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[Original Article]

Investigation of thyroid cancer cases that were not detected in the Thyroid Ultrasound Examination program of the Fukushima Health Management Survey but diagnosed at Fukushima Medical University Hospital

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Abstract

The Great East Japan Earthquake, which occurred on March 11, 2011, and its subsequent Fukushima Daiichi Nuclear Power Plant accident, prompted implementation of the Thyroid Ultrasound Examination (TUE) program as a part of the Fukushima Health Management Survey. The purpose of this program is to support residents of Fukushima Prefecture, and to analyze the health effects of the released radionuclides. Regardless of relatively high participation rates and a well-planned diagnostic flow, it is conceivable that not all thyroid cancer cases can be detected by the TUE program. The aims of the present study were to identify and characterize these “outside” cases, targeting patients at Fukushima Medical University (FMU) Hospital. As of June 30, 2017, we have successfully identified 11 outside cases. These corresponded to 5.7% of the 194 subjects who were identified as having thyroid cancer or suspected thyroid cancer in the TUE program. Although the outside subjects of other institutes were not investigated, the present study may have identified the majority of outside subjects in Japan, considering that FMU Hospital treats a large number of thyroid cancer subjects. Furthermore, the characteristics of the 11 subjects were not different from those of the subjects identified in the TUE program. These findings confirm that the TUE program was able to identify subjects of thyroid cancer adequately and sufficiently.

Key words : thyroid cancer, thyroid ultrasound examination, Fukushima Health Management Survey, Fukushima Daiichi Nuclear Power Plant accident.

Introduction

Following the Great East Japan Earthquake and the resulting devastating tsunami on March 11, 2011, the Fukushima Daiichi Nuclear Power Plant

accident occurred, releasing a large amount of radionuclides, including ¹³¹I, into the environment. An increase in childhood thyroid cancer was of great concern among the residents of Fukushima Prefecture, because more than 6,000 children with thyroid

cancer had been reported after the Chernobyl nuclear accident in 1986¹). The Thyroid Ultrasound Examination (TUE) program, therefore, was implemented on a voluntary basis as a part of the Fukushima Health Management Survey (FHMS), which was being conducted to support the residents of Fukushima Prefecture and analyze the health effects of radiation²). The TUE program targeted approximately 380,000 Fukushima Prefectural residents who were either aged 18 years or younger at the end of March 2011, or who were born in the following fiscal year, starting in April 2011. The first-round examination, also known as the Preliminary Baseline Survey, was started in October 2011 to obtain baseline data. The second-round examination, called the first Full-scale Survey (FSS), and the third-round examination, called the second FSS, were conducted in April 2014 and April 2016, respectively. An FSS was then to be conducted every two years thereafter.

In each round, thyroid ultrasonography was used in the primary examination as a screening tool for thyroid cancer. Subjects who did not have nodules or cysts, and those who had nodules ≤ 5.0 mm and/or cysts ≤ 20.0 mm were categorized as A category, and were recommended to receive a primary examination in the following round. Those who had nodules > 5.0 mm or cysts > 20.0 mm, which accounted for approximately 0.7-0.8% of all examinees, were categorized as either B or C. B category, which accounted for most of these cases, was for those who did not require urgent medical examination. Those requiring urgent medical examination were categorized as C. Subjects in the B and C categories were recommended to proceed to a confirmatory examination, which consisted of a second ultrasound examination, blood and urine tests, and, if indicated, fine needle aspiration cytology (FNAC) as previously reported in detail^{3,4}). At the completion of the second round, no relationship was assumed between the estimated total thyroid radiation dose and occurrence of the thyroid cancer⁵).

Regardless of the relatively high participation rates, i.e., 81.7% for the first round and 71.0% for the second^{6,7}), and the well-planned diagnostic flow^{3,4}), it is inevitable that not all thyroid cancer or suspected cancer cases can be detected by any kind of screening program, including the TUE program. As such cases are outside the list of subjects with thyroid cancer or suspected thyroid cancer found in the TUE program, and are not utilized for analyses of thyroid cancer occurrence, in the current manuscript the authors have named them "outside" cas-

es. The present study was undertaken to identify and characterize these outside cases, targeting patients at FMU Hospital.

