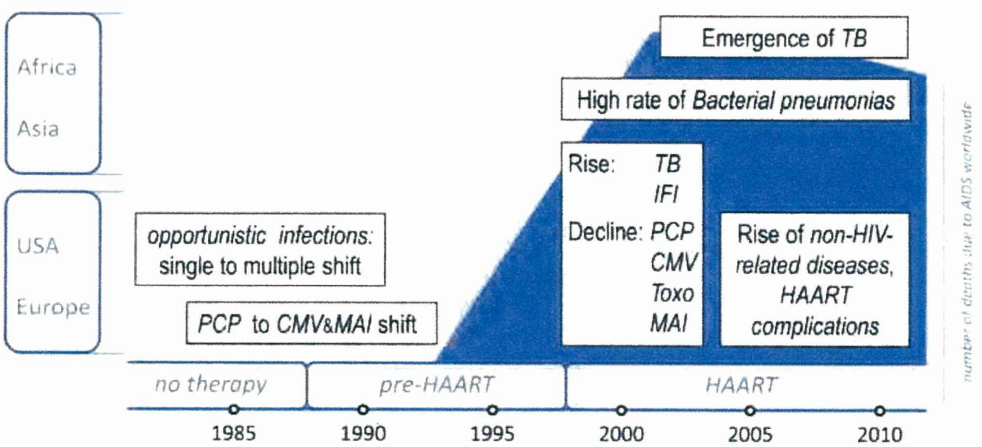
are chronic liver diseases, cardiovascular pathology and malignancies (d'Arminio Monforte, 2009; Friis-Møller et al., 2010; Lucas et al., 2008; Sackoff et al., 2006). Cases of hepatic involvement are extremely common in HIV-infected cohort of intravenous drug users with HCV co-infection which may die from liver cirrhosis or necrotizing liver failure (Guerra et al., 2001).

One of the important utilities of autopsy is the correlation between antemortem and postmortem diagnosis. A recent review from the UK spanning 23 years showed that the autopsy findings altered the primary diagnosis in 70% of cases, and that 36% of opportunistic infections were not diagnosed prior to death (Beadsworth et al., 2009). An Indian series showed discordance between antemortem and postmortem diagnosis in 42% cases (Lanjewar, 2011). Russian authors reported that in 7% of cases HIV infection (!) was detected only postmortem (Berdnikov et al., 2011). Both false positive as well as false negative antemortem diagnoses are described (Martinson et al., 2007). Infections such tuberculosis, *Cytomegalovirus* and invasive mycoses are missed with the highest rate (Antinori et al., 2009; Beadsworth et al., 2009; Eza et al., 2006; Tang et al., 2006; Wilkes et al., 1988).

3.3 Current trends

The most notable changes described in reviewed series are the rise of tuberculosis infection and bacterial pneumonias for last 10 years (Fig. 3). Tuberculosis is often represented by generalized and disseminated forms. Bacterial infections still occur more frequently than other opportunistic infections in patients with HIV. Multiple infections with involvement of several organs are common.



Abbreviations: PCP, pneumocystic pneumonia; CMV, *Cytomegalovirus* infection; MAI, *Mycobacterium avium-intracellulare* infection; TB, tuberculosis; IFI, invasive fungal infections; Toxo, toxoplasmosis

Fig. 3. Major changing patterns of AIDS reported in retrospective studies.

Lungs and central nervous system are the most common targets for pathological processes. The incidence of pneumocystic pneumonia has declined significantly as a result of antiretroviral therapy and chemoprophylaxis. Rates of CMV infection also had been decreased, but not so markedly as pneumocystosis.

The possible concern of described results is that early autopsy series from our set represent high-income developed countries and the most recent series are from low- and middle-income countries. Therefore, it is more correct to report about emergence of HIV-related tuberculosis in developing countries than all over the world. Actually, in Western world (high-income model) tuberculosis spreads through HIV-infected cohort, while in Russia and India social conditions drives tuberculosis in neglected population (alcoholics, imprisons, homeless), that is superimposed by HIV. Contribution of non-HIV-related pathology in AIDS mortality depends on availability of HAART and, consequently, economical development of the country.

Finally, we may suppose that current trends in AIDS mortality for low- and high-income countries are different. Emergence of tuberculosis and high prevalence of bacterial infections are typical for Sub-Saharan Africa, South-East Asia and Eastern Europe. Growth of non-AIDS-related diseases is observed in USA and Western Europe.

4. Conclusion

Through the whole timeline of HIV epidemics significant differences in epidemiology contributed to evolution of disease. Thus, changing patterns of geographic distribution, modes of infection, spectrum of secondary diseases were widely described and explained. Since the first reports on AIDS autopsy has playing an important role in study of HIV infection. Autopsy series and case reports provided abundance of data on various aspects of AIDS. Soon after introduction of HAART large retrospective autopsy studies covering several thousand cases were published (Jellinger et al., 2000; Morgello et al., 2002; Neuenburg et al., 2002; Vago et al., 2002). Results of comprehensive post-mortem examinations were in concordance with data from numerous clinical studies declaring efficacy of therapy and marked reduction of mortality from AIDS (de Martino et al., 2000; Mocroft et al., 1998; Palella et al., 1998). HAART contributed the most important shift in the history of HIV epidemics. However, currently only 10% (roughly) of HIV patients globally are receiving ART (Brown et al., 2010). Moreover, rates of non-adherence to antiretroviral therapy has been shown to range from 33% to 88% (Mills et al., 2006). Access to antiretroviral therapy in developing high-burden countries is restricted and number of AIDS-related deaths in only Sub-Saharan Africa for the last 10 years has exceeded 10 million (UNAIDS, 2009).

The total number of HIV autopsies declined worldwide after the advent of combination therapy. It is thought, that recruiting of such sophisticated studies like autopsy series to analysis of morbidity and mortality trends is not reasonable. Instead of that new methods are established to assess mortality statistics in developing countries (Bhattacharaya & Neogi, 2008). Currently, the popularity of studies evaluating AIDS-related mortality by means of verbal autopsy is increasing (Bundhamcharoen et al., 2011; Lopman et al., 2010; Negin et al., 2010).

We believe that autopsy series represent most reliable sources in estimation of mortality trends. While in the early years of HIV epidemics autopsy function was largely scientific (e.g. recognizing and describing), nowadays the epidemiological data are of main value. Systematic retrospective study of autopsy series worldwide is a valuable tool that should contribute to the study of AIDS epidemics evolution.

