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Review

Radiation Exposure and the Risk of Pediatric Thyroid Cancer

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Abstract. It has been more than three years since the unprecedentedly massive earthquake and tsunami struck eastern Japan on March 11, 2011, and the large accident occurred at the Fukushima Daiichi Nuclear Power Plant. To investigate the influence of radiation exposure, thyroid ultrasonography has been provided preliminarily for 360,000 children who lived in Fukushima Prefecture at the time of the accident. As of September 2013, 59 children had been diagnosed with thyroid cancer by fine-needle aspiration cytology, and 34 children had been treated surgically and ultimately diagnosed with papillary thyroid cancer. Here, I would like to describe the characteristics of pediatric thyroid cancer and typical thyroid images obtained by ultrasonography.

Key words: radiation exposure, pediatric thyroid cancer, ultrasonography, the accident at the Fukushima Daiichi Nuclear Power Plant

Introduction

More than three years after the unprecedentedly massive earthquake and tsunami struck eastern Japan on March 11, 2011, and the accident at the Fukushima Daiichi Nuclear Power Plant that followed, there is still a great number of people living in shelters as evacuees. Firstly, I would like to express my sincerest sympathy to those affected by the disaster. I pray that the souls of those who lost their lives in this tragedy may rest in peace, and I offer my heartfelt condolences to the bereaved families.

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Since October 2011, as part of the Health Survey of Fukushima Prefecture, for residents after the accident at the Fukushima Daiichi Nuclear Plant, thyroid ultrasonography has been provided for 360,000 children under the age of 18. I was engaged in thyroid gland medical examinations in Fukushima as a medical specialist in thyroid ultrasonography and had the opportunity to give a presentation at the 47th Annual Scientific Meeting of the Japanese Society for Pediatric Endocrinology on 10 October 2013. Here, I would like to discuss the outline of "Radiation Exposure and the Risk of Pediatric Thyroid Cancer."

Health Impairment Due to Radiation Exposure

The average background radiation in Japan is approximately 1.4 millisieverts (mSv) per year. The upper radiation dose limit for radiation

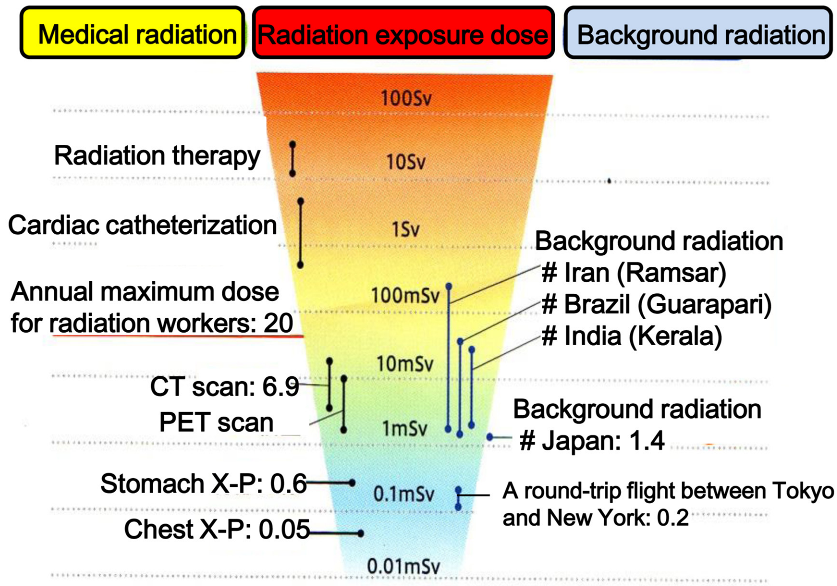


Fig. 1. Radiation exposure quick reference – quoted from the website of the National Institute of Radiological Sciences (partially modified).

workers to prevent injury from radiation is 20 mSv. According to comprehensive examinations based on previous epidemiologic studies and research results, it is generally concluded that no radiation doses below the limit have any negative impact on human health. Even though it is said that chromosomal abnormalities appear in the most sensitive human health areas, such abnormalities have not been observed with a radiation dose of 100 mSv or less. As shown by the radiation exposure doses shown in Fig. 1, a human subject is exposed to 0.2 mSv during a round-trip flight between Japan and New York, 0.6 mSv during a stomach examination using barium, and 6–10 mSv during a CT or PET examination (1). A human subject is also exposed to a few Sv during cardiac catheterization and approximately 10 Sv during radiation therapy. Thus, we are all affected by radiation in one way or another including exposure during medical examinations in our daily life.