Subjects and Methods

Among the target subjects of the TUE program, we enrolled those who had been diagnosed as having thyroid cancer or suspected thyroid cancer by FNAC and/or histological examination after surgery in Fukushima Medical University (FMU) Hospital by June 30, 2017, but had not been detected by the TUE program. In order to determine which subjects met these criteria, the first step was for both the Department of Thyroid and Endocrinology and the Department of Clinical Pathology at FMU Hospital to independently submit lists of candidates. The former department listed all patients born between April 2, 1992 and April 1, 2012 who had received surgical treatment for thyroid cancer or suspected thyroid cancer between October 9, 2011 and June 30, 2017. The latter department listed patients in the same age range who were diagnosed as having malignancy or suspicious of malignancy via FNAC and/or were diagnosed as having thyroid carcinoma by histological examination of surgical specimens. Patients who were assumed to be living in prefectures other than Fukushima Prefecture at the time of the accident were excluded. The lists from both departments were combined to eliminate overlap of names and other identifiers.

The next step was to send the combined list to the Radiation Medical Science Center, which is in charge of the FHMS, and investigate whether each listed subject was recorded as a case of malignancy or suspected malignancy by the TUE program. In cases where the subject was a target resident of the TUE program, but was not listed as having malignancy or suspected malignancy, he or she was categorized as an outside subject. The following information for each outside subject was obtained for detailed analysis from the Radiation Medical Science Center: area of residence at the time of the accident, and the subject's own history of participation in the TUE program, if any.

Written informed consent, including the use of collected information for research purposes, was obtained from each subject and/or their guardian. This research was approved by the Ethics Committee of FMU (no. 29221), which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. The results of

the present study were partly presented at the 10th Thyroid Ultrasound Examination Evaluation Subcommittee, held on July 18, 2018.

Results

The lists of surgical cases submitted by the two departments, i.e., the Department of Thyroid and Endocrinology and the Department of Clinical Pathology at FMU Hospital, matched exactly, and 160 surgically treated cases as of June 30, 2017 were identified. The latter department also presented a list of 20 subjects having received FNAC, which had been carried out at FMU Hospital in a clinical setting different from the TUE program. Among the 20 subjects, seven were diagnosed as having malignancy and one was diagnosed as having suspected malignancy; all eight of these subjects belonged to the 160 surgically treated cases. There were no subjects who had been diagnosed as having malignancy or suspected malignancy by FNAC, but had not undergone surgery. The remaining 12 subjects were diagnosed as having findings of “undetermined significance” by FNAC according to the Japanese Society of Thyroid Surgery⁸⁾, which corresponds to “Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance (AUS / FLUS)” according to the Bethesda system⁹⁾. One among these 12 subjects received surgery and was counted among the 160 surgically treated subjects. These findings indicate that all subjects who had received surgery for thyroid cancer or suspected thyroid cancer in FMU Hospital were listed and, in addition, all subjects diagnosed as such by FNAC were successfully identified and included among the 160 surgical-

ly treated cases in the present study.

Among the 160 surgically treated subjects, 148 were counted as having thyroid cancer or suspected thyroid cancer by the TUE program. The remaining 12 subjects, therefore, were considered to be possible outside cases.

The histological diagnoses in 11 of these 12 subjects consisted of thyroid cancer; the remaining case was deemed benign. FNAC, which had been performed at FMU Hospital in six subjects and in other institutions in the remaining six, resulted in diagnosis of malignancy or suspected malignancy in 11 subjects, and follicular neoplasm in one. The subject with follicular neoplasm underwent endoscopic surgery, and the diagnosis was histologically confirmed as follicular adenoma. This subject was not classified as an outside case, not only because the final diagnosis was histologically benign, but also because FNAC disclosed the diagnosis of follicular neoplasm; this is in contrast to the TUE program, where subjects are only classified as having malignancy or suspected malignancy by FNAC. Thus, the 11 cases diagnosed by FNAC that were then confirmed histologically were considered to be the outside cases.

How these 11 outside subjects were eventually diagnosed in relation to their participation in the TUE program was investigated (Table 1). One subject had not participated in the program at all, but was referred to FMU Hospital because of incidental ultrasound detection of a thyroid nodule by a family physician (a). The remaining ten subjects had joined the program at least once, with final participation in the first round for three subjects and in the second round for seven. Among the ten subjects, two were judged

Table 1. Routes by which thyroid cancer diagnoses were made on the 11 outside subjects

| | | Routes to diagnosis | Number of subjects | | |
|---|---|---|--------------------|----------------|---|
| a | | Referral to FMU Hospital by other institutes, with no participation in the TUE program or after A categorization in primary examination of the TUE program. | 3 | 3 ^a | |
| b | | B category at primary examination, no consultation with confirmatory examination, but direct referral to FMU Hospital by another institute. | 1 | 8 ^b | |
| c | B category at primary examination and consultation with confirmatory examination. | Transfer to health insurance-based system ^c without FNAC because of not meeting the indication criteria. | 5 | | 7 |
| d | | Transfer to health insurance-based system ^c after diagnosis of undetermined significance by FNAC. | 2 | | |

^a Diagnosis of thyroid cancer was not triggered by the TUE program.