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Letter to the Editor

Prevalence of antithyroid antibodies and thyroid-stimulating hormone concentration in young people

Yui Sekitani[1], Naomi Hayashida[1], Irina V. Karevskaya[2], Inna A. Zubareva[2], Alexander Kozlovsky[3], Shunichi Yamashita[4] and Noboru Takamura[1,*]

[1] Department of Radiation Epidemiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[2] Bryansk Consultative-Diagnosis Center, Klincy City, Bryansk Oblast, Russian Federation
[3] Gomel State Medical University, Gomel, Belarus
[4] Department of Molecular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Keywords: antithyroglobulin antibody; antithyroperoxidase antibody; children; thyroid-stimulating hormone; young adults.

Subclinical thyroid disease is common, particularly in middle aged and elderly people. There is mounting evidence to suggest that subclinical thyroid dysfunction may contribute to significant clinical conditions. Symptoms often develop unnoticed; therefore the clinical identification of thyroid disease can sometimes be difficult. Thyroid dysfunction is common in adulthood, but it is also present in childhood, although the incidence is considered to be low (1). Thyroid hormone plays an important role as a regulator of nervous system myelination, growth and onset of puberty, metabolism, and organ function. Although subclinical hypo- and hyperthyroidism in young people have not been widely studied, it is very important to identify thyroid dysfunction due to the influence on growth and development during childhood and adolescence. Previous studies have shown that serum thyroid stimulating hormone (TSH) concentrations are useful for determining the prevalence of abnormal thyroid dysfunction in the general population (2). Loviselli et al. also showed that antithyroid antibody is associated with an increased prevalence of subclinical hypothyroidism in schoolchildren (3). Therefore, it is also important to investigate the prevalence of the antithyroid antibodies, antithyroperoxidase antibody (TPOAb) and antithyroglobulin antibody (TGAb) in this age group. In the present study, we examined serum TSH concentrations and the prevalences of TPOAb and TGAb in children and young adults in Bryansk Oblast, Russian Federation.

We obtained informed consent from all study participants or their legal guardians, based on the approval by the Ethical Board of Nagasaki University and Bryansk Consultative-Diagnosis Center.

The subjects were 2111 children and young adults (750 males and 1361 females, 6–22 years of age) examined from 1998 to 2006 at Bryansk Consultative-Diagnosis Center, located in Klincy City, Bryansk Oblast. Serum TSH was measured with an Amerlite hormone analyzer (Amersham, Bunkyo-ku, Tokyo, Japan) using a commercial assay kit. The normal concentration of TSH was 0.4–4.0 μU/mL. Titers of TPOAb and TGAb were determined by an electrochemiluminescence immunoassay using commercial assay kits (Fujirebio, Tokyo). The prevalence of positive TPOAb and TGAb was evaluated using the χ^2-test. Statistical analysis was performed using SPSS Statistics 18.0® software (SPSS Japan, Tokyo, Japan). p-Values <0.05 were considered statistically significant.

The prevalence of positive TPOAb in study participants divided by serum TSH concentration is shown in Figure 1. In females, the prevalence of TPOAb was significantly higher with TSH concentrations <0.4 μU/mL ($p=0.02$) and in those with TSH concentrations >4.0 μU/mL ($p=0.01$) when compared with normal serum TSH concentrations. However, there were no significant differences in males ($p=0.14$) who had TSH concentrations <0.4 μU/mL and those with TSH concentrations >4.0 μU/mL ($p=0.64$). The prevalence of positive TGAb in study participants divided by serum TSH concentration is shown in Figure 2. In females, the prevalence of TGAb was significantly higher when TSH concentrations were <0.4 μU/mL compared with normal serum TSH concentrations ($p=0.043$), although this was not seen with TSH concentrations >4.0 μU/mL ($p=0.14$). Moreover, there were no significant differences in males ($p=0.56$) with TSH concentrations <0.4 μU/mL and with TSH concentrations >4.0 μU/mL ($p=0.15$).

We showed that there is a gender difference in the prevalences of TPOAb and TGAb among those with abnormal TSH concentrations. In people in the United States who are 12 years of age or older, TSH <0.4 μU/mL was associated with positive TPOAb, but not with positive TGAb (4). Loviselli et al. showed that the prevalence of positive antithyroid

*Corresponding author: Noboru Takamura, MD, PhD, Professor and Chairman of Department of Radiation Epidemiology, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan
Phone: +81-95-819-7170, Fax: +81-95-819-7172,
E-mail: takamura@nagasaki-u.ac.jp
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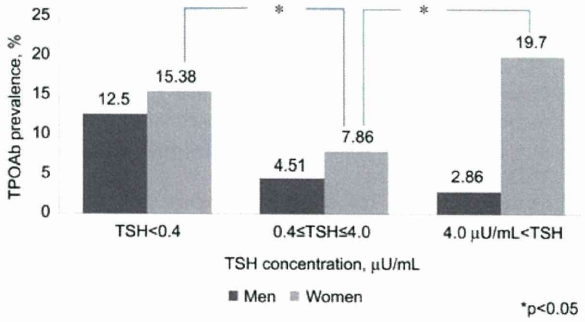

Figure 1 Comparison of the prevalence of positive TPOAb with respect to TSH divided by serum TSH concentration; <0.4 μU/mL, normal serum TSH concentrations (between 0.4 and 4.0 μU/mL), and >4.0 μU/mL.

antibody was significantly higher in children with serum TSH >5.0 μU/mL compared to concentrations found in children with normal serum TSH (0.2–5.0 μU/mL) (3). Kaloumenou et al. reported that girls 5–18 years of age with increased TSH values had increased positive TPOAb concentrations compared to those with normal TSH values (0.3–5.0 μU/mL). Moreover, there was a significant difference in the prevalence of TGAb in girls with increased TSH compared to that in girls with normal TSH. However, there was no significant difference in the prevalence of TPOAb or TGAb in boys with increased or normal TSH values (5). In children 16 years of age or younger, positive TPOAb and TGAb concentrations were detected in 60.4% of those with highly increased TSH (>10 μU/mL), 23.6% of those with increased TSH (5.5–10 μU/mL), and 39.3% with low TSH (<0.35 μU/mL), compared to only 15.9% of the children with normal TSH (0.35–5.5 μU/mL) (6). Even though the reference ranges for TSH concentrations vary among studies, these previous studies showed an association with abnormal TSH concentration and an increased prevalence of antithyroid antibody.

