Current progress and future challenges of Thyroid Ultrasound Examination Program in Fukushima: The Fukushima Health Management Survey

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Abstract. The Great East Japan Earthquake on March 11, 2011 and its subsequent tsunami caused the accident at the Fukushima Daiichi Nuclear Power Plant, in which extensive damage to the nuclear power reactors resulted in massive radioactive contamination. The Fukushima Prefecture started the Thyroid Ultrasound Examination (TUE) program as a part of Fukushima Health Management Survey project in response to residents' anxieties for health risks by radiation exposure. The TUE program covers residents in Fukushima aged 0 to 18 years at the time of the nuclear accident.

This program consists of the primary and the secondary confirmatory examinations. In the primary examination, survey of thyroid nodules and cysts was conducted with portable ultrasound apparatuses. In the second confirmatory examination, an interview about medical history, a physical examination, a detailed ultrasound examination, thyroid function tests, and urinalysis were performed. Fine needle aspiration biopsy (FNAC) was also carried out only when the sonographic findings of nodules or cysts meet the standardized guideline for implementation of FNAC.

In the Preliminary Baseline Survey (first round), 300,472 subjects were examined within 3 years after the accident and the participation rate was 81.7%. The proportions of the subjects who fell into the categories A1 (no nodules or cysts present), A2 (nodule ≤ 5 mm or cyst ≤ 20 mm diameter), B (nodule > 5 mm or cyst > 20 mm diameter) and C (immediate need for further investigation) were 51.5, 47.8, 0.8 and 0%, respectively; 2293 subjects in categories B and C were recommended to undergo the confirmatory examination. Of the 2091 subjects preformed the confirmatory examination, 116 were cytologically diagnosed as malignant or suspected malignancy. The prevalence of childhood thyroid cancer in Fukushima was determined to be 0.038% with no significant differences between evacuated and non-evacuated areas.

In the first Full-scaled Survey (second round) of the TUE, 270,540 subjects were examined until March 2016 and the participation rate was 71.0%. The proportions of the subjects who fell into the categories A1, A2, B, and C were 40.2, 59.0, 0.8 and 0%, respectively. Thyroid nodules cytologically diagnosed as malignant or suspected malignancy were found in 71 cases. There is no dose-response pattern between incidence of thyroid cancer and the geographical classification of estimated absorbed radiation dose in thyroid. Currently, we performed the secondary confirmatory examination of the second Full-scaled Survey (third round) and the third Full-scaled Survey (fourth round).

We would like to mention on-going challenges in our program such as actions against a risk of overdiagnosis in thyroid sonography, psychological supports for participants and their guardians, and more sufficient explanation for shared decision making before examinations. With advices and suggestions from international experts, we intend to continue our efforts to fulfill our mission and consider how best the thyroid examination can serve Fukushima residents.

KEYWORDS: Fukushima, Thyroid Ultrasound Examination, Thyroid cancer, Nuclear Accident.

1 INTRODUCTION

Japan had the Great East Japan Earthquake March 11th, 2011. Within 1-hour, huge tsunami came to the east coast of Japan, and the tsunami sometimes reached a height of more than 10m. The tsunami disabled the electric power supplies in Fukushima Dai-ichi Nuclear Power Plant and induced melting through of nuclear fuels. Then radionuclides were leaked form the reactors by hydrogen explosions.
Leaking of radionuclei induced radioactive contamination mainly in Fukushima Prefecture. Just after the nuclear accident, screening of thyroid dose was conducted using survey meters for 1,080 children at

area near the nuclear power plant. As a result, measured thyroid doses were all below 50 mSv. In the UNSCEAR's analysis of thyroid doses after the Chernobyl accident, the dose range below 50 mSv is considered to be the lowest dose range even in the non-evacuees in Belarus [1].

