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Radiation Dose Does Not Affect the Predictive Value of Thyroid Biopsy for Diagnosing Papillary Thyroid Cancer in a Belarusian Cohort Exposed to Chernobyl Fallout

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Abstract

Introduction: The Chernobyl nuclear accident exposed residents of contaminated territories to substantial quantities of radioiodines and was followed by an increase in thyroid cancer, primarily papillary thyroid cancer (PTC), among exposed children and adolescents. Although thyroid biopsy is an essential component of screening programs following accidental exposure to radioiodines, it is unknown whether the predictive value of biopsy is affected by different levels of environmental exposure.

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Statement of Ethics:
The current study was exempted from review by the Institutional Review Board of the University of California, San Francisco since it used only existing de-identified data. The original BelAm Cohort Study was approved by local institutional review boards in Belarus and the United States [66]. Signed informed consent was provided by all study participants or by accompanying guardians for minors.

Conflict of interest statement:
The authors have no actual or potential competing financial interests.

Author contributions:
The authors' contributions are as follows: conceptualization: R.J.Mc., P. O'K., K. M., L.B.Z.; methodology: R.J.Mc., P. O'K., K.M. L.B.Z.; investigation: R.J.Mc., O.K., P. O'K., E.G., A.V.R., V.V. Y., V.F.M., V.D., Y.Y., T.K., L.B.Z.; formal analysis: R.J.Mc., P. O'K., V.V.Y., V.F.M., V.D., Y.Y., T.K., M.P.L., E.K. C., L.B.Z.; writing-original draft preparation: R.J.Mc.; writing-review and editing: R.J.Mc., O.K., P. O'K., E.G., A.V.R., V.V.Y., V.F.M., V.D., Y.Y., T.K., K.M., M.P.L., E.K.C. L.B.Z.; project administration: A.V.R., K.M., E.K.C.

Methods: A cohort of 11,732 Belarusians aged ≤ 18 years at the time of the Chernobyl accident with individual thyroid radiation dose estimates was screened at least once 11–22 years later. Paired cytologic conclusions and histopathologic diagnoses were possible for 258 thyroid nodules from 238 cohort members. Cytologic conclusions were divided into five reporting categories, with all follicular lesion aspirates combined into a single indeterminate category. Standard performance indicators, risk of malignancy (ROM), and odds ratios for a correct cytologic conclusion were calculated, both overall and according to quintile of thyroid radiation dose.

Results: The arithmetic mean thyroid dose estimate for the study group was 1.73 Gy (range: 0.00–23.64 Gy). The final histopathologic diagnosis was cancer for 136 of 258 biopsies (52.7%; 135 papillary and 1 follicular). The overall ROM was 96.7% for cytologies definite for PTC, 83.7% for suspicious for PTC, 33.0% for indeterminate, 8.1% for benign, and 31.0% for non-diagnostic. The ROM showed little change according to level of radiation exposure. Overall, there was no association between thyroid radiation dose and the odds ratio for a correct cytologic conclusion (p=0.24). When analyzed according to dose quintile, the odds ratio for a correct conclusion increased two-fold at 0.10–0.29 Gy compared to a dose of 0.00–0.09 Gy and decreased at doses of 0.3–24 Gy (p-value for linear trend= 0.99).

Conclusions: At radiation doses received by a cohort of young Belarusians exposed to radioiodines by the Chernobyl accident, the predictive value of thyroid biopsy for diagnosing papillary thyroid cancer was not significantly affected by level of radiation exposure.

Keywords

Thyroid biopsy; risk of malignancy; radiation-induced papillary thyroid cancer; Chernobyl nuclear accident

Introduction

The Chernobyl nuclear power plant accident in April 1986 exposed the residents of contaminated territories to substantial quantities of radioiodines and was followed by an increase in the number of thyroid cancers, primarily papillary thyroid cancers (PTCs), within the pediatric population [1–8]. Although an increased risk of thyroid cancer also was reported for adult Chernobyl cleanup workers [9], these findings were not confirmed by a later study [10]. A decade after the accident, the U.S. National Cancer Institute partnered with the Ministries of Health in Belarus and Ukraine to establish two parallel cohort studies, one in Belarus (Belarusian-American Cohort Study; BelAm) and the other in Ukraine (Ukrainian-American Cohort Study; UkrAm), to screen for thyroid disorders that developed among exposed children and adolescents. The BelAm cohort consisted of those who were under 18 years of age at the time of the accident and who had direct thyroid radioactivity measurements taken within the next two months. Cohort members were invited for biennial screening starting in 1997 and those with thyroid nodules identified by ultrasound or palpation were referred for fine needle aspiration biopsy (FNAB) and surgery according to a well-defined protocol [6,7].

In a general population not exposed to radiation, FNAB has a high predictive value for diagnosing thyroid cancer in both adults [11–15] and children [16–21], while reported

outcomes in irradiated subjects differ according to level and type of radiation exposure [22–31]. Following high-dose external exposure to X-rays or after ^{131}I treatment of hyperthyroidism, the predictive value of FNAB for diagnosing thyroid cancer is substantially lowered by cellular atypia [22–25], while among children and adolescents exposed to lower X-ray doses used to treat benign conditions of the head and neck the predictive value is closer to that found in unexposed populations [26]. Information concerning internal exposure to environmental doses of radioiodines is not as robust [27–31]. The earliest cytologic studies of Chernobyl children suggested that most nodules were nonneoplastic, primarily chronic thyroiditis and cysts [27], and that the main diagnostic features of the PTCs were largely similar to those in unexposed adults [28]. The UkrAm study reported a positive predictive value for cytologies diagnostic of PTC of 100%, but it was based on only 78 nodules from a single screening cycle, did not calculate risk of malignancy (ROM) for different cytologic categories, and did not account for level of radiation exposure [29]. A study of children and adolescents who were exposed to much lower doses of radioiodines by the Fukushima nuclear accident [30] found that the distribution of cytologic interpretations within The Bethesda System for Reporting Thyroid Cytopathology was similar to that in unexposed adults [31] and that the risk of malignancy (ROM) was 99.4% for cytologies suspected or diagnostic for malignancy, but pathologic correlation was not available for all operated cases [32].