Mounting evidence indicates that subclinical thyroid dysfunction has important clinical effects and prognostic implications. Subclinical hypothyroidism has been associated with an increased risk for coronary and other heart diseases, as well as peripheral arterial disease, various biochemical abnormalities including increased low-density lipoprotein cholesterol, and depression. In addition, the major concern is the development of overt hypothyroidism over time. The annual risk for developing overt hypothyroidism after 20 years is 4.3% in women with increased TSH concentrations and antithyroid antibody, and 2.6% in women with subclinical hypothyroidism without thyroid antibodies (7). This indicates the value of examining antithyroid antibody in young people.

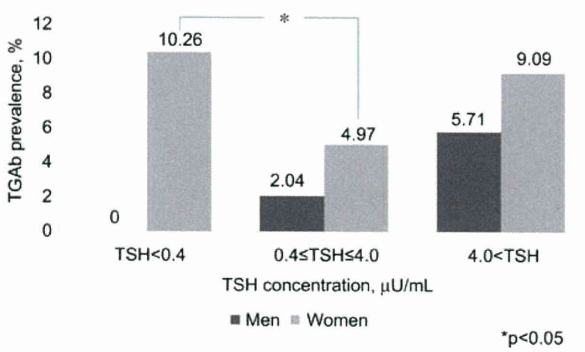

Figure 2 Comparison of the prevalence of positive TGAb with respect to TSH divided by serum TSH concentrations <0.4 μU/mL, normal serum TSH concentrations (between 0.4 and 4.0 μU/mL), and >4.0 μU/mL.

The influence of subclinical hyperthyroidism on health is not yet clear. However, evidence is accumulating that it has clinical importance, such as adverse effects on cardiac function, and more significantly, a higher incidence of arterial fibrillation and a decrease in bone density. Furthermore, subclinical hyperthyroidism may be associated with disproportionate mortality. Biondi et al. showed that early treatment of persistent endogenous subclinical hyperthyroidism should be considered not only in the elderly, but also in young and middle aged individuals to improve their quality of life, and avoid the consequences of long-term exposure of the cardiovascular system to small increases in thyroid hormone (8). In addition, children with hyperthyroidism usually present with behavioral disturbances, such as attention problems, difficulty with concentration, and hyperactivity, which may lead to poor cognitive performance (9). However, attention disturbances in children with hyperthyroidism become attenuated once euthyroidism is achieved through treatment (10). These results suggest the need to detect subclinical thyroid dysfunction at an early age.

In conclusion, we examined serum TSH concentrations and the prevalence of TPOAb and TGAb in children and young adults in a relatively large cohort. We found that the prevalence of TPOAb was significantly different in those with TSH concentrations <0.4 μU/mL and >4.0 μU/mL in females. Also, the prevalence of TGAb was significantly different in females with TSH concentrations <0.4 μU/mL compared to females with normal serum TSH. In contrast, there were no significant differences in the prevalence of TPOAb and TGAb with respect to TSH concentrations in males. The early identification of patients whose thyroid function might progress to overt hypo- or hyperthyroidism is important. We recommend that patients with values falling outside the reference TSH concentrations be evaluated further.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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Radiation Exposure Does Not Significantly Contribute to the Risk of Recurrence of Chernobyl Thyroid Cancer

Pavel O. Rumyantsev, Vladimir A. Saenko, Alexey A. Ilyin, Valery F. Stepanenko, Ulyana V. Rumyantseva, Aleksandr Yu. Abrosimov, Evgeny F. Lushnikov, Tatiana I. Rogounovitch, Yoshisada Shibata, Norisato Mitsutake, Anatoly F. Tsyb, and Shunichi Yamashita

Department of Radiosurgery (P.O.R., A.A.I., U.V.R.), Department of Pathology (V.A.S., A.Yu.A., E.F.L.), Laboratory of Medical-ecological Dosimetry and Public Radiation Safety (V.F.S.), and Department of Radiology (A.F.T.), Medical Radiological Research Center of Russian Academy of Medical Sciences, Obninsk 249036, Russian Federation; and Department of Molecular Medicine (T.I.R., Y.S., N.M., S.Y.) and Department of International Health and Radiation Research (V.A.S., S.Y.), Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8523, Japan

Context: Papillary thyroid carcinoma (PTC) in patients exposed to environmental radioiodine after the Chernobyl accident is thought to have a relatively aggressive clinical course. Long-term results of treatment are not well known, especially in comparison with sporadic PTC.

Objective: The determination of risk factors for PTC recurrence in a controlled for baseline factors group of patients with radiation-related and sporadic PTC.

Design: Retrospective cohort study involving patients treated for PTC and followed-up in 1991–2008. Risk factors were assessed by stratified analysis using the proportional hazard model.

Setting: Referral center–based.

Patients: A total of 497 patients were enrolled. Patients exposed to radioiodine were 172 individuals with reconstructed individual radiation thyroid doses ranging 51–3170 mGy. Patients with sporadic PTC included 325 individuals matched to exposed patients for sex, age ± 5 yr and time to treatment ± 2 yr.

Main Outcome Measure: Cancer recurrence.

Results: Nodal disease increased the recurrence rate (HR = 5.21; 95% CI = 1.63–16.7) while the presence of tumor capsule (HR = 0.17; 95% CI = 0.06–0.45) and, particularly, treatment according to the Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer significantly reduced it (HR = 0.16; 95% CI = 0.06–0.42). None of the tested variables interacted with radiation factor.

Conclusions: PTC developing after internal exposure to radioiodine does not display specific risk factors for recurrence different from those in sporadic PTC. Common treatment approaches for patients with PTC should be recommended regardless of a history of radiation exposure. ***J Clin Endocrinol Metab* 96: 385–393, 2011)**

The carcinogenic effects of thyroid gland exposure to ionizing radiation in childhood and adolescence are widely recognized (1–3). Epidemiologic studies demonstrate that the risk of malignancy is proportional to radiation dose to the thyroid and that it remains elevated for decades after exposure (1, 3).