Outbreak of thyroid cancer due to radiation exposure, such as the case in the Chernobyl accident, had not been expected [2]. However, childhood thyroid cancer is of great concern in Fukushima Prefecture, and the fear of cancer has been a prominent one throughout Japan. Therefore, it was necessary to conduct surveys for the social demand [3]. Fukushima Prefecture decided to start a thyroid examination by using ultrasonography and common standardized diagnostic criteria. The Thyroid Ultrasound Examination (TUE) program was started on October 9th, 2011, seven months after the earthquake, for residents aged 18 years or younger who lived in Fukushima Prefecture at the time of the earthquake [3-5].

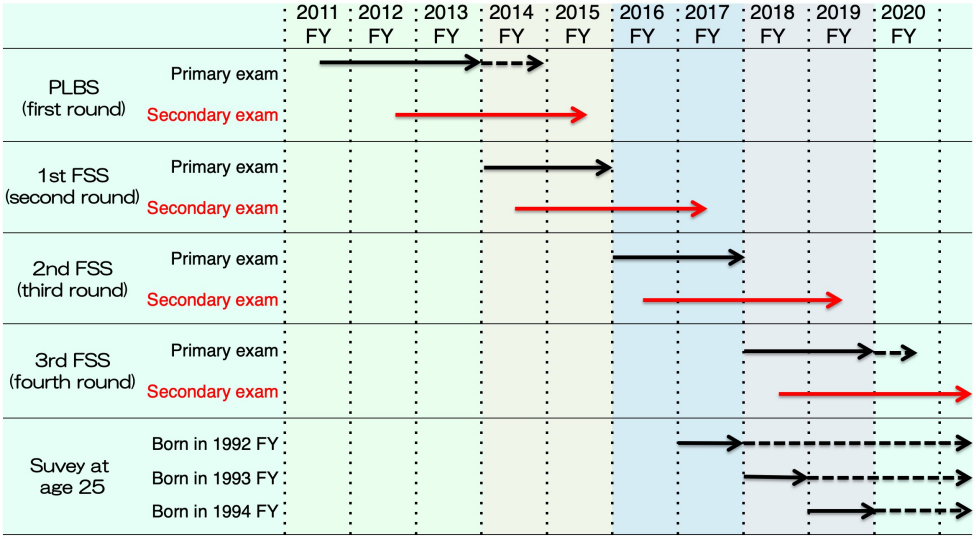
2 PROTOCOL OF TUE PROGRAM

2.1 Outline of the TUE program

The TUE program consists of two consecutive parts; the Preliminary Baseline Survey (PBLS) and the Full-scale Survey (FSS) [6]. PBLS was conducted for about two and a half years from October 2011 to March 2014, and some subjects who could not be examined were also examined for a following year (Fig. 1) [5, 7]. The subjects were approximately 360,000 residents aged 18 years or younger in Fukushima Prefecture when the accident occurred. This first-round survey during the first 3 years following the accident was evaluated as baseline data prior to the period in which radiation effects on the thyroid gland could potentially occur.

Since April 2014, FSS has added approximately 25,000 subjects who may still be in the mother's uterus at the time of the accident. The first FSS was carried out from April 2014 to March 2016. Thereafter, FSS is performed every two years until the subject is over 20 years old. From April 2020, the fourth FSS, the fifth-round survey, has been started. After reaching 25 years of age, the examination was scheduled for every 5 years. Survey at age 25 has been started from April 2017 (Fig. 1).

Figure 1: The progress of the TUE program



PLBS: Preliminary Baseline Survey, FSS: Full-scale Survey

2.2 The primary examination

The TUE program consists of the primary and secondary confirmatory examinations (Fig. 2) [4, 5]. In the primary examination, thyroid ultrasonography is performed mainly at schools and public facilities

in each area of Fukushima Prefecture, using portable ultrasonic diagnostic equipments, and specialized medical institutions outside the prefecture. Interpretations of the primary examination are categorized as Judgments A (A1, A2), B, or C (Table 2). Judgments B indicates a nodule measuring ≥ 5.1 mm or/and a cyst measuring ≥ 20.1 mm in diameter. Category C is judged when a very large suspicious thyroid nodule, overt extra-thyroid extension, or large metastatic lymph node is found, which requires immediate examination. Participants in Judgment B or C are encouraged to take the secondary confirmation examination.