The relationship between radiation dose and carcinogenic risk indicates that beyond the level of 100 mSv or more, the carcinogenic risk generally increases 0.05-fold for every 100 mSv increase. However, at a radiation exposure level below 100 mSv, no statistically significant increase in the number of cancer cases has yet been observed, and the carcinogenic risk at even lower levels remains unclear. Therefore, in terms of radiological protection, "the linear no-threshold model (LNT hypothesis)" is currently used for the relationship between radiation dose and carcinogenic risk. In short, the current measurements are obtained assuming that even low-level radiation exposure below 100 mSv can impact human health.

Increase in the Number of Pediatric Thyroid Cancer Patients after the Chernobyl Nuclear Power Plant Accident

In the Chernobyl Nuclear Power Plant accident, which occurred in 1986, a vast amount of iodine-131 spread over a few hundred square kilometers. Children in the region consumed milk with a high concentration of iodine-131 (17–450 times higher than the regulatory dose limit in Japan), causing a distinct increase in the number of pediatric thyroid cancer cases. In Belarus, the number of pediatric thyroid cancer cases for 11 yr preceding the accident was 7, but in the 11 yr following the accident, the number of thyroid cancer cases increased to 508, which is 73 times higher than before the accident (2). In addition, it is reported that 97.6% of children who had thyroid cancer were under the age of 10 (Fig. 2). The estimated amount of radioactive iodine exposure for the thyroid gland was in the range of 100 mSv to 2000 mSv. It is said that the higher the exposure dose, the higher the rate of contracting thyroid cancer. According to the summary report of the joint world conference "10 years after the Chernobyl accident" held by the IAEA (International Atomic Energy Agency), the WHO (World Health Organization) and the EU (European Union) in Vienna, Austria, in 1996, as of that time, the only health repercussion for which a clear causal relationship with the accident could be identified was pediatric thyroid cancer. Furthermore, in 2006, a report (4) titled "Cancer consequences of the Chernobyl accident: 20 years on" (Fig. 3) was published. It was indicated that the number of thyroid cancer cases in children aged between 0 and 14 started

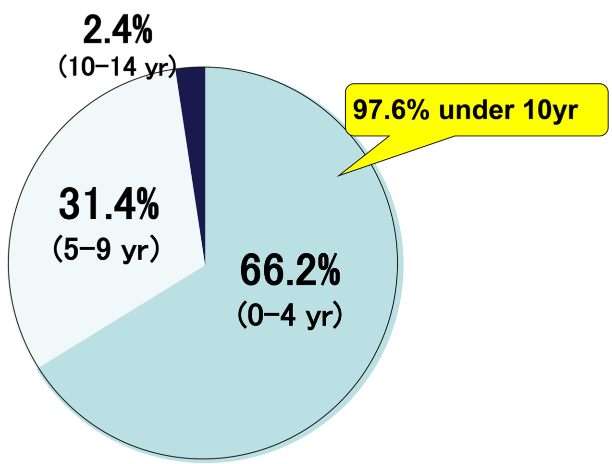


Fig. 2. Age distribution of pediatric thyroid cancer after the Chernobyl Nuclear Power Plant accident.