Since 1991, a dramatic increase in childhood and adolescent thyroid cancer incidence was documented in Belarus,

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Abbreviations: DFS, Disease-free survival; PTC, papillary thyroid carcinoma; RAI, radioiodine.

Ukraine, and Russia, countries contaminated by radioactive fallouts from the Chernobyl nuclear power station accident. Several investigations revealed causative association of thyroid cancer with internal exposure to radioiodine (4–6).

Clinical studies of Chernobyl thyroid cancers have demonstrated a high prevalence of papillary thyroid carcinoma (PTC) (7–10), an aggressive clinical course especially in cases with short latency (7, 8) and an elevated recurrence rate (11). Most of these studies, however, being ecological in design, have not taken accurate account of thyroid radiation doses and other baseline characteristics as well as of treatment protocols which may influence prognosis. Recurrence pattern has also been poorly addressed so far, perhaps due to the relatively short follow-up period.

Clinical behavior of external radiation-related thyroid cancers and long-term results of treatment do not appear to be different from sporadic thyroid malignancies of similar histotypes (2, 12–14). With regard to internal radiation-related cancers, no similar studies have been done to date. The aim of this work was to analyze risk factors for thyroid cancer recurrence in patients with radiation-related (internal exposure to radioiodine after Chernobyl) and sporadic PTC. Here we report for the first time the results of a center-based cohort study of a large group of patients from Russia.

Materials and Methods

Study cohort and terms

A total of 1753 thyroid cancer patients admitted to and/or followed-up at the Medical Radiological Research Center of Russian Academy of Medical Sciences (MRRC RAMS, Obninsk, Russia) during 1982–2008 were initially considered. PTC was diagnosed in 1513 (86.3%) cases including patients of all ages from both radiation-contaminated areas and other regions of the European part of the country; all these geographic regions are characterized by the low to moderate iodine deficiency (15). Seven hundred four patients were aged less than 18 yr at the time of the Chernobyl accident (April, 1986); diagnosis in these cases was verified by the Pathology Panel of the international Chernobyl Tissue Bank project (16). Of these patients, 352 individuals lived in April 1986 in the regions (oblasts) officially recognized as radiation-contaminated. For all these patients the individual radiation doses for the thyroid were reconstructed (5, 17). The remaining 264 patients were residents of noncontaminated regions; none of them had prior history of radiation. Of the 704 patients meeting age criterion, 37 who were followed-up fewer than 6 months or had persistent disease were excluded from the study.

The study period was from January 1, 1991 to December 31, 2008, leaving 657 patients for further consideration.

The study subjects consisted of two etiological groups. At first we identified all patients in whom reconstructed individual thyroid doses were >50 mGy (51–3170 mGy); this group was designated RI-PTC. Next, among the remaining patients we identified 341 individuals with reconstructed thyroid dose <5 mGy and then selected approximately two patients matching each RI-PTC patient by sex, age at diagnosis (±5 yr), and also calendar time of diagnosis (±2 yr) to avoid bias due to diagnostic and treatment advancements with time and to account for sampling incidence; this group was designated SP-PTC. Thus defined, as outlined in Fig. 1, a cohort of 172 RI-PTC patients and 325 SP-PTC patients was composed.

The study and the protocols were approved by the Institutional Review Board and the Ethics Committee of each participating institution.

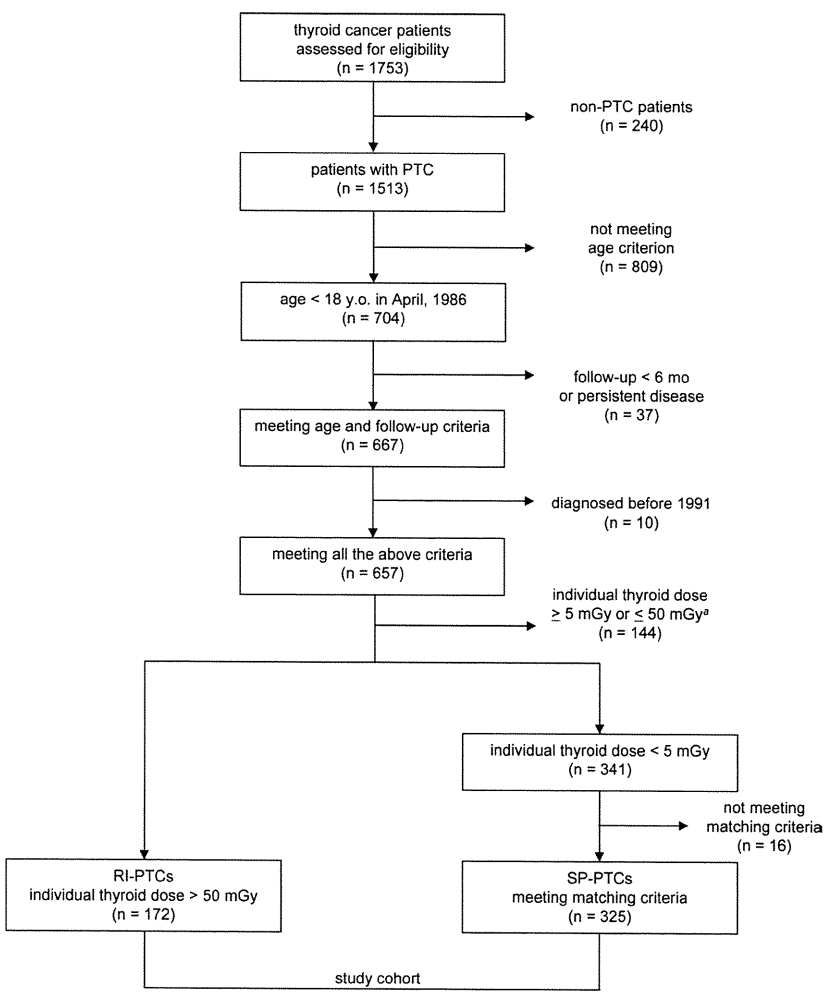

FIG. 1. Selection of patients for the study and reasons for exclusion. [a], Patients were excluded from the study in view of uncertainty in the risk of developing thyroid cancer after internal exposure within this dose range.

Clinical characteristics, treatment, and follow-up

Tumor staging was according to UICC TNM classification of malignant tumors, 6th edition (18). Pathological diagnosis was based on the WHO standards (19).