Figure 2: The Flow chart of Thyroid Ultrasound Examination program

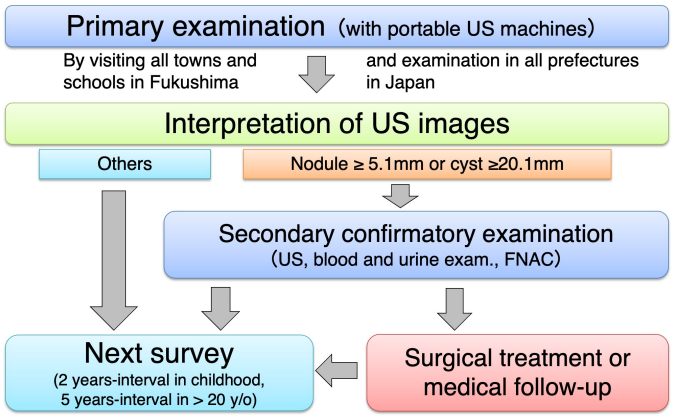


Table 1: Diagnostic criteria in the primary examination

Judgment	Interpretation	Recommendation
A	No nodule and/or cyst[(a)]	
(A1)	No nodule and/or cyst[(a)]	Next primary examination
(A2)	Nodule ≤ 5.0mm[(b)] or/and cyst ≤ 20.0mm	Next primary examination
B	Nodule ≥ 5.1mm or/and cyst ≥ 20.1mm	Confirmatory examination
C	Required immediately examination	Urgent confirmatory examination

[(a)] Mixed cystic-solid nodules are considered as "nodules".
[(b)] Some examination results A2 may be classified as B when clinically indicated.

2.3 The secondary confirmatory examination

In the secondary confirmatory examination, we perform medical examination, ultrasonic examination using precision equipment, and blood / urine examinations. Blood tests measure TSH, FT3, FT4, thyroglobulin, TPOAb, and TgAb, and urinalysis measures urinary iodine concentration. Fine needle aspiration cytology (FNAC) is performed only when the Japanese guideline for the implementation of FNAC is met [6]. Also, it is not recommended to repeat FNAC if the participants who had FNAC on a previous thyroid examination had similar ultrasound results to their previous findings.

3 RESULTS OF THE TUE PROGRAM

3.1 PLBS, the first-round survey

81.7% of 367,637 subjects, 300.472, have undergone the primary examination. The judgment of the primary examinations resulted in 154,605 (51.5%) for A1 judgment, 143,573 (47.8%) for A2 judgment,

2,293 (0.8%) for B judgment, and 1 (0.0%) for C judgment (Table 2). The detection rate of nodules and cysts found was 1.3% (3,988) and 47.9% (143,911), respectively [8].

Of the 2,293 examinees whose primary examination was judged as B to C, 2,130 (92.9%) underwent the secondary confirmatory examination, and 2,091 (91.2%) confirmed the results (Table 2). As a result of the secondary examination, nodules in 116 examinees, 39 males and 77 females, were diagnosed as malignant or suspected to be malignant by FNAC. Mean of the age at the examination of these examinees was 17.3 ± 2.7 years (8 to 22 years), and mean nodule diameter was 13.9 ± 7.8 mm (5.1 to 45.0 mm). Most of surgically treated cases were pathologically diagnosed as papillary thyroid carcinoma (Table 2).

Table 2: Results of the TUE program

		PBLS (first round)	1st FSS (second round)	2nd FSS (third round)	3rd FSS (fourth round)
Fiscal year		2011-2013	2014-2015	2016-2017	2018-2019
Subjects		367,637	381,244	336,670	294,240
Participation rate		81.7%	71.0%	64.7%	61.4%
Judgement in the primary examination	A1	51.5%	40.2%	35.1%	33.7%
	A2	47.8%	59.0%	64.2%	65.5%
	B	0.8%	0.8%	0.7%	0.7%
	C	0.0%	0.0%	0.0%	0.0%
Subjects for the 2nd exam		2,293	2,227	1,501	1327
Participation rate of the 2nd exam		92.9%	84.1%	73.4%	55.8%
Malignant or suspicious (FNAC)		116	71	31	21
Examinees surgically treated		102	52	27	13
Pathological diagnosis	PTC	100	51	27	13
	PDTC	1			
	Others	1	1		

Data shown in Table 2 as of March 31, 2020.

