Cytological examination of the thyroid in children and adolescents after the Fukushima Nuclear Power Plant accident: the Fukushima Health Management Survey

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Abstract. The Fukushima Daiichi Nuclear Power Plant accident occurred on March 11, 2011, following the Great East Japan Earthquake and tsunami. Radioactive materials, including I-131, were released into the environment after the accident. Shortly after, the prefectural government initiated the Fukushima Health Management Survey for monitoring the long-term health conditions of the residents of Fukushima Prefecture. In the survey, thyroid ultrasonography was scheduled for all people aged 18 years or younger who were living in Fukushima Prefecture at the time of disaster. The total number of examinees was approximately 370,000 in the Preliminary Baseline Survey (PBLS), and 380,000 in the first Full-scale Survey (FSS). First, thyroid ultrasonography was performed as the Primary Examination. When a thyroid nodule that meets the fine needle aspiration cytology (FNAC) guideline is detected, thyroid FNAC is performed. By the end of June 2017, the cytological specimens of 187 examinees had been interpreted as Malignant or Suspicious for Malignancy (SFM). In this article, the cytological results of whole categories are presented using the criteria of The Bethesda System for Reporting Thyroid Cytopathology. The total numbers of examinees with SFM or Malignant in PBLS and at the first FSS were 106 (62.0%) and 71 (38.0%), respectively. The data of the cytological results of SFM and Malignant were already reported. However, this is the first report of cytological data from categories other than SFM and Malignant. The results of the current study will contribute to future research into the thyroid conditions of children and adolescents.

Key words: Fine needle aspiration cytology, Radiation exposure, Thyroid ultrasonography, Childhood thyroid cancer, Fukushima Health Management Survey
The numbers of examinees diagnosed as having Malignant or Suspicious for Malignancy (SFM) have been already reported [14, 15]. However, the numbers of examinees diagnosed as having other categories have not yet been disclosed. We here report the cytological results of whole categories using The Bethesda System for Reporting Thyroid Cytopathology [16-18]. The results of the current study will contribute to future research into the thyroid conditions of both children and adolescents.

Materials and Methods

Outline of the Fukushima Health Management Survey

Fukushima Medical University consigned by Fukushima Prefecture have been conducting the Fukushima Health Management Survey (FHMS) to gain a detailed understanding of the health status of the prefecture’s residents, in order to provide thoughtful care and further promote wellbeing for all. This survey consists of two parts; a basic survey and a detailed survey (Table 1). In the Basic Survey, external radiation doses were individually estimated for all residents. Thyroid Ultrasound Examination (TUE) program carries out as a part of the detailed survey for residents aged 18 years or younger in Fukushima Prefecture at the time of accident.

The TUE program: the preliminary baseline survey and the full-scale survey

The TUE program is composed of two consecutive parts; the Preliminary Baseline Survey (PBLS) and the Full-scale Survey (FSS).

In the PBLS, ultrasound examination was scheduled for all subjects until March 2014. The subjects were approximately 360,000 residents aged 18 years or younger in Fukushima Prefecture when the accident occurred. In the Chernobyl Nuclear Power Plant accident, the number of children with thyroid cancer rapidly increased 4 or 5 years after the accident. These cancers were recognized as radiation-induced. Therefore, thyroid cancers detected within 4 or 5 years after the accident in Fukushima can be estimated as spontaneously developed malignancies.

In the FSS after April 2014, 25,000 were also added as the subjects who were still embryos or fetuses at the time of the accident. The first FSS was carried out from April 2014 to March 2016. To check for the development of thyroid cancer, ultrasound examination is received every 2 years until the subjects became older than 20 years old. After reaching 25 years of age, the examination was scheduled for every 5 years, for the remainder of the participant’s lifetime.

The TUE program: the primary and secondary confirmatory examinations

Both the PBLS and FSS have primary and secondary confirmatory examinations. In the primary examination, all subjects received ultrasound examinations using portable apparatus. Interpretations of ultrasound examination of the thyroid are categorized as Judgments A (A1, A2), B or C (Table 2). Judgments B means a nodule measuring >5.0 mm or/and a cyst measuring >20.0 mm in diameter. Category C required immediate examination due to a finding of a large or suspicious thyroid nodule or lymph node. Participants with judgment B or C are recommended to have a secondary confirmatory examination.