The extent of surgery, depending on tumor spread, was total thyroidectomy, near-total or hemithyroidectomy with or without neck dissections. Prophylactic central neck dissections (level VI) were done frequently while therapeutic lateral neck dissection was performed for biopsy-proven clinically involved lymph nodes in levels II–V (Table 1). The relationship between tumor aggressiveness and surgical treatment is shown in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Postoperative radioiodine (RAI) thyroid remnant ablation was performed by administration of 50–70 mCi of ^{131}I not later than 6 months after surgery. Some low-risk patients were not subjected to this procedure, in line with national guidelines. Whole-body RAI scanning was done on d 5 in all patients after RAI ablation to detect extrathyroidal disease. If ^{131}I uptake was registered outside the thyroid bed, patients received RAI therapy (100–200 mCi) or surgery, depending on clinical indications. All patients received TSH suppression therapy. Serum TSH levels (hTSH RIA) as well as serum Tg (hTG IRMA) and TgAb (AB-hTG IRMA, all kits from Cis Bio international, Gif-sur-Yvette, France) were measured every 6 or 12 months in high- or low-risk patients, respectively, during follow-up clinical examination which also included ultrasound neck area examination, consultations with an endocrinologist and oncologist, as well as RAI scanning, x-ray, or other imaging if necessary.

For every participant of the study we determined the appropriateness of treatment approach by comparing it to the recommendations in the Revised American Thyroid Association (ATA) Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer (hereafter referred to as the Guidelines), which were regarded as the gold standard (20). Compliance with recommendations rated A, B, E, and F was considered mandatory; recommendations C and D were weighed in each individual case, recommendation I was omitted. Note that accordance with the Guidelines was not observed in all patients because some of them were initially treated at nonspecialized hospitals.

Recurrence as the end point

Disease recurrence was defined as surgically removed and pathologically verified local tumor focus or regional metastasis, or distant metastasis detected by ultrasound or RAI imaging not earlier than 6 months after initial treatment. In thyroidectomized patients, stimulated serum Tg test was done before imaging. Patients with negative neck ultrasound, serum Tg <2 μg/liter after thyroid hormone withdrawal with TSH level >30 mIU/liter, negative TgAb and no other evidence of disease were considered disease-free. Serum Tg >2 μg/liter was considered as an indication for further diagnostic means. For radioiodine-based diagnostic procedures, uptake in or outside of the thyroid bed or in a previously unaffected area was interpreted as recurrence. The time to recurrence (only the earliest was taken into account) was calculated based on the date of reoperation or on the date of recurrence detection by imaging.

Statistical analysis

Baseline factors, cancer-related characteristics, and treatment modalities in RI-PTC and SP-PTC groups were compared using Fisher's exact test or its extension for categorical data and Wilcoxon rank-sum test for continuous measurements.

Factors affecting disease-free survival (DFS) were assessed by stratified analysis using Cox proportional hazard model, where the 172 strata were defined by (RI-PTC)-(SP-PTC)-(SP-PTC) triads or (RI-PTC)-(SP-PTC) pairs. The following variables were tested: age at diagnosis (years, a continuous variable), sex, exposure to radioiodine (Yes/No), tumor size ($\leq$10 mm *vs.* $>$10 mm), lymph node metastasis, distant metastasis, vascular invasion, tumor multifocality, extrathyroidal extension, presence of tumor capsule (any extent), histopathological variant (classical, follicular, other), and treatment according to the Guidelines (categorical variables). The Guidelines contain differential recommendations for the initial and post initial management of PTC, including the extent of thyroid surgery, neck dissections, and RAI ablation, depending on indications. We did not test each parameter separately but determined the general treatment compliance with the Guidelines for all patients. Thus, the impact of each modality is integrated in the model to reflect treatment adequacy. In addition, interactions of all the variables with the environmental exposure to radioiodine were examined.

Model optimization was performed using Akaike information criteria (21), starting from the full model including all the variables listed above. Once the most appropriate model was determined, the maximum likelihood estimates of the respective parameters and their Wald-type 95% confidence intervals were calculated. DFS rates were compared between RI-PTC and SP-PTC using log-rank test for selected combinations of the risk factors.

The UNIVARIATE procedure (SAS Procedures Guide Version 8. SAS Institute, Cary, NC), and NPAR1WAY, FREQ, LIFETEST, and PHREG (with STRATA statement) procedures in the SAS system (SAS/STAT User's Guide Version 8. SAS Institute, Cary, NC) were used for calculations, and GraphPad Prism 4 (GraphPad Software Inc., La Jolla, CA) was used to plot the Kaplan-Meier estimates of survival functions. The PROC UNIVARIATE was used to calculate the mean, SD, minimum and maximum for continuous measurements; PROC NPAR1WAY was used to perform Wilcoxon rank-sum test for comparing the distributions of the continuous measurements between RI-PTC and SP-PTC groups; PROC FREQ was used to perform Fisher's exact test and its extension for categorical data; PROC LIFETEST was used to perform log-rank test; and the PHREG was used to perform the stratified analysis using Cox proportional hazard model. The P value less than 0.05 was regarded as indicating statistical significance.

Results

Descriptive characteristics of the study groups

Table 1 shows the comparison between RI-PTC and SP-PTC groups with respect to baseline factors, cancer characteristics, and treatment modalities.

Although the baseline characteristics of RI-PTC and SP-PTC groups, such as age at diagnosis and time to treatment differed significantly (19.6 *vs.* 25.1 yr old and 109.1 *vs.* 123.7 months, respectively, $P < 0.001$), we note that these differences were within the prespecified matching limits.