Since understanding the predictive value of FNAB over a range of radiation doses is important to screening populations exposed to environmental doses of radioiodines, the objective of this study was to assess the predictive value of FNAB for diagnosing PTC, both overall and according to level of radiation exposure. We used data from the BelAm cohort to evaluate FNAB predictive value among subjects who underwent thyroid surgery and had paired cytology and pathology observations over three cycles of screening from 1997 to 2008.

Materials and methods

Cohort description and screening

The design and methods of BelAm have been described in detail [33]. Briefly, the Belarusian cohort was assembled from those who were living in contaminated territories and were ≤ 18 years of age at the time of the accident on 26 April1986, and who had direct thyroid radioactivity measurements taken over the next two months. Beginning in 1996, we began to trace exposed subjects and invite them for thyroid screening. It included 11,732 individuals who were initially screened from 1997 to 2000, and then twice again, from 2002 to 2004 and from 2004 to 2006. Study participants referred for FNAB or surgery during the final screening cycle were followed through September 30, 2008 [7].

Subjects were examined either by mobile teams working at local medical facilities in their oblast of residence (an oblast is a Belarusian administrative unit similar to a state or province) or by stationary teams based in Minsk and Gomel cities. Although the original protocol called for biennial screening, the Belarusian Ministry of Health decreed that all cohort members who were under 18 years of age be invited for annual screening. All examiners were blinded to radiation dose and screening was carried out according to a

well-defined protocol that stipulated an ultrasound examination and independent thyroid palpation by both an endocrinologist and an ultrasonographer [33].

FNAB and cytologic procedures

Patients with thyroid nodules more than 10 mm in greatest dimension detected on either palpation or ultrasonogram were referred to designated centers in Minsk and Gomel for ultrasound-guided FNAB. Patients also were referred for biopsy if their nodules measured 5 to 10 mm in greatest dimension and were sonographically suspicious for malignancy (hypoechoic, indistinct border, calcified inclusions of any size or texture, extension through the thyroid capsule, interval growth, or suspicious lymphadenopathy) or were accompanied by diffusely abnormal thyroid tissue with unexplained cervical lymphadenopathy. In the case of multiple nodules, up to three were biopsied, including the most suspicious nodule.

The presence of an adequate number of epithelial cells was determined on site by cytologic examination of air-dried slides stained with either Giemsa or DiffQuik®. Adequacy of the stained smears was defined by the presence of a minimum of two slides with six clusters of well-preserved thyroid follicular cells [34].

Specimens were reviewed by BelAm project cytologists and separately confirmed by one of the authors (E.G.), with special consideration given to aspirates suspicious for FN, which exhibited some, but not all, of the features characteristic of FN, such as high cellularity, cellular crowding, presence of microfollicules, scant colloid, and absence of the nuclear features of PTC. Cytologic conclusions were classified into the following categories according to conventional criteria in use at the time of the study [35]:

- Nondiagnostic
- Non-neoplastic (e.g., nodular goiter [NG], chronic thyroiditis, granulomatous thyroiditis)
- Suspicious for follicular neoplasm (FN) or Hürthle cell tumor
- Definite for FN or Hürthle cell tumor
- Suspicious for PTC
- Definite for PTC

Thyroid surgery and histopathologic procedures

Patients were referred for surgery if the cytology was diagnostic or suspicious for FN in a nodule or diagnostic or suspicious for PTC in a nodule or a lymph node, or according to the judgement of the study endocrinologist despite a benign or non-diagnostic FNAB interpretation. In the case of a non-diagnostic specimen, the biopsy was repeated at the same time or at a subsequent visit, and up to three attempts were made within any 12-month period. In case of persistently non-diagnostic cytology, patients were referred to surgery at the discretion of the study endocrinologist. Most operations were performed at the Minsk Oncopathology Center and consisted of a complete or partial thyroidectomy according to the judgment of the surgeon.

Postoperative study of paraffin sections stained with hematoxylin-eosin was performed at the Minsk Oncopathology Center. A specially convened International Pathology Panel (IPP), established within the framework of the Chernobyl Tissue Bank (36), reviewed all suspected thyroid cancers and FNs. Panel members were not aware of subjects' radiation doses. In total, the IPP reviewed surgical specimens and agreed upon diagnoses from 269 operated cases. Those cases that the IPP was unable to categorize as definitely benign or malignant were classified as well-differentiated tumors of uncertain malignant potential (WDTUMP) [5,7].

Dosimetry

The methods used to estimate thyroid dose due to ^{131}I intake previously have been previously described in detail [37–39]. In brief, individual dose estimates and their uncertainties were based on a combination of direct radiation measurements of ^{131}I thyroid activity made during April-June 1986; a radioecological transfer model; and personal interviews, which provided information on residential and dietary history during the two months after the accident. The dose reconstruction model accounted for age-specific thyroid volumes [40] and for contribution of external and internal radioactive contamination of the body and of the clothes on the results of the direct thyroid measurements [41, 42]. Only dose estimates for ^{131}I are considered in this paper, as these accounted for 92% of the total thyroid dose [37].

Characteristics of the study population

Over the three cycles of screening, 2,246 referrals for FNAB were made for 1,092 study subjects, and 2,130 procedures were completed (compliance rate 94.8%); subsequently, 343 cohort members were referred for surgery and 269 of them underwent operations (compliance rate 78.4%) [7]. We subsequently excluded 31 patients (12%) from further consideration: (a) eight had no preoperative FNAB report available; (b) five had neck dissections for metastases in lymph nodes; (c) four each had a completion thyroidectomy or location of nodule not specified at FNAB; (d) three each had a lymph node biopsy or there was no pathomorphology form available; (e) two had no review of pathology by the IPP; and (f) one each had a thyroid remnant biopsied or the subject was missing the radiation dose. After exclusions, paired cytologic conclusions and histopathologic diagnoses were possible for 258 nodules from 238 cohort members. Overall, 221 subjects had solitary nodules, 14 had two nodules, and three had three nodules. Incidentally revealed microscopic PTCs (7) and FNs (6) that had not been the target nodule were excluded from analysis.