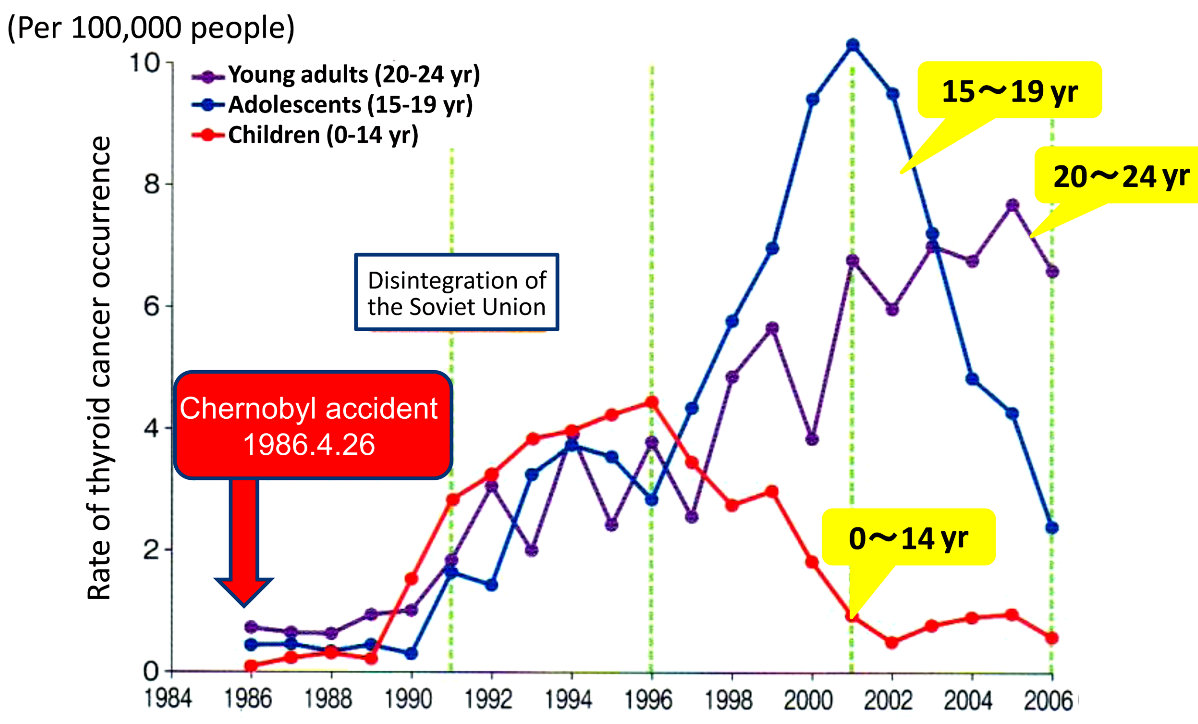


Fig. 3. The number of thyroid cancer cases and changes over time after the Chernobyl Nuclear Power Plant accident.

to increase 4–5 years after exposure and then reached a peak at about 10 yr, and for those aged between 15 and 18, the peak was reached 15 yr after exposure. Also, the report from the International Conference "Twenty-Five Years after the Chernobyl Accident" held in Kyiv in April 2011 states that the total number of thyroid cancer patients has reached approximately 6,000, with 15 deaths (0.3%) (5). It has also been reported that the observed 5- and 10-yr survival rates for a group including 740 pediatric patients with thyroid cancer were 99.5% and 98.8%, respectively (6).

According to a report (7) presented in 2010 by Shunichi Yamashita, who conducted a molecular epidemiology survey and study on thyroid cancer after the Chernobyl Nuclear Power Plant accident, the differences between childhood-onset papillary cancer and adult-onset papillary cancer were as follows: (1) Pediatric thyroid cancer showed many cases of hardening and fibrosis, while for adult thyroid cancers, typical papillary growth was dominant. (2) For childhood onset cases, there were many incidences of abnormal rearrangement such as RET/PTC, while adult cases showed a high frequency of BRAF point mutation. (3) In terms of clinical concerns, pediatric thyroid cancer due to radiation exposure showed no difference in its prognosis and recurrence rate compared with sporadic thyroid cancers that were not caused by radiation exposure, indicating that appropriate medical treatment can result in an excellent prognosis for patients.

Radiation Exposure after the Fukushima Daiichi Nuclear Power Plant Accident

Even though the details of the Fukushima Daiichi Nuclear Power Plant accident were compiled in a report (8) from the Science Council of Japan in May 2011, Tokyo Electric Power Company, for the first time after the accident, announced in May 2012 that the total amount of radiation emitted into the atmosphere was 900,000 terabecquerels (tera: trillion-fold (10^{12})), which represents 17% of the estimated emission, 5,200,000 terabecquerels, in the Chernobyl Nuclear Power Plant accident. Furthermore, in April 2012, WHO released a report outlining the estimated exposure doses of the residents one year after the Fukushima Daiichi Nuclear Power Plant accident. According to the report, the exposure doses for residents in the one-year period after the accident in Namie and Iitate in Fukushima Prefecture, situated approximately 20 km northeast of the Nuclear Power Plant, were 10–50 mSv, and the amounts for residents in other regions in the same prefecture were significantly lower at 1–10 mSv per year; the levels for residents in other neighboring regions were 0.1–1 mSv per year.