3.2 The first FSS, the second-round survey

270,540 examinees, 71.0% of 381,244 subjects, have undergone the primary examination. The judgment of the primary examinations resulted in 108,718 (40.2%) for A1 judgment, 159,584 (59.0%) for A2 judgment, 2,227 (0.8%) for B judgment (Table 2). The detection rate of nodules and cysts found was 1.3% (3,789) and 53.4% (160,369), respectively.

Of the 2,227 examinees whose primary examination was judged as B to C, 1,874 (84.1%) underwent the secondary confirmatory examination, and 1,826 (82.0%) confirmed the results (Table 2). As a result of the secondary examination, nodules in 71 examinees, 32 males and 39 females, were diagnosed as malignant or suspected to be malignant by FNAC. Mean of the age at the examination of these examinees was 16.9±3.2 years (9 to 23 years), and mean nodule diameter was 11.1 ± 5.6 mm (5.3 to

35.6 mm). Same as the PLBS, most of surgically treated cases were pathologically diagnosed as papillary thyroid carcinoma (Table 2).

3.3 The second and third FSS, the third- and fourth-round surveys

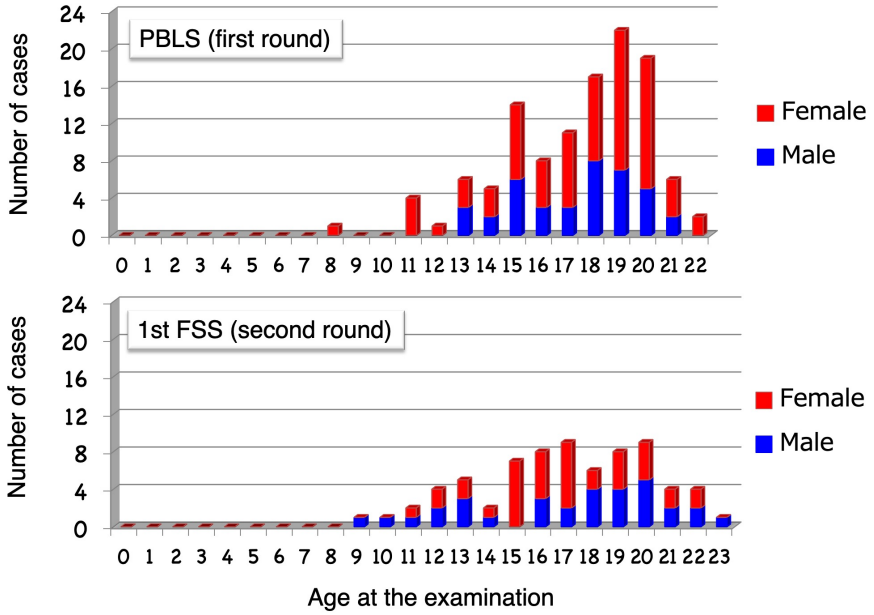
The second FSS, the third-round survey, are nearing completion, and analysis of the results is currently underway. In addition, the third FSS, the fourth-round survey, are currently undergoing the secondary confirmatory examination. Table 2 shows these preliminary results.

4 THE EFFECTS OF RATIATION EXPOSURE

4.1 Relationship between the detection of pediatric thyroid cancer and examinees' age

In order to clarify the relationship between the radiation dose and the detection of thyroid cancer in children and adolescents, we analyzed the results of the first- and second-round surveys on several points of interest. Firstly, age distribution of cases diagnosed with malignant or suspicious were shown in Fig. 3. Thyroid cancer was mainly found in elder examinees, especially no one with thyroid cancer was found in those under 8 years of age at the time of examination, i.e., no thyroid cancer was found in subjects at younger age at the time of the accident. In contrast to Fukushima, more thyroid cancers were found in younger children in Belarus after the Chernobyl nuclear accident [9].