Among cancer-related characteristics, T1 tumors were observed more frequently in RI-PTCs while T2, T3, and T4 in SP-PTCs ($P = 0.015$ for distribution). Tumor size in RI-PTC group was smaller than that in SP-PTCs (12.5 mm *vs.* 14.8 mm, $P = 0.019$), and also extrathyroidal tumor

TABLE 1. Baseline, cancer, and treatment characteristics

	RI-PTC, *n* = 172	SP-PTC, *n* = 325	*P*
Baseline factors			
Age at diagnosis, mean ± SD (range), yr	19.6 ± 6.9 (6–36)	25.1 ± 6.8 (8–37)	<0.001
Sex			0.745
Male	44 (25.6%)	79 (24.3%)	
Female	128 (74.4%)	246 (75.7%)	
Sex ratio	0.34	0.32	
Thyroid radiation dose (range), mGy	[77.0, 123.5, 221.5][a] (51–3170)	[0, 0, 1][a] (0–5)	<0.001
Period of latency, mean ± SD (range), yr[b]	15.1 ± 4.1 (5–21)	NA[c]	
Age at Chernobyl accident, mean ± SD (range), yr	5.8 ± 4.7 (0–17)	10.1 ± 5.1 (0–17)	<0.001
Follow-up period mean ± SD (range), months	93.1 ± 44.6 (26–201)	74.9 ± 45.4 (24–208)	<0.001
Time to treatment, mean ± SD (range), months[d]	109.1 ± 45.1 (11–179)	123.7 ± 49.3 (4–189)	<0.001
Cancer characteristics			
pT category			0.015
T1	145 (84.3%)	231 (71.1%)	
T2	14 (8.1%)	49 (15.1%)	
T3	12 (7.0%)	41 (12.6%)	
T4	1 (0.6%)	3 (0.9%)	
TX	1 (0.6%)	1 (0.3%)	
N1	94 (54.7%)	156 (48.0%)	0.187
N1a	55 (58.5%)	74 (47.4%)	0.117
N1b	39 (41.5%)	82 (52.6%)	
M1	6 (3.5%)	18 (5.5%)	0.383
Tumor size, mean ± SD (range), mm	12.5 ± 8.7 (0–60)	14.8 ± 10.3 (0–60)	0.019
≤10 mm	86 (50.0%)	137 (42.2%)	0.024
>10 and ≤20 mm	67 (39.0%)	122 (37.5%)	
>20 mm	19 (11.0%)	66 (20.3%)	
Extrathyroidal extension	11 (6.4%)	40 (12.3%)	0.043
Vascular invasion	7 (4.1%)	6 (1.9)%	0.150
Tumor multifocality	48 (27.9%)	115 (35.4%)	0.108
Tumor capsule[e]	67 (39.0%)	140 (43.1%)	0.391
Full	30 (44.8%)	58 (41.4%)	0.794
Prominent (≥50% perimeter)	22 (32.8%)	53 (37.9%)	
Partial (<50% perimeter)	15 (22.4%)	29 (20.7%)	
Histopathology variant			0.041
Classic papillary	105 (61.0%)	235 (72.3%)	
Follicular	52 (30.2%)	69 (21.2%)	
Solid	7 (4.1%)	7 (2.2%)	
Hurthle cell	1 (0.6%)	5 (1.5%)	
Diffuse sclerosing	7 (4.1%)	7 (2.2%)	
Other	0	2 (0.6%)	
Treatment modalities			
Extent of thyroid resection			0.027
Total thyroidectomy	88 (51.2%)	171 (52.6%)	
Near-total thyroidectomy	3 (1.7%)	22 (6.8%)	
Hemithyroidectomy	81 (47.1%)	132 (40.6%)	
Lymph node dissection	144 (83.7%)	245 (75.4%)	0.039
Central neck dissection (level VI)	104 (72.2%)	158 (64.5%)	0.119
Central + lateral neck dissection (levels VI, II–V)	40 (27.8%)	87 (35.5%)	
Radioiodine ablation	69 (40.1%)	119 (36.3%)	0.437
TSH suppression therapy	172 (100%)	340 (100%)	1.000
Accordance with the Guidelines	127 (73.8%)	202 (62.2%)	0.010

SD, standard deviation.

[a] 25%, 50%, and 75% quartiles.

[b] Calculated as an interval between April 26, 1986 and the date of the first surgery.

[c] Not applicable.

[d] Calculated as an interval between the beginning of the study and the date of the first surgery.

[e] Any extent of tumor capsule on pathology, from full to patchy, was interpreted as the capsule presence; otherwise, the tumors were considered nonencapsulated.

TABLE 2. Recurrence data

	RI-PTC, n = 172	SP-PTC, n = 325	P
Type of recurrence (% of n)			0.372
Regional	21 (84.0%)	49 (76.6%)	
Regional + local	2 (8.0%)	9 (14.1%)	
Regional + distant (lung)	1 (4.0%)	0	
Local	0	4 (6.2%)	
Distant (lung)	1 (4.0%)	2 (3.1%)	
Total	25 (14.5%)	64 (19.7%)	0.177
Recurrence site (% of total number of sites)			0.254
Regional (lymph node metastases)	24 (85.8%)	58 (79.5%)	
Local (thyroid bed)	2 (7.1%)	13 (17.8%)	
Distant (lung)	2 (7.1%)	2 (2.7%)	
Total number of sites	28	73	

spread was observed in the former group less frequently (6.4% *vs.* 12.3%, $P = 0.043$). These differences were likely due to ultrasound screening programs implemented in the regions contaminated with radionuclides that allowed the detection of early-stage malignancies more often. The overall prevalence of nodal disease and the frequencies of vascular invasion and multifocal tumors did not differ between the groups.

Histological data demonstrated the presence of tumor capsule in about 40% cases in both groups. The classical papillary variant of tumor morphology was predominant and more frequent among SP-PTCs (72.3% *vs.* 61.0%), while the follicular variant was more prevalent in the RI-PTC group (30.2% *vs.* 21.2%). Frequencies of tumors with less common histological variants of PTC occurred with comparable frequencies in both groups. Overall, the distributions of histological variants in RI- and SP-PTC groups differed significantly ($P = 0.041$).

Total thyroidectomy was done in approximately 50% of all patients. Near-total thyroidectomy was rather infrequent (1.7–6.8%), hemithyroidectomy was performed in 47.1% and 40.6% of RI-PTC and SP-PTC patients, respectively ($P = 0.027$ for distribution). The relatively high frequency of organ-preserving surgeries was due to national guidelines recommending such for small solitary cancers confined to the thyroid without evidence of regional and/or distant metastases. Lymph node dissections were done in most cases (78.3% totally), but they were more frequent in RI-PTC group than in SP-PTCs (83.7% *vs.* 75.4%, $P = 0.039$), perhaps because surgeons were partly influenced by earlier reports on high aggressiveness of Chernobyl thyroid cancers. RAI ablations were performed in about one-third of cases (37.6% totally) with comparable proportions of patients receiving this treatment in both groups. Suppression hormone therapy was prescribed to all patients in this study; attained serum TSH levels were ≤0.1 mU/liter in all disease-free patients throughout the follow-up period. Overall compliance of treatment with the Guidelines in the cohort was 66.2%. However, in RI-PTC group it was significantly more frequent than in the SP-PTC (73.8% *vs.* 62.2%, $P = 0.010$).

