intra-thyroidal dissemination (OR = 0.63 [95% CI OR = 0.41 – 0.96]; p = 0.034) were less often noted.

iv) Adjusted for age and gender multivariate analysis of patients with externally irradiated papillary thyroid carcinoma versus patients in the “sporadic” cohort (table 2)

Papillary thyroid carcinomas from the “external radiation-related” group have smaller size when compared to those from the “sporadic” group (OR = 0.37 [95% CI OR = 0.14-0.91); p = 0.033). Moreover, these radiogenic papillary micro-carcinomas were more locally advanced: OR = 9.09 (95% CI [OR = 2.31-46.5]; p = 0.03). In addition, papillary thyroid carcinoma tended to metastasize in central (N1a) rather than in lateral (N1b) cervical lymph nodes (OR = 0.39 [95% CI OR = 0.14 - 0.99]; p = 0.057). Blood vessel invasion occurred relatively more frequently (OR = 2.53 [95% CI OR = 0.90-6.74]; p = 0.068) in patients with “radiogenic” papillary thyroid carcinoma when compared to those in the “sporadic” group.
Discussion

Several potential selection biases were noted in the study. Some of these are connected to the “external radiation-related” group's childhood cancers that are could themselves be associated with factors of the increased risk of papillary thyroid carcinoma, rather than the external irradiation that the patients received. Moreover, direct measurement of dose of radiation received by every patient is not feasible for these cases. Nevertheless, patients with papillary thyroid carcinoma associated with external irradiation had apparent age and gender peculiarities attributed to the first malignancy, the lowest proportion of cases with background pathologies, and absence of multi-focal papillary thyroid carcinoma. Also, these carcinomas were distinguished by morphological features such as higher frequency of vascular invasion, follicular pattern, infiltrative growth and extra-thyroidal extension.

Morphological differences accompanied post-Chernobyl papillary thyroid carcinomas were noted during all the periods. In patients operated from June, 1999 to September, 2005, no clinical dissimilarities were noted when compared to those with “sporadic” papillary thyroid carcinoma. However, discrepancies were observed as in the occurrence of multi-focal growth, psammoma bodies’ intra-thyroid dissemination and the relative frequency of conventional and follicular variant of papillary thyroid carcinoma. In addition, the follicular or solid architecture were more common in both radiogenic groups of papillary thyroid carcinoma compared to their “sporadic” counterparts. In “sporadic” group of papillary thyroid carcinoma, conventional histological variant comprised approximately half of all cases. This prevalence is similar to the results noted in non-radiation exposure area [7].
Conclusions

To the best of our knowledge, the current report comprises the largest number of juveniles with papillary thyroid carcinoma thoroughly analyzed for their clinical and morphological features. We hypothesize that the diverse sources of irradiation and disproportion of radiation-induced tumours are the reasons for the differences between the subgroups of patients suffering from papillary thyroid carcinoma after Chernobyl accident. The issue appears to be more complicated because the majority of children and adolescents surgically treated during the years 1990-2005 were in the most sensitive age at exposure (0-6 years old) that makes them vulnerable for radiation carcinogenesis. Molecular pathology approach could be used to identify the differences between internally or externally radiation-induced and sporadic papillary thyroid carcinomas.
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Authors declare no competing financial interests exist. Each author made equal contributions to the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content.

ii. **Human rights:**
The Institutional review board in Belarus Medical Academy of Post-Graduate Education, Minsk, Belarus approved the study protocol. Informed consent to share epidemiological, clinical, and morphological individual data set in further scientific investigations was obtained on admission to the hospital from the patients or from accompanying guardians for minors.

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References