Figure 3: Age and gender of cases diagnosed with malignant or suspected for malignancy by FNAC in the PLBS and the first FSS



4.2 Relationship between the detection of pediatric thyroid cancer and expected thyroid dose

We then analyzed odds ratio for thyroid cancer detection according to absorbed doses in thyroid glands, as estimated by UNSCEAR [10]. Municipalities in Fukushima were classified into 4 groups by estimated thyroid doses. Fig 4A and 4B shows adjusted odds ratio for the detection of malignant or suspicious for malignancy in subjects aged 6-14 and ≥ 15 years at the time of the earthquake, respectively. In both the first and second round, no dose-dependent pattern emerged from the geographical distribution of absorbed doses.

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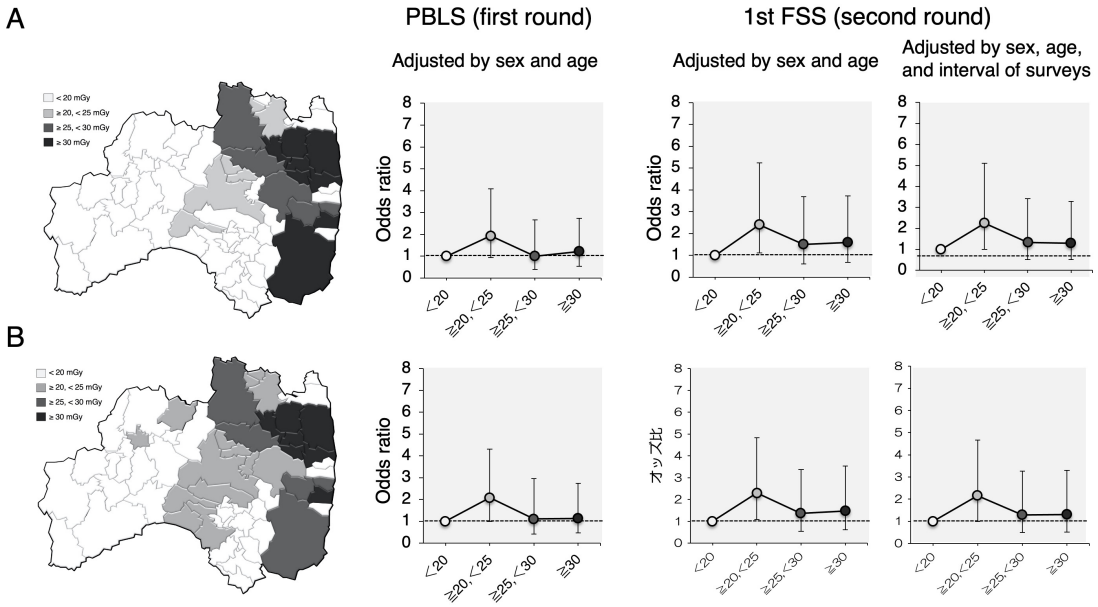
Figure 4: Adjusted odds ratio (95% CIs) for thyroid cancer according to maximum absorbed doses in thyroid glands, as estimated by UNSCEAR



Adjusted odds ratio for the detection of malignant or suspected malignancy in subjects aged 6-14 years (A) and aged ≥ 15 years (B) at the time of the earthquake, classified by the maximum estimated thyroid absorbed dose by municipality

4.3 Genetic alteration in pediatric thyroid cancer found in Fukushima

We also analyzed genetic alterations in thyroid cancers. The BRAFV600E mutation was highly prevalent and found in 96 (69.6%) cases. RAS mutations were not detected in the current series. Chromosomal rearrangements such as involving RET, NTRK, and ALK, were found in 23 (16.7%) cases [11]. The genetic pattern with high prevalence of the BRAF point mutation and low frequency of chromosomal rearrangements was completely different from post-Chernobyl papillary thyroid carcinomas. These results suggest that thyroid cancers found in the first- and second-round survey might not associate with radiation exposure.