The study population consisted of 134 females and 104 males (gender ratio 1.3:1) exposed to an estimated arithmetic mean thyroid dose of 1.73 Gy (range 0.00–23.64 Gy). At exposure, most subjects were young children (mean age 7.4 years; range 18 days-17.5 years); at surgery, most were adolescents or young adults (mean age 23.8 years; range 13.1–37.6 years). The mean latency from exposure to surgery was 16.0 years (range 11.3–22.1 years) and the mean time between completion of the final preoperative FNAB and surgery was 3.9 months (range 2 days-3.3 years).

Statistical analysis

All statistical analyses were performed on the cytologic conclusion from the last FNAB completed prior to thyroid surgery and the data were analyzed in three different ways.

First, we established standard indicators of test performance for paired cytologic conclusions and final histopathologic diagnoses:

Sensitivity: true positives/ (true positives + false negatives)

Specificity: true negatives/ (true negatives + false positives)

Since our study protocol considered a cytologic conclusion of FN to be a “positive” (neoplastic) finding that required referral to surgery, true positives were defined as those suspicious or definite for PTC and either suspicious or definite for FN on cytology and confirmed to be cancer upon final histopathologic examination. If the corresponding histopathologic diagnosis was follicular adenoma (FA) or benign NG, the case was considered a false positive. True negatives were those negative for malignant cells on cytology and FA or NG at histopathology; if the corresponding histopathologic diagnosis was cancer, the case was considered a false negative.

Next, the risk of malignancy (ROM) was calculated as number of malignant nodules at final histopathology out of all resected nodules in a given category. Our cytologic classification of nonneoplastic corresponds to the benign category (Bethesda II) of The Bethesda System for Reporting Thyroid Cytopathology 2023 [43]. Because our cytologists did not recognize the category “atypia of undetermined significance” (AUS) and made a distinction between suspicious for FN and definite for FN, for analytic purposes we combined the two follicular categories suspicious for FN and definite for FN into a single indeterminate category in order to correspond to Bethesda categories III (AUS) and IV (follicular neoplasm) together, similar to other studies and published guidelines [44,45].

Finally, to assess a possible dose-response, we calculated the odds ratios for correct cytologic conclusions (true positives and/or true negatives) according to estimated thyroid dose quintiles for diagnostic FNABs. Cut points were chosen to equally distribute cytologies between dose categories. Potential confounders considered were sex; age at exposure; age at biopsy; oblast of residence at the time of the accident (Brest, Gomel, Minsk, Vitebsk); and oblast of residence at screening, as a surrogate marker for iodine intake. While none was statistically significant, we retained sex, oblast of residence at screening, and age at biopsy, as they had the largest effect on the model deviance and on risk estimates. All statistical tests were 2-sided and considered statistically significant for $P<0.05$, and were conducted using SAS [46] and Epicure [47] software.

Results

Sensitivity and specificity of FNAB for diagnosing thyroid cancer

Out of 258 FNABs, 229 were diagnostic and 29 were non-diagnostic. A cross tabulation for all cytologic conclusions and final histopathologic diagnoses is presented in Table 1. Cytologies diagnostic for PTC made up 23.6% of all specimens, suspicious for PTC 16.7%,

indeterminate 34.1%, benign 14.3%, and non-diagnostic 11.2%. The final histopathologic diagnosis was cancer for 127 of 229 diagnostic FNABs (55.5%; 126 PTC and 1 FTC) and 9 of 29 non-diagnostic FNABs (31.0%; all PTCs). Treating WDTUMP as a benign tumor, the sensitivity for diagnostic specimens was 97.6% and specificity was 33.3%. When WDTUMP was treated as a cancer, neither sensitivity (96.9%) nor specificity (33.7%) changed appreciably, so WDTUMP was treated as a benign tumor for all other analytical purposes. If FA were considered to be a neoplastic instead of a benign histopathologic diagnosis as stipulated in our protocol, the sensitivity for diagnostic aspirates decreased slightly (90.9%) and the specificity increased (38.9%).

ROM and predictive value of FNAB for diagnosing papillary thyroid cancer according to radiation dose

At the lowest dose category of 0.00–0.09 Gy, indeterminate cytologies made up 60.6 % of all biopsies, then varied from 28.0–34.1% at higher doses (Table 2). Those definite for PTC made up 18.2 % of FNABs at the lowest dose, trended upwards and peaked at 32.0 % doses between 0.30–0.59 Gy, and then gradually declined.

The overall ROM for cytology definite for PTC was 96.7%, suspicious for PTC 83.7%, indeterminate 33.0%, and benign 8.1% (Table 3). From the lowest to the highest dose quintile, the ROM for aspirates definite or suspicious for PTC fell modestly, while that for indeterminate cytologies fell by approximately 40%. The two false positive cytologies definite for PTC were FAs at final histopathologic examination (shown in Fig. 1) and the cytologic conclusion for the only follicular thyroid carcinoma was definite for FN. Of the 59 false positive indeterminate aspirates, 42.4% were NG (shown in Fig. 2) and 57.6% FA/WDTUMP. The ROM for the 29 non-diagnostic specimens was 31.0%.