Disease recurrence

As shown in Table 2, during the study period recurrences were registered in 89 (17.9%) patients, of them in 25 patients of the RI-PTC and in 64 patients of the SP-PTC groups (14.5% *vs.* 19.7%, $P = 0.177$).

Eighty-six cases of recurrence were confirmed by histological examination of surgically removed tumor tissues; one of these cases was accompanied by distant metastases in the lung. In the remaining three cases distant metastases were revealed on diagnostic whole-body scintigraphy during follow-up.

The most common recurrence sites were regional lymph nodes (totally 81.2%). Local recurrence (in the thyroid bed) was observed in 14.9%. Distant metastases (in the lung) were diagnosed in 4.0%. No lethal outcomes were registered.

Disease-free survival analysis

As specified in Table 3 showing the estimates of risk factors remained in the optimal model, environmental exposure to radioiodine and tumor size had insignificant effects on disease-free survival while the presence of tumor capsule (HR = 0.17; 95% CI = 0.06 to 0.45), nodal disease (HR = 5.21; 95% CI = 1.63 to 16.7), and treatment according to the Guidelines (HR = 0.16; 95% CI = 0.06 to 0.42) had a marked influence. The strongest factor appeared to be namely the latter one: adequate treatment significantly decreased chance of recurrence. Somewhat unexpectedly, the presence of tumor capsule also strongly improved prognosis. Lymph node involvement is a known condition increasing chance of recurrence, it held true in our series. All other potential risk factors tested had insignificant effect. Importantly, no evidence of interaction of any variable with radiation exposure was found attesting to the absence of risk factors specific to radiation-related or sporadic PTC.

TABLE 3. Proportional hazard ratio analysis of risk factors for disease recurrence in the cohort

Variable	Comparison	Hazard ratio	Wald's 95% CI	*P*
Internal radiation exposure	Yes/No	0.54	0.26–1.13	0.104
Tumor size >10 mm	Yes/No	1.47	0.51–4.20	0.472
Presence of tumor capsule	Yes/No	0.17	0.06–0.45	0.0003
Regional metastases (N1)	Yes/No	5.21	1.63–16.7	0.0053
Treatment in accordance with the Guidelines	Yes/No	0.16	0.06–0.42	0.0002

DFS was compared between RI-PTC and SP-PTC for all combinations of the three dichotomous variables found to be significantly associated with it. As demonstrated in Fig. 2, risk for disease recurrence was not higher in patients with radiation-related PTC compared with those with sporadic PTC in any scenario considered.

Discussion

This study analyzed clinicopathological characteristics and risk factors for recurrence in a group of young patients with PTC of different etiology. The advantages of our work include the center-based implementation according to a uniform protocol, the availability of individual thyroid radiation dose estimates, the inclusion of pathologically verified PTC cases, an opportunity to accrue a relatively large group of young patients with sporadic PTC, and the control for baseline factors.

A source of potential bias could be the systematic ultrasound screening of the residents of contaminated regions. The influence of this factor perhaps explains the lower pT category ($P = 0.015$) as well as the smaller tumor