^b Diagnosis of thyroid cancer was triggered by the TUE program

^c Transfer from the confirmatory examination of the TUE program to the health insurance-based system (separate from the TUE program) was selected, because further periodic and close observation for possible diagnosis of thyroid cancer was considered preferable to waiting for the next round of the TUE program.

Table 2. Characteristics of the 11 outside subjects in comparison with those of the subjects identified in the TUE program^{6,7,10)}

| | | Subjects outside the TUE program | Subjects identified in the TUE program (first round ⁶ , second round ⁷ , and third round, as of June 30, 2017 ¹⁰⁾) |
|----|--|----------------------------------|--|
| 1. | Total number | 11 | 194 |
| 2. | Male : female | 4 : 7 | 75 : 119 |
| 3. | Age at the accident | 13.8±4.0 years | 14.9±2.6, 12.6±3.2 and 10.6±1.6 years |
| 4. | Age (at diagnosis or surgery) | 18.3±3.8 years (at surgery) | 17.3±2.7, 16.9±3.2 and 16.1±1.8 years (at diagnosis) |
| 5. | Area of residence at the accident ^a | 4 : 4 : 3 : 0 | 34 : 108 : 34 : 17 (total of 193 cases ^b) |
| 6. | Tumor size | 14.0±5.1 mm | 13.9±7.8, 11.1±5.6 and 12.1±3.1 mm |
| 7. | Histological diagnosis after surgery | 11 papillary thyroid carcinomas | 152 papillary thyroid carcinomas, one poorly differentiated thyroid carcinoma, one benign tumor, one other thyroid carcinoma |

^a Area of residence was categorized as : the 13 evacuation municipalities, the Nakadori area, the Hamadori area, and the Aizu area.

^b One histologically diagnosed benign case was excluded.

as A category in the primary examination, which does not necessitate a confirmatory examination, but were later referred to FMU Hospital from other institutions for consultation of thyroid nodules (a). Their thyroid abnormalities had been detected by a private thyroid screening test in one subject and found by an ultrasound test by a physician during an incidental consultation in the other subject. The remaining eight subjects were categorized as B in the primary examination, which necessitates confirmatory examination (b-d). One subject, however, did not receive confirmatory examination and was eventually referred to FMU Hospital three years later from another medical institute because of suspected malignancy by FNAC (b). The other seven subjects proceeded to undergo the confirmatory examination (c, d). Five subjects among the seven did not receive FNAC, because they did not meet the indication criteria for FNAC (c); the other two received FNAC and were diagnosed as having findings of undetermined significance (d). All seven subjects were then transferred to a public health insurance-based system because of the necessity for further periodic and close observation for possible diagnosis of thyroid cancer. This kind of observation is essential for such individuals, and cannot be achieved if they have to wait for the following examination in the TUE program. The average duration between the first visit to insurance-based medical practice and surgical treatment in these seven subjects was 613±534 days (median : 565 days, range : 400-1,184 days).

The characteristics of the 11 outside subjects were investigated, and are included in Table 2. There were four males and seven females, and the

average ages were 13.8±4.0 years at the time of the accident and 18.3±3.8 years at the time of surgery. The numbers of subjects aged 0-4, 5-9, 10-14, 15-19, and 20-25 years at the time of the accident were one, one, four, five and zero, respectively, and the numbers of subjects in the same age groups at the time of surgery were zero, one, zero, six and four, respectively. Regarding area of residence at the time of the accident, four subjects were living somewhere in the 13 municipalities of the nationally designated evacuation zones, four were living in the Nakadori area (the central part of Fukushima Prefecture), three were living in the Hamadori area (the eastern part), and none were in the Aizu area (the western part). The tumor size was defined as the larger of two diameters, both measured at the tumor's widest point; one measured by ultrasonography performed immediately before surgery, and the other physically measured after the tumor had been excised, was 14.0±5.1 mm (6.3-24.6 mm) on average. The histological diagnoses were papillary thyroid carcinoma in all cases (classic type in nine, follicular type in one, and solid sclerosing type in one).