In the secondary confirmatory examination, ultrasound examination using precise apparatus, and blood and urine tests were performed. Fine needle aspiration cytology (FNAC) was recommended for: nodules >5 mm in diameter if thyroid carcinoma was strongly suspected; nodules >10 mm in diameter if carcinoma is suspected; all nodules >20 mm in diameter; and all cystic lesions >20 mm in diameter [19]. These guidelines were made to avoid unnecessary FNAC, especially for nodules between 5 and 10 mm in diameter. In participants who had undergone FNAC in the PBLS and whose ultrasound examination findings in the FSS were similar to those in the PBLS, the repeated FNAC was not recommended.
Case selection and methods

The number of examinees who received cytological examination between April 12, 2012 and June 9, 2017 was 760; this number was comprised of 552 examinees who participated in the PBLS, and 208 who participated in the FSS.

For cytological examination, fine needle aspiration cytology (FNAC) was performed. At the beginning of this survey, preparation consisted of application of a direct smear only. After that, both direct smear and liquid-base preparation (LBP) were applied in the same participant. First, the aspirated sample was used for direct smear. The rest of the sample in the aspiration needle was employed for the LBP. Papanicolaou staining was used in every case.

Cytological interpretation was made using the The Bethesda System [17] (Table 3). In Japan, Reporting System of Thyroid Cytology also appears in the General Rules of the Description of Thyroid Cancer, 7th edition (2015) by the Japanese Society of Thyroid Surgery [20]. The Bethesda System and the Japanese general rules have basically the same interpretation categories. A total of three cytopathologists and three cytotechnologists engaged on making cytdiagnoses in the Consensus Meeting. They are certified specialists qualified by The Japanese Society of Clinical Cytology. One of them was a Fellow of International Academy of Cytology, a cytopathology specialist qualified by the International Medical Society. Monthly Consensus Meetings for cytdiagnosis were held at the Department of Pathology, Fukushima Medical University.

The confirmed results of SFM and Malignant cases were discussed in detail with the patients in question and their guardians, who would then elect either surveillance or surgery. When the patients underwent surgery for thyroid cancer, treatment management was switched over to the National Health Insurance system. In principle, participants, whose nodule was interpreted as Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS), were recommended to repeated FNAC. When the repeated FNAC had the same result, most participants were recommended to receive medical follow-up. When the nodule was interpreted as Follicular Neoplasm or Suspicious for a Follicular neoplasm (FN/SFN), the participants were recommended to have further clinical examinations or medical follow-up. The TUE program does not include a survey for surgical treatment after medical follow-up. In addition, the protocol of the Fukushima Health Management Survey does not include the molecular tests of the examinees.

Results

The cytology results of the SFM and Malignant cases are shown in Table 4.

Regarding sex distribution, there were more females than males in both the PBLS and first FSS. The mean ages at diagnosis were 17.7 and 16.9 years in the PBLS and first FSS, respectively. The duration between the time of disaster and at pathological diagnosis was 2.4 years in the PBLS and 4.3 years in the first FSS. The

Table 3  Cytodiagnostic categories of The Bethesda System [17]

|   | Cytodiagnostic categories                  |
|---|-------------------------------------------|
| I | Nondiagnostic or Unsatisfactory (ND/UNS)  |
| II| Benign                                    |
| III| Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS) |
| IV| Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN) |
| V | Suspicious for Malignancy (SFM)           |
| VI| Malignant                                 |

Table 4  Suspected for Malignancy and Malignant cases in the preliminary baseline survey (PBLS) and the first full-scale survey (1st FSS) diagnosed by fine needle aspiration cytology

|                              | PBLS | 1st FSS |
|------------------------------|------|--------|
| No. of Suspected for Malignancy and Malignant cases | 116  | 71     |
| Male/Female                  | 39/77| 32/39  |
| Mean age ± SD at the secondary examination (minimum–maximum) | 17.3 ± 2.7 years (8–22 years) | 16.9 ± 3.2 years (9–23 years) |
| Mean age ± SD at the time of disaster (minimum–maximum) | 14.9 ± 2.6 years (6–18 years) | 12.6 ± 3.2 years (5–18 years) |
| Mean tumor size ± SD (minimum–maximum) | 13.9 ± 7.8 mm (5.1–45.0 mm) | 11.1 ± 5.6 mm (5.3–35.6 mm) |

PBLS, the Preliminary Baseline Survey; 1st FSS, the first Full-scale Survey.
average and maximum tumor sizes in the PBLS were larger than those in the first FSS.

The final cytological interpretations according to The Bethesda System are shown in Table 5. The total numbers of examinees with Nondiagnostic or Unsatisfactory (ND/UNS), Benign, AUS/FLUS, FN/SFN, SFM, and Malignant were 37, 404, 37, 95, 16 and 171, respectively. In principle, the examinees with ND/UNS and those with AUS/FLUS were recommended to undergo cytology for a second time. The total numbers of examinees with SFM and Malignant in the PBLS and first FSS were 106 (21.0%) and 71 (34.1%), respectively.