In unadjusted logistic regression analyses (Table 4), thyroid radiation dose was not associated with a cytologic conclusion that correctly predicted the final histopathologic diagnosis (true positive and/or true negative; OR at 1 Gy=1.18; 95% CI: 0.95, 1.47; p=0.13). Adjustment for sex, oblast of residence at screening, and age at biopsy did not change the estimate for radiation dose (OR adjusted at 1 Gy=1.14; 95% CI: 0.92, 1.42; p=0.24). There were no significant differences according to sex, oblast of residence at screening, or age at biopsy. The odds of a correct cytologic conclusion showed a biphasic response, highest for the dose category 0.10–0.29 Gy (OR=2.22; 95% CI: 0.79, 6.20), then falling monotonically at higher levels of exposure. However, the test for overall trend was not statistically significant (p=0.99).

Discussion

We believe that this is the first study of the association between radiation dose and the predictive value of FNAB for diagnosing PTC following exposure to radioiodines by Chernobyl fallout. Because of the nature of our cohort and study protocol, we feel that our observations are valid and generally applicable to screening programs of radiation-exposed populations.

In our study population, the last preoperative cytologic conclusion was compared with the final histopathologic diagnosis for 258 nodules from 238 subjects with individual thyroid dose estimates and who were operated upon within the framework of the BelAm cohort study. In the surgical group, which was exposed to an estimated arithmetic mean thyroid dose of 1.73 Gy, the ROM for cytologies definite (96.7%) or suspicious for PTC (83.7%) is similar to those found among both unexposed adults [11–15,42] and children [16–21]. These results also are comparable to those from the UkrAm cohort [29], which received an estimated arithmetic mean dose of 0.79 Gy, and to those among children exposed to the Fukushima nuclear accident [32]. However, direct comparison to the latter cohort is not possible since Fukushima subjects with Bethesda I-IV cytologies were followed medically and only those with Bethesda V or VI were offered surgery [32] Additionally, the estimated individual thyroid doses received by Fukushima children typically were less than 0.02 Gy [48], leading to the conclusion that the increased incidence of pediatric thyroid cancers was not due to radiation exposure but rather to sensitive ultrasound screening procedures [49,50].

Since our study subjects mostly were adolescents and young adults (mean age 23.8 years) at operation, straddling the pediatric and adult populations, comparisons with results from unexposed groups are problematic, especially for indeterminate cytologies. Studies suggesting a higher ROM for pediatric nodules compared to adult nodules [51] have resulted in different management guidelines depending on patient age [45,51,53]. However, a recent study suggests that The Bethesda System for Reporting Thyroid Cytopathology may underestimate the true ROM for Bethesda III, IV, and V cytologies in the adult population [54]. In addition, a meta-analysis of pediatric thyroid nodules found that the ROM for indeterminate cytologies (Bethesda III and IV) was not statistically different between children and adults and suggested a reconsideration of published guidelines [55]. Our ROM for indeterminate nodules (33.0%) is comparable to the results of the meta-analysis, which reported a ROM of 31.9% in adults and 37.7% in children, and the ROM for benign cytologies is identical (8.1 and 8.0%, respectively) [55]. The major difference between our study and the meta-analysis is that our ROM for non-diagnostic cytologies is twice as high (31.0% vs 15.7%), potentially due to selection bias, since benign and non-diagnostic FNABs could be referred to surgery at the discretion of the study endocrinologist, thereby inflating the ROM among operated patients. These results are summarized in Table 5, where they are compared to those from the Fukushima Health Management Survey [32].

Although the frequency and ROM of cytologies definite for PTC peaked at doses 0.30–0.59 Gy and then trended downward at higher levels of exposure, the declines were small. Likewise, the odds of a correct cytologic conclusion (true positive and/or true negative) showed a biphasic response, highest for doses 0.10–0.29 Gy and then falling monotonically. However, the differences were not significant, suggesting that the level of radiation exposure received by our cohort did not affect the predictive value of FNAB for diagnosing PTC.

Major strengths of our study are the availability of individual ^{131}I thyroid doses based on thyroid radioactivity measurements made within two months of the accident and the completion of all procedures according to well-defined and standardized criteria that blinded all examiners to dose [33]. Our protocol resulted in a high rate of compliance with FNAB and surgery, a short interval between FNAB and surgery, review of cytologic specimens by

a single cytopathologist, and an independent review of all histopathologic specimens by an international panel of experts. Furthermore, while the majority of studies of the predictive value of FNAB for diagnosing cancer in general populations have been retrospective, our cohort was examined prospectively according to a well-defined protocol. We believe that these features make our findings unique in terms of correlating FNAB conclusions with histopathologic diagnoses at different levels of radiation exposure.

To address the difficulties presented by the use of an older cytologic classification that did not recognize AUS and that made a distinction between suspicious for FN and definite for FN, we combined our two follicular categories into a single indeterminate category in order to account for both AUS and FN, similar to other studies and recent management guidelines (44,45,55). In addition, we recognize a number of important limitations. The cohort resided in an area of relative iodine deficiency, potentially altering cancer risk compared to iodine sufficient populations [56]. Furthermore, our study was completed before the widespread availability of molecular testing [57], which would have decreased the number of indeterminate cytologies sent to surgery. Similarly, the lack of molecular testing precluded linking genetic alterations to dose in any of the cytological categories and although the modest fall in ROM for cytologies definite or suspicious for PTC at higher doses could be due to increased radiation-induced cytologic atypia, this was not evaluated in a formal manner by project cytologists. Our decision to treat WDTUMP as a benign tumor agrees with current classifications regarding it as a low-risk neoplasm that merits conservative management [58,59]. Additionally, our findings come from a radiation-exposed population that was intensively screened and had referral patterns to biopsy and surgery that are not necessarily applicable to a general medical setting.

Finally, it is important to note that the IPP did not account for noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [60, 61], which was not recognized as a distinct pathological entity at the time of cohort screening. Experience suggests that the greatest impact would be on indeterminate cytologies and those suspicious for PTC (shown in Figure 3) [62,63], thereby decreasing the ROM for these categories. Similarly, NIFTP could also account for some of those aspirates that were WDTUMP (shown in Fig. 4) or even those definite for PTC that were FA on final histopathology (shown in Fig. 1) [64]. It is also reasonable to conclude that increased recognition of the cytological features of NIFTP would result in a shift from Bethesda VI to Bethesda V cytologies in irradiated populations as has already occurred in general populations. However, since NIFTP is a histopathologic and not a cytologic diagnosis, this would not change management, which would remain surgical [65].