Therefore, if the dispersal of a large amount of radioactive material into the atmosphere can be prevented in the future, we can consider the incidence of thyroid cancer due to an accident to be minimal. In fact, it is reported that the amount of radioactive iodine measured after the accident was one-tenth or less that measured after the Chernobyl accident, and the radiation exposure dose measured in children from neighboring regions after the accident was at a near negligible level. However, the long-term impact due to radiation exposure must be considered carefully in the future.

Prefectural Human Health Management Survey and Ultrasonography of the Pediatric Thyroid in Fukushima

Given the circumstances of radioactive contamination in the prefecture due to the accident at Tokyo Electric Power Company's Fukushima Daiichi Nuclear Power Plant, Fukushima Prefecture assigned Fukushima Medical University to implement the Fukushima Health Management Survey for all residents in the prefecture, aiming to ensure the long-term health of people in the prefecture and enhance the safety and peace of mind of people in the

Table 1 Fukushima Prefectural Health Management Survey of the thyroid glands of children by ultrasonography (as of September 2013)

	Examined (no. of people)	Diagnostic results			
		A1	A2	B	C
10/2011 to 3/2012	47,766	26,187 (63.3%)	14,936 (36.1%)	216 (0.5%)	0 (0.0%)
4/2012 to 3/2013	163,264	74,920 (54.7%)	61,045 (44.6%)	970 (0.7%)	1 (0.0%)
4/2013 to 9/2013	78,930	20,418 (43.2%)	26,472 (56.0%)	372 (0.8%)	0 (0.0%)
Total	289,960	121,525 (53.9%)	102,453 (45.4%)	1,588 (0.7%)	1 (0.0%)

A1: No abnormalities. A2: Cysts of 20 mm or less and/or nodules of 5 mm or less. B: Cysts of 20.1 mm or more and/or nodules of 5.1 mm or more. C: A secondary examination required immediately.

prefecture. The Radiation Medical Science Center is now in operation on the campus of Fukushima Medical University. Fukushima Medical University has conducted thyroid ultrasonography on children aged between 0–18 in Fukushima since October 2011. Of the 360,000 children targeted for the thyroid ultrasonography, approximately 240,000 had been examined as of September 2013. According to the data (9) (Table 1) collected, 53.9% of the examined children had no abnormalities, who were diagnosed as "A1," and 45.4% were diagnosed as "A2 (cysts of 20 mm or less and/or nodules of 5 mm or less)"; only a few children, amounting to 0.7%, were diagnosed as "B (cysts of 20.1 mm or more and/or nodules of 5.1 mm or more)." In addition, 0% of the examined children were diagnosed as "C (nodules that necessitated an immediate secondary examination)." For the B and C cases, a more extensive secondary examination was performed at Fukushima Medical University. As of September 2013, 59 children were suspected or diagnosed as having thyroid cancer by fine-needle aspiration cytology (FNAC), and the mean age was 16.8 ± 2.6 yr old; the mean tumor size was 14.9 ± 8.3 mm. Among this group, 34 children had already been treated surgically, and histologically confirmed to have papillary thyroid cancer.

The current examination, however, was only preliminary and did not directly investigate the impact of radiation exposure on these children. From this point forward, thyroid ultrasonography will be performed on evacuated children at designated hospitals in individual prefectures across Japan, and the resulting data along with ultrasonographic images will be centralized for long-term storage at the Radiation Medical Science Center.