Discussion

The present study was undertaken to identify and characterize the outside subjects of the TUE program, targeting patients at FMU Hospital. Surgically treated cases were fully detected utilizing a combination of lists submitted by two departments, which included eight subjects who had been diagnosed as having malignancy or suspected malignancy by FNAC performed at FMU Hospital, implying

that all pertinent subjects were recruited. The TUE program ends with the diagnosis of malignancy or suspected malignancy in each subject, and the clinical information thereafter is not covered by the protocol of the program. The current study was conducted at FMU Hospital, which provides health insurance-based services, in cooperation with the Radiation Medical Science Center responsible for the FHMS after approval by the ethics committee of FMU.

The present study revealed that the number of outside subjects seen at FMU Hospital was 11 as of June 30, 2017. Since the TUE program had identified 194 subjects with thyroid cancer and suspected thyroid cancer by that same date^{6,7,10}, the outside subjects accounted for 5.7%, indicating that the majority of subjects with thyroid cancer had been detected by the TUE program. The characterization of the outside subjects is also important, because some subjects with particular characteristics might be predominantly detected or undetected by the TUE program. The characteristics of the outside subjects are summarized in comparison with those of the subjects identified in the TUE program in Table 2. Gender ratios, ages and tumor sizes were similar. Area of residence at the time of the accident could not be meaningfully compared because of the small numbers of cases. Histological diagnoses in both series were papillary thyroid carcinoma in most cases, with only a few exceptions. Thus, it is unlikely that these outside subjects, if taken into consideration, would affect the whole picture of thyroid cancer in the younger generations of Fukushima Prefecture.

In the current study, how the malignancies and suspected malignancies of the outside subjects went undetected by the TUE program was also investigated (Table 1). It is not surprising that: some residents did not participate in the program (a); some were diagnosed during the intervals between the rounds (a); and some, having been categorized as B in the primary examination, were diagnosed by FNAC in a medical institute but not through the confirmatory examination of the TUE program (b). While these irregular cases do exist, it was also shown that such instances were rare. More discussion may be needed on the seven subjects who had been evaluated in the confirmatory examinations, but were transferred to the health insurance-based system, and were eventually diagnosed. One may argue that further prolongation of the confirmatory examination itself will effectively diminish the number of outside subjects. The necessary period for

such observation, however, seems too long, as shown in the present study; the average duration between the first visit to a medical practice and surgical treatment in these seven subjects was 613 ± 534 days. Since a period of 15 months after completion of the primary examinations was needed to obtain the fixed data of each of the first and second rounds^{6,7}, further delay would seriously disturb any timely analyses. Repeated and long-standing confirmatory examination would also be a great burden in practicing the TUE program. Therefore, it may be practical to prolong confirmatory examinations only in cases where diagnosis can be reached in a relatively short time.

There are two limitations in the present study. Firstly, the outside subjects enrolled were from FMU Hospital only. One may point out that there should also be a considerable number of outside subjects from other institutes. The actual number of such cases could not be determined by the current study alone. However, we do not believe that it would be a large number considering that: (1) among the total of 187 subjects who had been diagnosed as having malignancy or suspected malignancy in the first and second rounds, only nine subjects (4.8%) were identified in the confirmatory examination performed in prefectures other than Fukushima; and (2) among the 132 subjects who underwent surgery for thyroid cancer as of March 2016, only seven (5.3%) underwent surgery in institutes other than FMU Hospital¹¹. Therefore, it seems likely that the majority of outside subjects diagnosed across Japan were detected in the present study. Secondly, the present study was undertaken as of June 30, 2017, and the results of a similar study conducted in the future may be different. The number of outside cases may increase as participation rates decrease and examinations performed outside Fukushima Prefecture increase. To accurately identify all subjects with thyroid cancer in the future, utilization of national and regional cancer registries will probably become a more potent method⁵.

In conclusion, the present study successfully identified 11 outside subjects with thyroid cancer or suspected thyroid cancer, seen at FMU Hospital as of June 30, 2017. These accounted for 5.7% of the 194 subjects whom the TUE program had identified. Although outside subjects from other institutes were not investigated, the present study seemed to cover a major part of the outside subjects in Japan overall. These findings confirm that the cases of malignancy and suspected malignancy detected by the TUE program were accurate and their

data were sufficient for various kinds of analyses.

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Conflict of Interest Disclosure

The authors declare that they have no conflicts of interest related to this study.

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