The subclassifications of ND/UNS and benign in the final cytological interpretation are shown in Table 6. Among the examinees interpreted as having cyst fluid only, no malignancy was detected in repeated cytology. Benign follicular nodules were the most common of the benign conditions, followed by Hashimoto thyroiditis. There were no cases of granulomatous (subacute) thyroiditis.

**Discussion**

This article is the first to report the results of all categories of cytological interpretation in the Fukushima Health Management Survey. The main purpose of this article was to report the case distribution of each category of cytological evaluation using The Bethesda System for Reporting Thyroid Cytopathology. The results of the survey will contribute to future research of thyroid cancer in children and adolescents.

Sonographic examination for children’s thyroid in Fukushima began for the clarification of scientific aspects and for response to social requests. In response to the recent worldwide increase in diagnosis of thyroid cancer, The US Preventive Services Task Force recommends against screening for thyroid cancer in asymptomatic adults [21]. However, this recommendation does not apply to those at increased risk of thyroid cancer due to history of exposure to ionizing radiation by medical treatment or radiation fallout. In addition, Japanese guideline for implementation of FNAC, which was applied for this survey, might reduce unnecessary FNAC...
for small thyroid cancers with lower risks.

The prevalence of latent thyroid cancer is high in Japanese adults, and has been reported as 10–20% or more [22, 23]. In addition, previous reports have indicated that sonographic examination of the thyroid gland was able to detect thyroid cancer in 0.1–1.5% of subjects in the adult general population [24]. However, there have been few reports on the prevalence of thyroid cancers in children. Therefore, in order to obtain control data, ultrasound and cytological examinations were performed on 4,365 asymptomatic children under the age 18 years living in Aomori, Yamanashi and Nagasaki Prefectures in Japan with the same protocol [24, 25]. These prefectures are located far from Fukushima Prefecture. The prevalence of SFM and Malignant in these three Prefectures was similar to that of Fukushima.

In the present study, the distribution of cytological interpretations by The Bethesda System was similar to the results of previous clinical reports for adults [26, 27]. The number of FNACs and findings of cytologically benign and follicular lesions in the first FSS tended to be lower than those in the PBLS. These phenomena would be attributed to omission of FNAC in 1st FSS, when findings of the ultrasound examination in the 1st FSS were similar to those of PBLS. Especially FN/SFN category is treated as the final diagnosis on cytology, and repeated cytology is generally not recommended.

A limitation of this study was that pathological diagnoses of resected thyroid nodules were not subjected. However, it was reported that most resected thyroid cancers were of a classical subtype of papillary carcinoma [14]. Special subtypes, namely follicular variant, diffuse sclerosing variant, and cribiform-morular variant, are quite rare. We also experienced a case of poorly differentiated carcinoma. Because of the design of this study, it was, however, very difficult to make the pathological diagnoses after medical follow-up, especially in subjects interpreted as FN/SFN or AUS/FLUS. Therefore, at this moment, false negative cases or borderline thyroid tumors in this study could not be evaluated. On the other hand, we have, to the best of our knowledge, one case of a patient pathologically diagnosed as having a benign nodule in the group of SFM. This suggested quite a low false positive rate in this study.

Nearly 80% of the examinees, who were diagnosed as having SFM or being Malignant on cytology, received thyroidectomy [13]. However, a part of the others has been clinically followed up without surgery. Total thyroidectomy was performed in 8.8% of surgically-treated patients, and remaining patients (91.2%) underwent lobectomy or hemithyroidectomy [13]. In the cases where thyroidectomy was performed, 17.4% and 20.0% cases were classified as T1a and N0, respectively [28]. Therefore, the problems concerning overtreatment basically do not occur in this survey. For patients given malignant cytological diagnosis in the United States, total thyroidectomy with an additional irradiation is recommended, according to the American Thyroid Association Guidelines [29]. However, the Guideline for Treatment of Thyroid Tumors by The Japanese Association of Endocrine Surgeons and The Japanese Society of Thyroid Surgery includes several alternatives for thyroid cancer treatment [30]. In particular, for patients with low risk papillary carcinoma of the thyroid, active surveillance (follow up without surgery) is recommended.

In conclusion, we report the detailed results of FNAC in the first (PBLS) and second (first FSS) round surveys of the Thyroid Ultrasound Examination program in the Fukushima Health Management Survey. This is the first report that cytological data of categories other than SFM and Malignant were disclosed. The results of the current study will contribute to future research into the thyroid conditions of children and adolescents.

Statement of Ethics

In this study, the examinees and their guardians provided written informed consent for the study, and the study protocol was approved by the institutional ethics committee of Fukushima Medical University, Fukushima, Japan.

Disclosure Statement

The authors declare that there was no conflict of interest.

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