Characteristics of Pediatric Thyroid Cancer

Pediatric cancer consists of malignant tumors that occur before the age of 15, and leukemia (acute and chronic) accounts for 30–40% of such cases of cancer. Of the remaining cases, central nervous system tumors (brain and spinal tumors) account for approximately 20% of cases, neuroblastoma accounts for 10–20% of cases and other types of cancer account for 10% of cases: cases of thyroid cancer as said to be few, one or two cases of pediatric thyroid cancer out of 1 million, and for children aged 15 or younger, cases of thyroid cancer are extremely rare, accounting for only 0.03% of cases (10). The characteristics of pediatric thyroid cancer are as follows: (1) It is extremely rare in newborn babies. Onset occurs at age 6 or younger in 5% of cases and at 7 to 9 in 10% of cases, while the rate increases as the age for children 10 yr olds and older. Furthermore, girls have a higher frequency at approximately 4 times that of boys. (2) Regarding the histological types of thyroid cancer, the papillary type accounts for 90–95% of

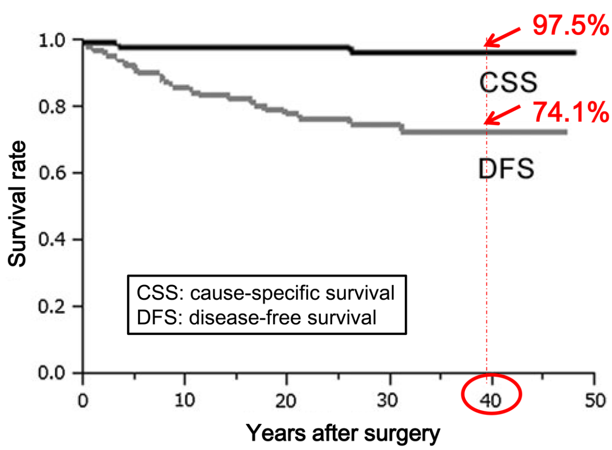


Fig. 4. Long-term prognosis of pediatric thyroid cancer (papillary carcinoma) in Japan.

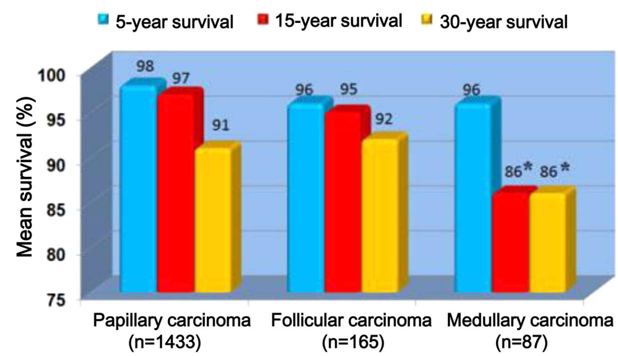


Fig. 5. Long-term prognosis of pediatric thyroid cancer by each histological type in the United States of America.

cases, and the follicular type accounts for 5% of cases; anaplastic carcinoma and undifferentiated carcinoma are rare. (3) There are many cases of cervical lymph node metastasis and distant metastasis. (4) Finally, when pediatric thyroid cancer is discovered, the size of the carcinoma is large. It is rare to discover it as a microcarcinoma (the frequency of microcarcinoma is reported to be 9% for childhood onset and 22% for adult onset). The review by Vaisman and his associates (11) also states that pediatric thyroid cancer only accounts for 0.5–3% of all types of cancers, that girls have a 4 times higher frequency rate than boys, that the size of the tumors is large, that there are many cases of cervical lymph node metastasis and distant metastasis, and many cases of NIS (sodium-iodide transporter) occurrence and RET-PTC rearrangement are observed.

In 2012, Enomoto *et al.* (12) summarized 142 cases of pediatric thyroid papillary cancer and reported their characteristics and long-term prognosis (Fig. 4). According to their report, 3 cases of lung metastasis and 33 cases of obvious cervical lymph node metastasis were observed at the time of diagnosis. Surgery (subtotal or total thyroidectomy) was performed for all 142 cases. External radiation therapy was performed on 59 patients after surgery. As a result, recurrence in the regional lymph nodes was found in 25 patients. However, in the 40 yr after surgery, the disease-free survival (DFS) and cause-specific survival (CSS) showed extremely favorable results of 74.1% and 97.5%, respectively. Factors affecting the prognosis were: (1) age under 16 yr, (2) family history of thyroid cancer, (3) cervical lymph node metastasis, (4) large-size tumor, and (5) distant metastasis. A paper (13) (Fig. 5) published overseas, which examined the long-term prognosis of thyroid cancer by tissue type, also indicates that for papillary carcinoma, the 15-yr and 30-yr survival rates were 97% and 91% respectively and that they were 95% and 92% for follicular carcinoma respectively, both of which were satisfactory results. On the other hand, for medullary carcinoma, the rates were lower, 86% and 86% respectively. The results of multivariate analysis indicated that male gender, thyroid cancer other than papillary carcinoma, distant metastasis and inoperability can be independent prognosis factors.