5 OUR ACTIONS AGAINST THE RISK OF OVERDIAGNOSIS AND OF THYROID CANCER

In recent years, especially in South Korea, the US and European countries, dealing with overdiagnosis of low-risk thyroid cancer has become an important issue in the diagnosis and treatment of thyroid cancer [12]. In Japan, we have pioneered the publication of guidelines that was able to manage the risk of overdiagnosis and were already applied them in the clinical practice.

In the TUE program, we do not recommend the secondary examination if the nodule is less than 5.1 mm in diameter in the primary examination. This protocol may contribute to the exclusion of latent thyroid cancer, which has been reported to be found in more than 10% of autopsy cases (Table 3).

In the secondary confirmatory examination, we perform ultrasound-guided FNAC only for subjects selected with the management guideline for thyroid nodules [6]. According to this guideline, FNAC is recommended for nodules of 5.1 to 10.0 mm in diameter with strongly suspicious sonographic findings for malignancy; nodules of 10.1 to 20.0 mm with any suspicious findings; and all nodules over 20 mm. As a result of examining the implementation rate of FNAC in the first-and second-round survey, the implementation rate in the nodules of 5.1-10.0 mm was as low as 20% and 7%, respectively. And, the implementation rate increased as the size increased. The guideline-based management of thyroid

nodules in the secondary examination may contribute to reduce excessive FNAC implementation (Table 3).

In addition to the action in the TUE examinations, thyroid cancer management including follow-up of thyroid cancer may contribute to reducing overtreatment of low-risk thyroid cancer in clinical practice. As a result of these efforts, it has been shown that the proportion of low-risk thyroid cancers, such as T1aN0M0, among surgically treated thyroid cancers is extremely low [13].

6 OUR ACTIONS FOR ANXIETY IN PARTICIPANTS IN THE TUE PROGRAM

Although the TUE program was started in response to concerns about risks on health caused by radiation exposure in Fukushima, there might be a risk that this examination may cause other concerns. Therefore, we are making efforts to respond to various questions and anxieties that the examinees and their family may have. Even before or after the primary examination, examinees and their families may have a question concerning to arrange the primary exam or anxiety concerning to the result of the primary exam. To cope with these, we have opened call center for general questions and arrangement of examinations and a medical hotline for counseling about medical issues. In addition, we have sent periodic news letters to examinees 2 times in a year to explain the details about ultrasound examinations and FAQs, and we have opened small booths with medical doctors to explain tentative results just after examinations.

In the secondary confirmatory examination and subsequent surgical treatment, strong anxiety may be occured in examinees and their families, such as anxiety concerning to the results of the secondary examination or to surgical treatment and medical follow-up. To take measures against these, we have organized the Thyroid Support Team consisted with clinical psychologists, medical social workers, nurses, and supports examinees consistently throughout the surgical treatment and the observation period. At the time of the first visit, a member of this team listens carefully to the examinee and help the examinees and families relax. At the medical examination, they accompany the examinee for medical and ultrasound examination. After the examination, they check if the examinee and the family have any questions and provide any necessary information.

7 CONCLUSION

In this article, we have introduced the outline of the TUE program, which has been performed since the accident at the nuclear power plant occurred in 2011 and our ongoing challenges. With advices and suggestions from international experts, we intend to continue our efforts to fulfill our mission and consider how best the thyroid examination can serve Fukushima residents. We believe that our efforts to resolve the issues in the TUE program will lead to further challenges for the future of Fukushima Prefecture.

8 ACKNOWLEDGEMENTS

We acknowledge the commitment of all collaborators in the Radiation Medical Science Center for the Fukushima Health Management Survey in Fukushima Medical University: Drs. Takashi Matsuzuka, Satoru Suzuki, Satoshi Suzuki. Tetsuya Ohira, Seiji Yasumura, Hitoshi Ohto, and all members in the Department of Thyroid Ultrasound Examination. We also gratefully acknowledge Drs. Shin-ichi Suzuki and Manabu Iwadate in Department of Thyroid and Endocrinology and Dr. Susumu Yokoya in Thyroid and Endocrine Center in Fukushima Medical University. The authors declare no conflict of interest.

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