To summarize, in a large cohort exposed as children and adolescents to radioiodines at Chernobyl and screened according to a standardized protocol 11–22 years later, we confirm that the overall predictive value of FNAB for diagnosing PTC is similar to that in unexposed general populations. When predictive value is analyzed according to radiation dose, the response is biphasic, increasing two-fold at lower and moderate doses and decreasing monotonically at higher levels of exposure, with a non-significant linear trend across the whole dose range. We conclude that level of radiation exposure did not significantly affect

the predictive value of FNAB for diagnosing PTC at the doses received by members of the BelAm cohort.

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Data Availability Statement:

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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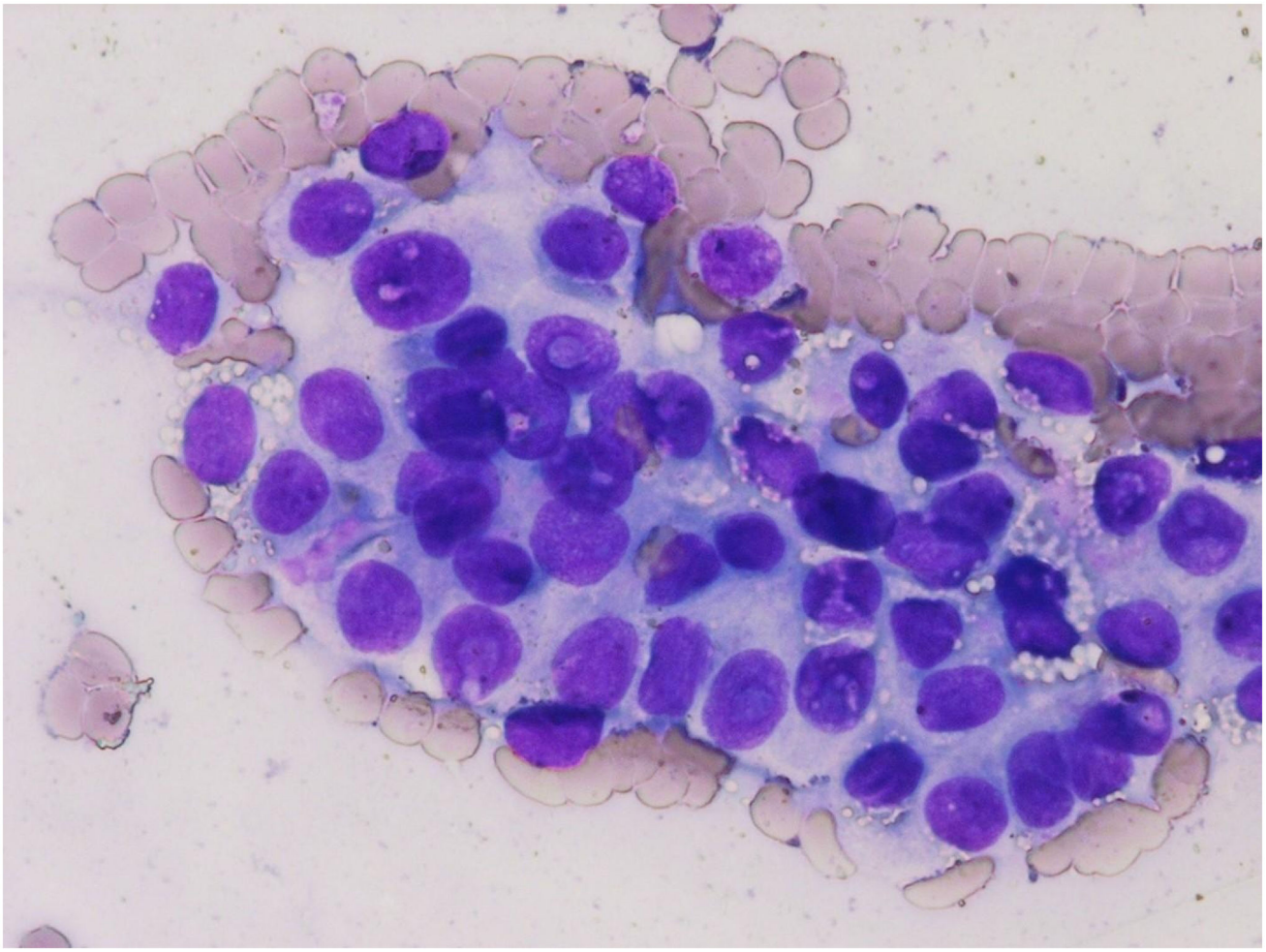

Fig. 1.

FNAB specimen from a 20-year-old female exposed to 1.4 Gy showing enlarged, oval-shaped nuclei, nuclear overlapping, and few intranuclear cytoplasmic invaginations that was interpreted as definite for papillary thyroid carcinoma and diagnosed as a follicular adenoma by the International Pathology Panel (Giemsa × 40).