Even in radiation exposure during medical diagnosis or treatment, children are more sensitive to radiation and at risk for a longer period of time than adults, increasing the risk of cancer. In fact, it is said that the younger the individual is, the higher the risk of radiation-related cancers becomes (12). There is also another report indicating that girls and young women have a higher risk of breast cancer as

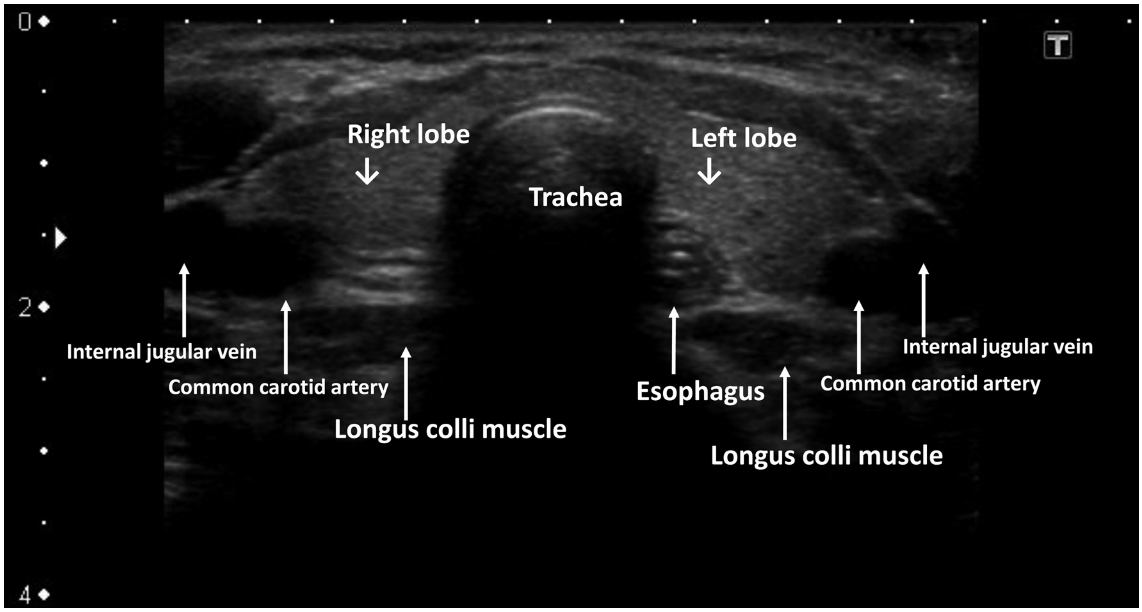


Fig. 6. Ultrasonographic imaging of a normal thyroid gland (transverse section image).

Height (cm)	Average ±SD (cm3)
-99	2.5±0.6
100-109	3.8±1.2
110-119	4.3±1.1
120-129	5.4±1.1
130-139	8.1±1.2
140-149	8.5±2.3
150-159	8.6±2.4
160-	12.4±2.3

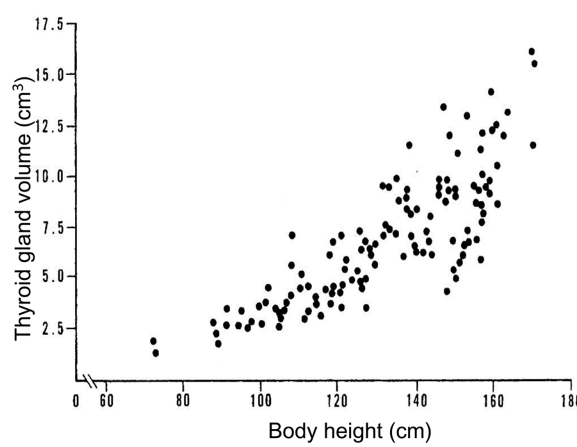


Fig. 7. Thyroid gland volumes of normal children by height.

a result of radiation exposure from medical examination (14). Cancers related to radiation exposure generally include thyroid cancer, breast cancer, brain tumors, skin cancer excluding melanoma, and leukemia.