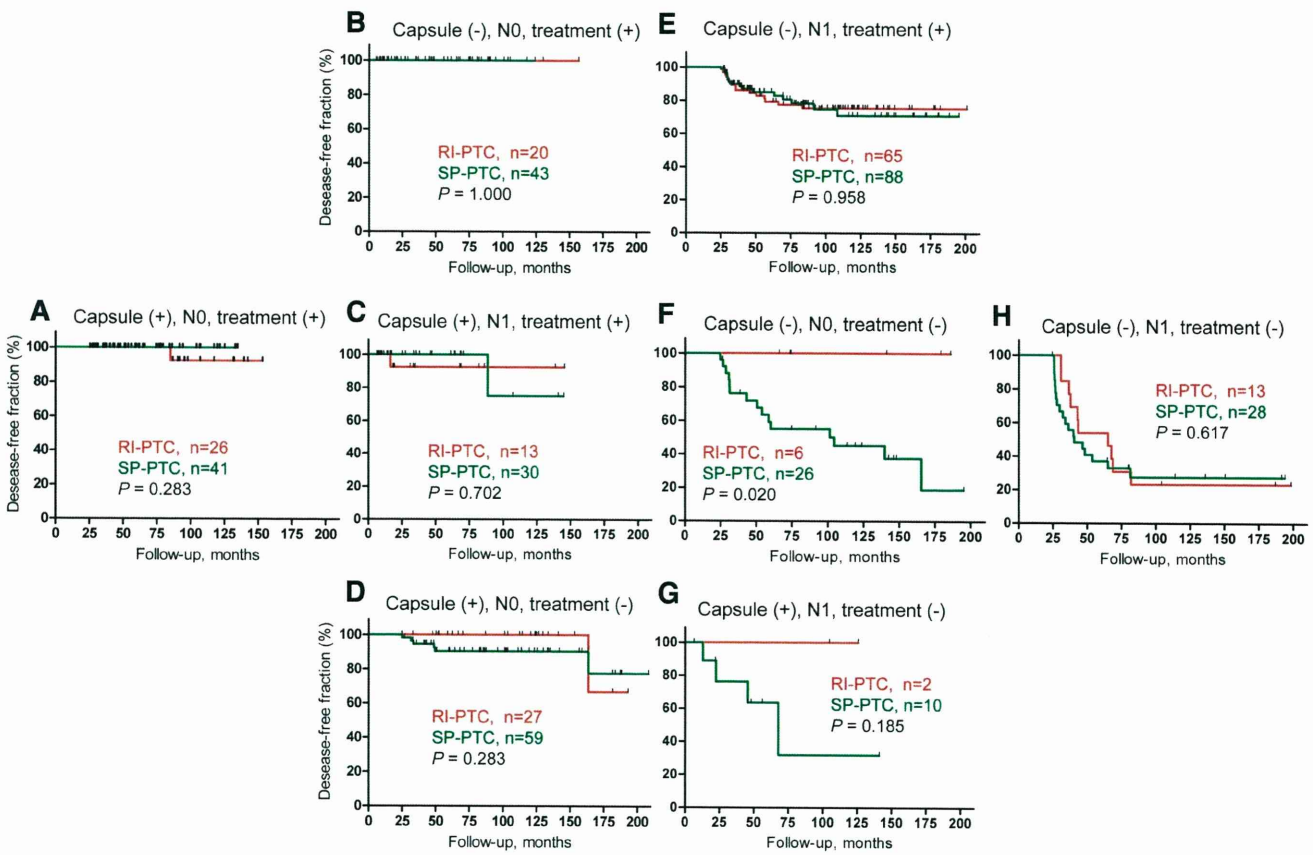

FIG. 2. Disease-free survival analyses of the effects of tumor capsule, nodal disease, and treatment adequacy in the RI-PTC and SP-PTC groups. The (+) or (−) signs in the graph titles indicate the presence or absence of tumor capsule or reflect the compliance of treatment with the Guidelines; N0 or N1 indicate nodal disease status. The *vertical tick-marks* correspond to censored data. Graph A is a survival plot for the RI-PTC and SP-PTC patients with 0 risk factors; B–D, one risk factor; E–G, possible combinations of two different risk factors; H, subgroups with three risk factors. Note that apparent differences in graphs F and G are due to the small number of RI-PTC patients. The *P* values were calculated using log-rank test.

size (12.5 *vs.* 14.8 mm, $P = 0.019$) and the lower prevalence of extrathyroidal invasion (6.4% *vs.* 12.3%, $P = 0.043$) in patients of RI-PTC group compared with SP-PTCs. Because all patients with radiation thyroid doses exceeding 0 mGy (*i.e.* all 172 RI-PTC patients and 130 patients of SP-PTC group with doses <5 mGy) were subjected to ultrasound screening, it was impossible to distinguish whether it was radiation exposure or ultrasound screening which associated with the less advanced tumor spread. However, if patients of SP-PTC group were considered regardless of radiation dose, similar trends were detected on a supplementary analysis (data not shown). We therefore are inclined to attribute the above-mentioned differences namely to ultrasound screening.

Despite the general absence of difference in the frequency of nodal disease between RI-PTCs and SP-PTCs (54.7% *vs.* 48.0%, $P = 0.187$), the central neck lymph nodes tended to be more frequently involved in the former group (N1a stage, 58.5% *vs.* 47.4%, $P = 0.117$). Because it could not be ruled out that this was a radiation-related trait, a complementary multivariate regression analysis was done which showed that nodal disease interacted with treatment but not with radiation exposure (data not shown). Indeed, lymph node dissections were done more frequently in RI-PTC than in SP-PTC cases (83.7% and 75.4%, respectively, $P = 0.039$) and thus clinically insignificant at the time of surgery regional micrometastases were removed and revealed on pathology. We believe prophylactic central-compartment neck dissection was one of the major circumstances that decreased the chance of recurrence which in most instances (81.2% sites cumulatively) manifested as regional metastasis.

Analysis of risk factors for PTC recurrence demonstrated that among all variables tested only three (*i.e.* nodal disease, the presence of tumor capsule, and adequate treatment) were significant.

Nodal disease has been shown to be an adverse prognostic factor for PTC recurrence including Chernobyl childhood cancers (10, 22, 23). Therefore it was rather expected that patients with regional metastases may be at higher risk (HR = 5.21). Similarly, adequacy of treatment, especially the extent of surgery, is a well-known factor to affect DFS (10, 11, 23–27). It appeared to have the strongest effect on decreasing chance of recurrence (HR = 0.16) according to our investigation. Spinelli and colleagues reported a significantly higher recurrence rate in childhood thyroid cancer patients from Chernobyl regions compared with Italian patients (64% *vs.* 3%, $P < 0.0001$) (11). However, it was pointed out that this diversity was probably due to the differences in treatment approaches: total thyroidectomy was done in 8% and 92% cases in the corresponding groups. In our opinion, the Guidelines expound well-balanced strategies of treatment justification. Treatment according to the Guidelines in our series was more frequently given to RI-PTC patients (73.8% *vs.* 62.2% in SP-PTC, $P = 0.010$), and it is likely that the better DFS observed in the former group was in part the direct result of it.

Among other predictors of PTC recurrence, the best known are the older age of patients, the greater tumor size, and extrathyroidal tumor invasion (23, 28, 29). The oldest patient in our study was 37 yr old, and within this narrow range the effect of age on DFS was not detected. On the other hand, previous works demonstrated that the younger age may also be a risk factor for PTC recurrence in young patients (10, 22). The reasons for age effect was not revealed in our analyses may be a different statistical model (proportional hazard in this study *vs.* logistic regression) and prophylactic neck dissections in the majority of cases in our series.

Tumor size is an important factor influencing PTC prognosis (23, 27, 30). In our study tumor size did not associate with the risk for recurrence ($P = 0.472$). Perhaps this was due to the relatively young age of enrolled patients, ultrasound screening which allowed detection of small tumors, and frequent central neck dissections performed regardless of tumor size.

An interesting finding was the strong effect of tumor capsule (HR = 0.17). Its beneficial influence on thyroid cancer prognosis was (31–33) or was not (13) reported in previous works. Our experience suggests that tumor capsule frequently occurs in PTC (considering both fully and partly encapsulated tumors). Tumor capsule presence can tentatively be evaluated preoperatively on high-resolution ultrasound, during surgery by cross-sectioning the removed neoplasm, and definitely verified on intraoperative pathology. Our data demonstrate that tumor capsule could be a marker of better DFS and therefore may be considered as a favorable prognostic factor. Longer follow-up is required to validate its power to affect management recommendations.

It is necessary to emphasize that none of potential risk factors tested was specific to the radiation-related or sporadic PTC group. Previous analyses of risk factors for recurrence show no principal difference between those in sporadic and external radiation-related thyroid cancer (2, 12–14). Our study largely arrives at similar findings. We found no evidence of etiology-associated risk factors for recurrence in the cohort that included both sporadic and internal radiation-related PTCs. We conclude that similar treatment approaches should be recommended for both

nonexposed patients and for those exposed to internal radiation.

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Address all correspondence and requests for reprints to: Vladimir Saenko, Department of International Health and Radiation Research, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan. E-mail: saenko@net.nagasaki-u.ac.jp.

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