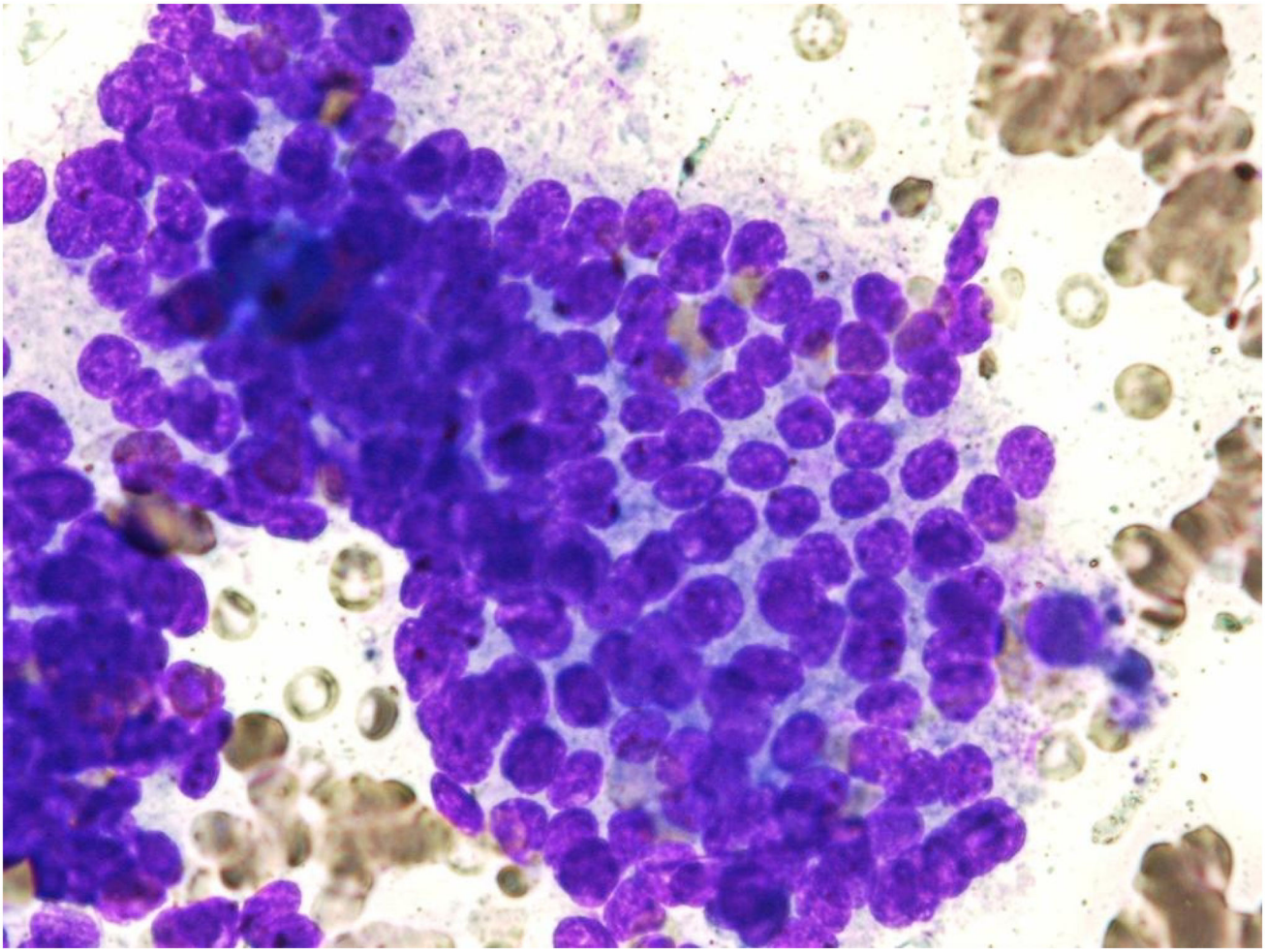

Fig. 2.

FNAB specimen from a 34-year-old female exposed to 4.1 Gy showing a highly cellular smear with suggestion of microfollicle formation, scant colloid, and nuclear crowding and overlapping that was interpreted as suspect follicular neoplasm and diagnosed as nodular goiter by the International Pathology Panel (Giemsa × 40).