Ultrasonographic Images of Thyroid Nodular Lesions

The current form of ultrasonography for children examines the size of the thyroid gland and the possible existence of a nodular lesion. An ultrasonographic image (transverse section image) of a normal thyroid gland is shown in Fig. 6, and the normal size of the thyroid gland by height is shown in Fig. 7 (15). Since the thymus is developed in children, the characteristic finding of the thymus coming into contact with a lower lesion of the thyroid gland (Fig. 8a) is frequently observed as echogenic

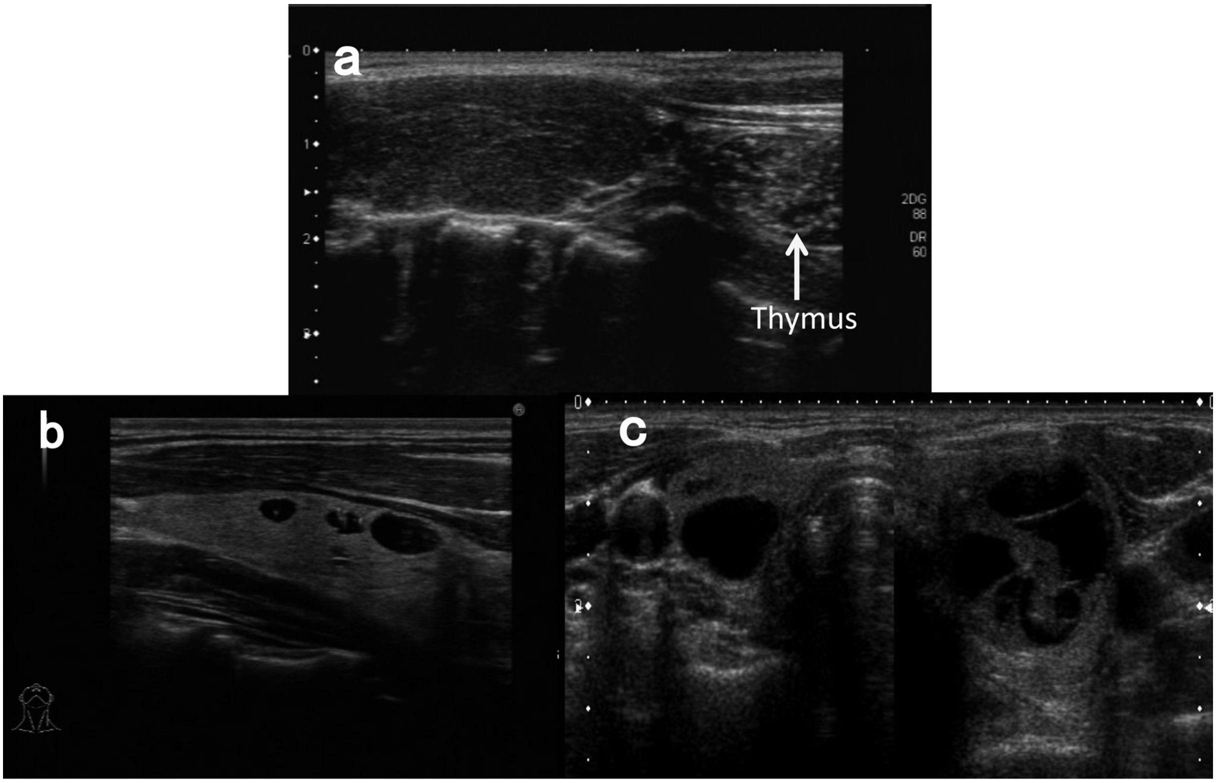
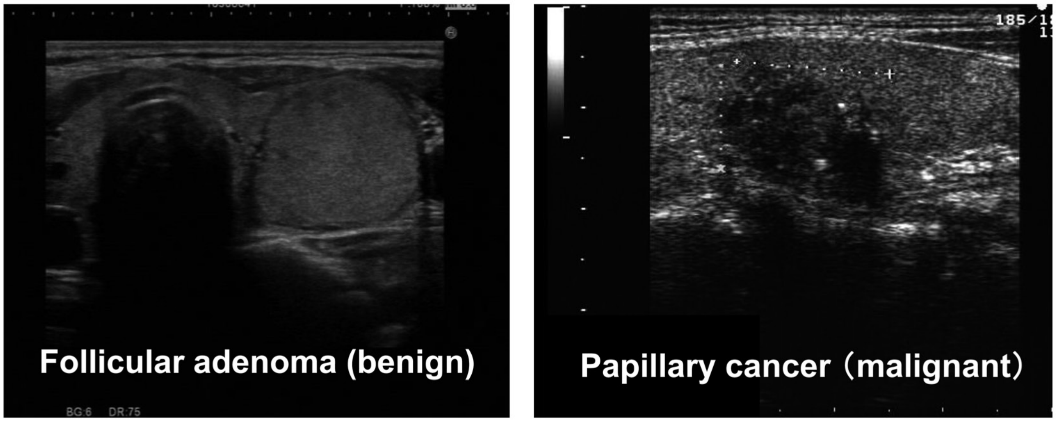