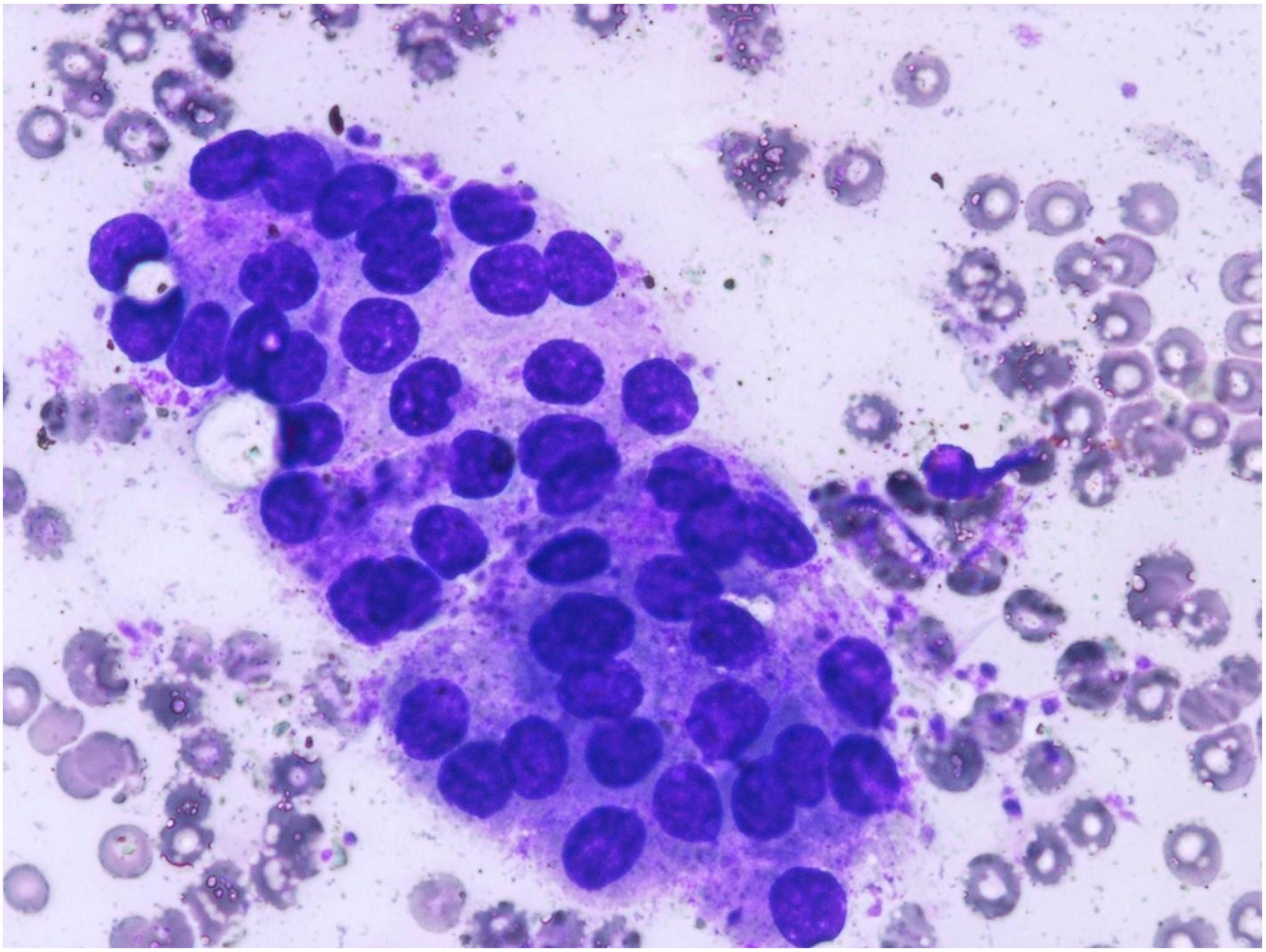

Fig. 3.

FNAB specimen from a 30-year-old female exposed to 0.7 Gy showing enlarged and oval nuclei with focal chromatin clearing and nuclear overlapping that was interpreted as suspicious for papillary thyroid carcinoma and diagnosed as a follicular adenoma by the International Pathology Panel (Giemsa × 40).

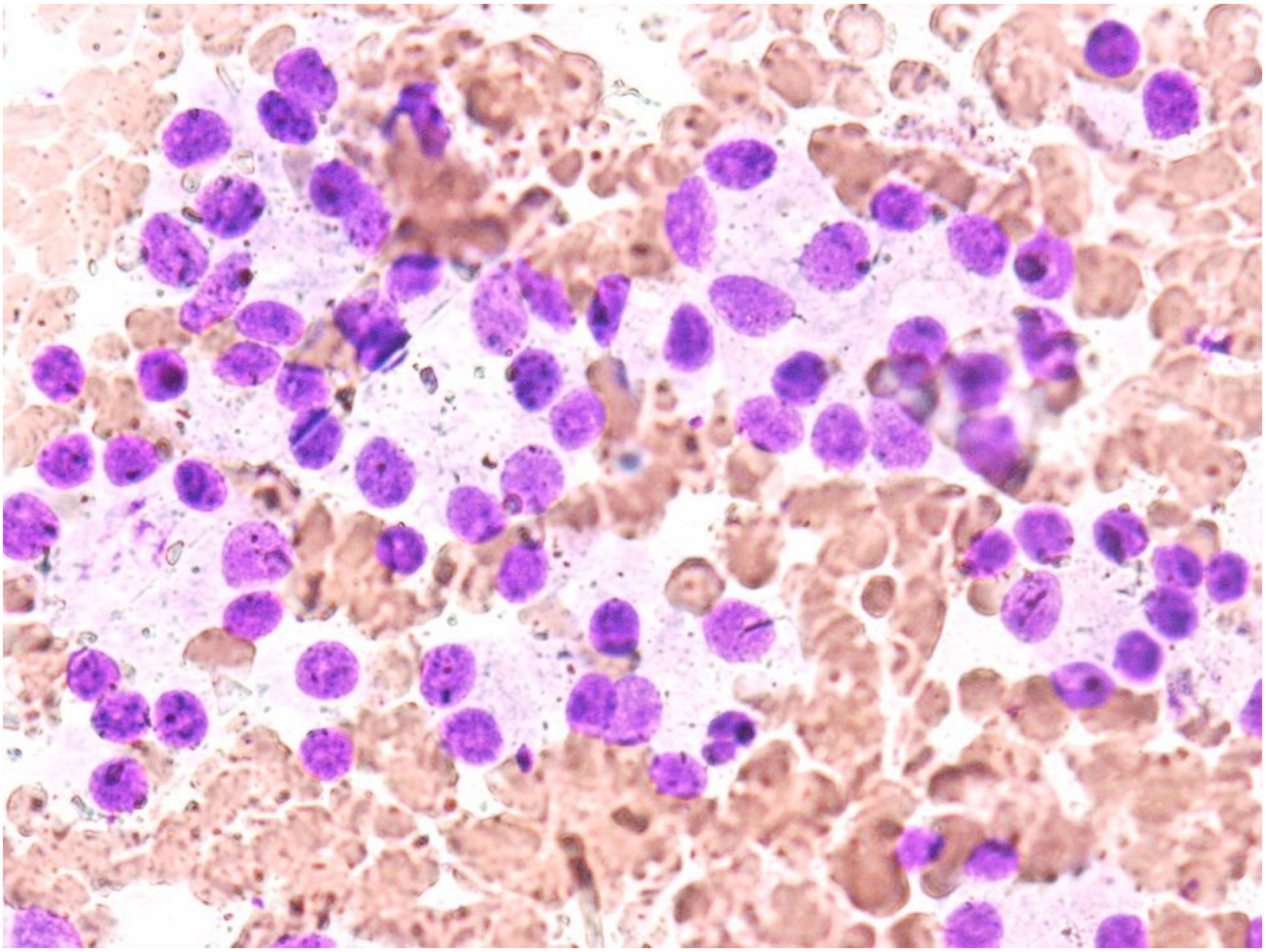

Fig. 4.

FNAB specimen from a 16-year-old male exposed to 0.8 Gy showing a moderately cellular specimen with evenly dispersed round nuclei and suggestion of microfollicle formation interpreted as suspect follicular neoplasm and diagnosed as a well-differentiated tumor of uncertain malignant potential by the International Pathology Panel (Giemsa × 40).

Table 1:

Distribution of final histopathologic diagnoses for 258 pre-operative cytologic conclusions. Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases (1997–2008).

	Histopathologic Diagnosis					
Cytologic conclusion	**PTC**	**FTC**	**FA**	**WDTUMP**	**NG**	**Total**
Definite for PTC	59	0	2	0	0	61
Suspicious for PTC	36	0	2	0	5	43
Indeterminate *	28	1	31	3	25	88
Benign	3	0	13	1	20	37
Non-diagnostic	9	0	8	0	12	29
Total	135	1	56	4	62	258

Abbreviations:

PTC Papillary thyroid cancer

FTC Follicular thyroid cancer

FA Follicular adenoma

WDTUMP Well-differentiated tumor of uncertain malignant potential

NG Nodular goiter

* Definite or suspicious for follicular neoplasm or Hürthle cell tumor

Table 2:

Distribution of 258 cytologic conclusions according to quintile of estimated thyroid radiation dose. Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases (1997–2008).

Radiation Dose, Gy	Cytologic Category					
	Definite for PTC N (%)	Suspicious for PTC N (%)	Indeterminate* N (%)	Benign N (%)	ND N (%)	Total Cytologic Conclusions N (%)
0.00–0.09	6 (18.2)	2 (6.1)	20 (60.6)	3 (9.0)	2 (6.1)	33
0.10–0.29	10 (22.7)	9 (20.5)	15 (34.1)	8 (18.2)	2 (4.5)	44
0.30–0.59	16 (32.0)	9 (18.0)	14 (28.0)	7 (14.0)	4 (8.0)	50
0.60–1.49	15 (25.9)	12 (20.7)	17 (29.3)	7 (12.1)	7 (12.1)	58
1.50–24	14 (19.2)	11 (15.1)	22 (30.1)	12 (16.4)	14 (19.2)	73
Total Cytologic Conclusions N (%)	61 (23.6)	43 (16.7)	88 (34.1)	37 (14.3)	29 (11.2)	258 (100)

Abbreviations:

PTC Papillary thyroid cancer

ND Non-diagnostic

*Definite or suspicious for follicular neoplasm or Hürthle cell tumor

Table 3.

Risk of malignancy for 258 cytologic conclusions according to quintile of estimated thyroid dose. Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases (1997–2008).

Radiation Dose, Gy	ROM, %				
	Definite for PTC	Suspicious for PTC	Indeterminate*	Benign	ND
0.00–0.09	100.0	100.0	40.9	0.0	0.0
0.10–0.29	100.0	100.0	33.3	12.5	50.0
0.30–0.59	100.0	66.7	35.7	14.3	25.0
0.60–1.49	93.3	75.0	41.2	14.3	28.6
1.50–24	92.9	90.9	22.7	0.0	35.7
Overall	96.7	83.7	33.0	8.1	31.0

Abbreviations:

ROM Risk of malignancy

PTC Papillary thyroid cancer

ND Non-diagnostic

*Definite or suspicious for follicular neoplasm or Hürthle cell tumor

Table 4.

Odds ratios for a correct cytologic conclusion for diagnostic fine needle aspiration biopsies according to quintile of estimated thyroid radiation dose. Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases (1997–2008).

Variable	Values	Correct Conclusion[a]	Incorrect Conclusion[b]	Odds Ratio[c]	95 % Confidence Interval	P-value[d, e]
Dose, Gy	0.00–0.09	13	18	1.00		
	0.10–0.29	11	31	2.22	(0.79, 6.20)	
	0.30–0.59	13	33	2.03	(0.73, 5.61)	
	0.60–1.49	15	36	1.90	(0.67, 5.39)	0.612[d]
	1.50–24	19	40	1.79	(0.63, 5.13)	0.990[e]
Sex	Male (reference)	24	70	1.00		
	Female	47	88	0.59	(0.32, 1.09)	0.089[d]
Oblast of residence at screening	Minsk City and Oblast (reference)	18	33	1.00		
	Gomel Oblast	49	107	1.05	(0.52, 2.14)	
	Other Oblasts[f]	4	18	2.50	(0.72, 8.70)	0.269[d]
Age at biopsy (per 10 years)				1.36	(0.78, 2.39)	0.275[d]

[a] Cytologic conclusion correctly predicted the final histopathologic diagnosis (true positive and/or true negative).

[b] Cytologic conclusion incorrectly predicted the final histopathologic diagnosis (false positive and/or false negative).

[c] Odds Ratio for a correct cytologic conclusion. All estimates are adjusted for other variables in the model.

[d] P-value for adding categorical dose variable to the model with confounders (sex, oblast of residence at screening, age at biopsy), a test of heterogeneity.

[e] A test for linear trend.

[f] Vitebsk, Brest

Model deviance=274.88.

Table 5.

Comparison of risk of malignancy according to The Bethesda System for Reporting Thyroid Cytopathology in unexposed adults and children, The Fukushima Health Management Survey, and the Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases (1997–2008).

Bethesda Category	Unexposed Adults[a]	Unexposed Children[a]	Fukushima[b,c]	BelAm[d]
Non-diagnostic	19.1	15.7	NA	31.0
Benign	8.0	4.6	NA	8.1
Indeterminate	31.9[e]	37.7[e]	NA	33.0[f]
Suspicious for Malignancy	79.6	90.5	99.4[g]	83.7
Definite for Malignancy	99.1	98.9		96.7

[a] From Vuong et al. [54]

[b] From Shimura et al. [32]

[c] Estimated individual thyroid doses < 0.02 Gy [48]

[d] Estimated mean thyroid dose 1.73 Gy

[e] Bethesda categories III and IV combined

[f] Definite or suspicious for follicular neoplasm or Hürthle cell tumor

[e] Cytology definite or suspicious for malignancy

Fukushima: The Fukushima Health Management Survey

BelAm: Belarusian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases

NA: Not available