Fig. 8. Ultrasonography of nonneoplastic thyroid lesions. a: Normal thymus, b: Thyroid cysts, c: Multinodular goiter.

spots in ultrasound imaging. In some cases, it is also observed within the thyroid gland. The most frequently observed thyroid gland lesions in medical examinations are nonneoplastic lesions such as thyroid cysts and adenomatous nodules (frequent cases of multinodular goiter) as shown in Figs. 8b and 8c. When benign follicular adenoma is compared with malignant papillary carcinoma, typical ultrasonographic images can be distinguished according to the ultrasonography criteria for thyroid nodules (16) as shown in Fig. 9. Recently, a systematic review and meta-analysis of published studies of clinical and ultrasonographic features of thyroid nodules were performed to quantify the risk of malignancy (17). The meta-analysis included 41 studies, for a total of 29678 thyroid nodules. A higher risk of malignancy, expressed as odds ratios (ORs) was found for shape nodule height greater than width (OR: 10.15), absent halo sign (OR: 7.14), microcalcifications (OR: 6.76), irregular margins (OR: 6.12), hypoechogenicity (OR: 5.07), solid nodule structure (OR: 4.69), intranodular vascularization (OR: 3.76), family history of thyroid carcinoma (OR: 2.29), nodule size ≥4 cm (OR: 1.63), single nodule (OR: 1.43), history of head/neck irradiation (OR: 1.29) and male gender (OR: 1.22).

Furthermore, in recent years, the rapid advancement of ultrasonographic instruments has facilitated equipment with a wide range of modalities: blood flow conditions can be examined by color Doppler imaging, and in addition, by examination with tissue elasticity imaging (elastography), the characteristics of lesions can be differentiated to determine which of them are benign and malignant tumors in more detail. Please refer to the ultrasonography guidebook for more information about thyroid ultrasonographic images (18).



	Shape	Border clearness/condition	Internal echo		Fine/high echo	Low echo band at the border area
			Echo level	Homogeneity		
Benign	Round/oval	Clear/smooth	High – Low	Homogenous	None	Clear
Malignant	Distorted/irregular	Unclear/rough	Low	Inhomogeneous	Frequent	Distorted/none

Fig. 9. Distinction between benign and malignant thyroid tumors in B mode ultrasonography.

Conclusion

In the more than three years since the Fukushima Nuclear Power Plant accident, there have been many children living as evacuees with great anxiety. I think that the impact of psychological stress from the continuous anxiety of "being aware that they have been exposed to radiation" is more significant than the impact of radiation exposure itself. For child care at the time of a disaster, enabling children to live each day normally and with peace of mind through their relationships with teachers, parents and friends is a fundamental task. As the depression and anxiety of parents can unsettle the state of a child's mind, it is important for parents to have proper knowledge about radiation exposure issues and not to worry too much. Bullying and posttraumatic stress disorder (PTSD) must be responded to as part of child care at the time of a disaster, and if personalized guidance is necessary, a specialist at a hospital or other institution should be consulted. Concerning thyroid ultrasonography, children from Fukushima Prefecture who are now living in other areas of Japan as evacuees have been able to receive medical examinations at hospitals across Japan, and I would like to ask that all of the children concerned receive appropriate medical checks at a nearby hospital.

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