K, Nakamura M, Nagahama H, Sasaki Y, Miyakawa Y, Ishibashi H.					
Sakamoto N, Tanaka Y, Nakagawa M, Yatsuhashi H, Nishiguchi S, Enomoto N, Azuma S, Nishimura-Sakurai Y, Kakinuma S, Nishida N, Tokunaga K, Honda M, Ito K, Mizokami M, Watanabe M.	ITPA gene variant protects against anemia induced by pegylated interferon-α and ribavirin therapy for Japanese patients with chronic hepatitis C.	Hepatol Res	40	1063-1071	2010

研究成果の刊行に関する一覧表

(‘2010年4月1日～2011年3月31日迄)

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takatsuki M, Eguchi S, Yamanouchi K, Hidaka M, Soyama A, Miyazaki K, Tajima Y, Kanematsu T	The outcomes of methicillin-resistant Staphylococcus aureus infection after living donor liver transplantation in a Japanese center.	J Hepatobiliary Pancreat Sci.	17	839-843	2010
Yanaga K, Eguchi S, Takatsuki M, Okudaira S, Tajima Y, Kanematsu T.	Two-staged living donor liver transplantation for fulminant hepatic failure.	Hepatogastroenterology.	57	146-148	2010
Eguchi S, Takatsuki M, Yamanouchi K,	Regeneration of graft livers and limited contribution of	Dig Dis Sci.	55	820-825	2010

Kamohara Y, Tajima Y, Kanematsu T.	extrahepatic cells after partial liver transplantation in humans.				

研究成果の刊行に関する一覧表

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Akita S, Akino K, Hirano A, Ohtsuru A, Yamashita S	Non-cultured autologous adipose-derived stem cells therapy for chronic radiation injury	Stem cells International	in press	in press	in press
Akita S, Akino K, Yakabe A, Tanaka K, Anraku K, Yano H, Hirano A	Basic fibroblast growth factor is beneficial for post-operative color uniformity in split-thickness skin grafting	Wound Repair Regen	18	560-566	2010
Akita S, Akino K, Hirano A, Ohtsuru A, Yamashita S	Mesenchymal stem cell therapy for cutaneous radiation syndrome	Health Physics	98	858-862	2010

研究成果の刊行に関する一覧表

(‘2010年4月1日～2011年3月31日迄)

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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Murata H, Nagaishi C, Tsuda A, Sumikawa K	Laryngeal mask airway Supreme for asleep- awake- asleep craniotomy	Br J Anaesth	104	389-390	2010
Murata H, Inoue H, Sumikawa K	Anesthetic management of a patient undergoing liver transplantation who had previous coronary artery bypass grafting using an in situ right gastroepiploic artery	J Anesth	24	264-267	2010

研究成果の刊行に関する一覧表

(‘2010年4月1日～2011年3月31日迄)

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Inoue N, Isomoto H, Matsushima K, Hayashi T, Kunizaki M, Hidaka S, Machida H, Mitsutake N, Nanashima A, Takeshima F, Nakayama T, Ohtsuru S,	Down-regulation of microRNA 10a expression in esophageal squamous cell carcinoma cells.	Oncol lett	1	527-531	2010

Nakashima M, Nagayasu T, Yamashita S, Nakao K, Kohno S					
大津留晶, SOH sang-ryol, 朝長万左男 山下俊一	在外被爆者検診・健康相談事業の現況と展望	長崎医学会雑誌	85	33-36	2010

研究成果の刊行に関する一覧表

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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamoti A, Tada T, Tanaka J, Yoshizawa H	Predictive value of tumor markers for hepatocarcinogenesis in patients with hepatitis C virus	J Gastroenterol	in press	in press	in press

研究成果の刊行物・別刷

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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

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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.

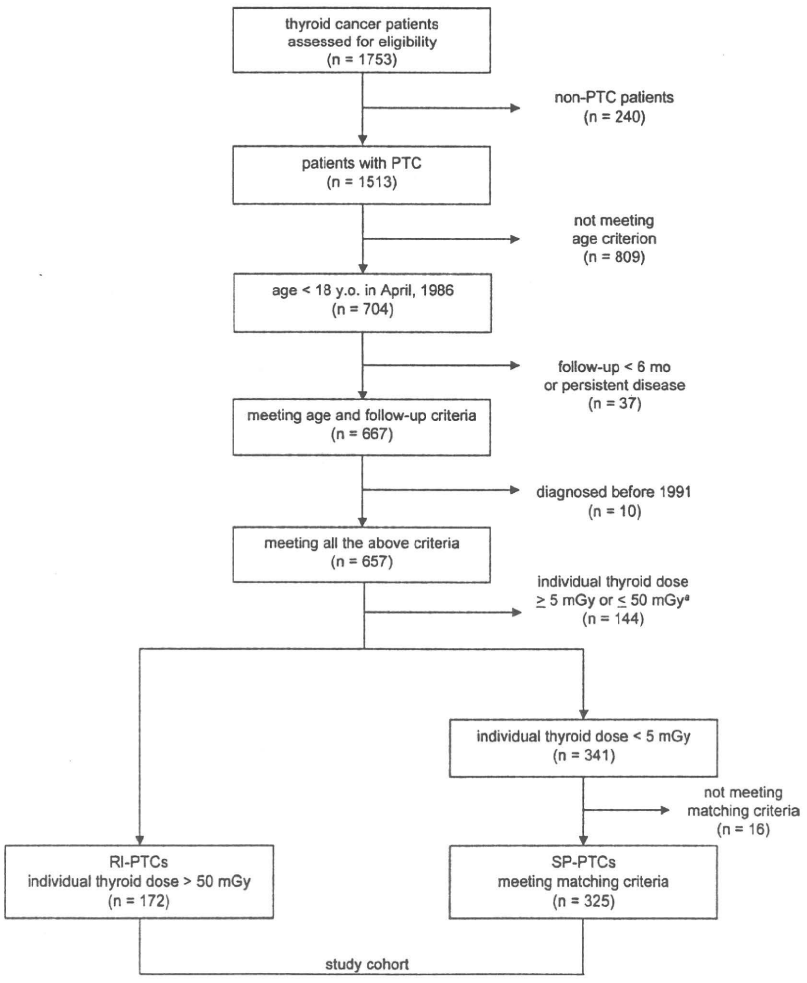

FIG. 1. Selection of patients for the study and reasons for exclusion. [a], Patients were excluded from the study in view of uncertainty in the risk of developing thyroid cancer after internal exposure within this dose range.

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.

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

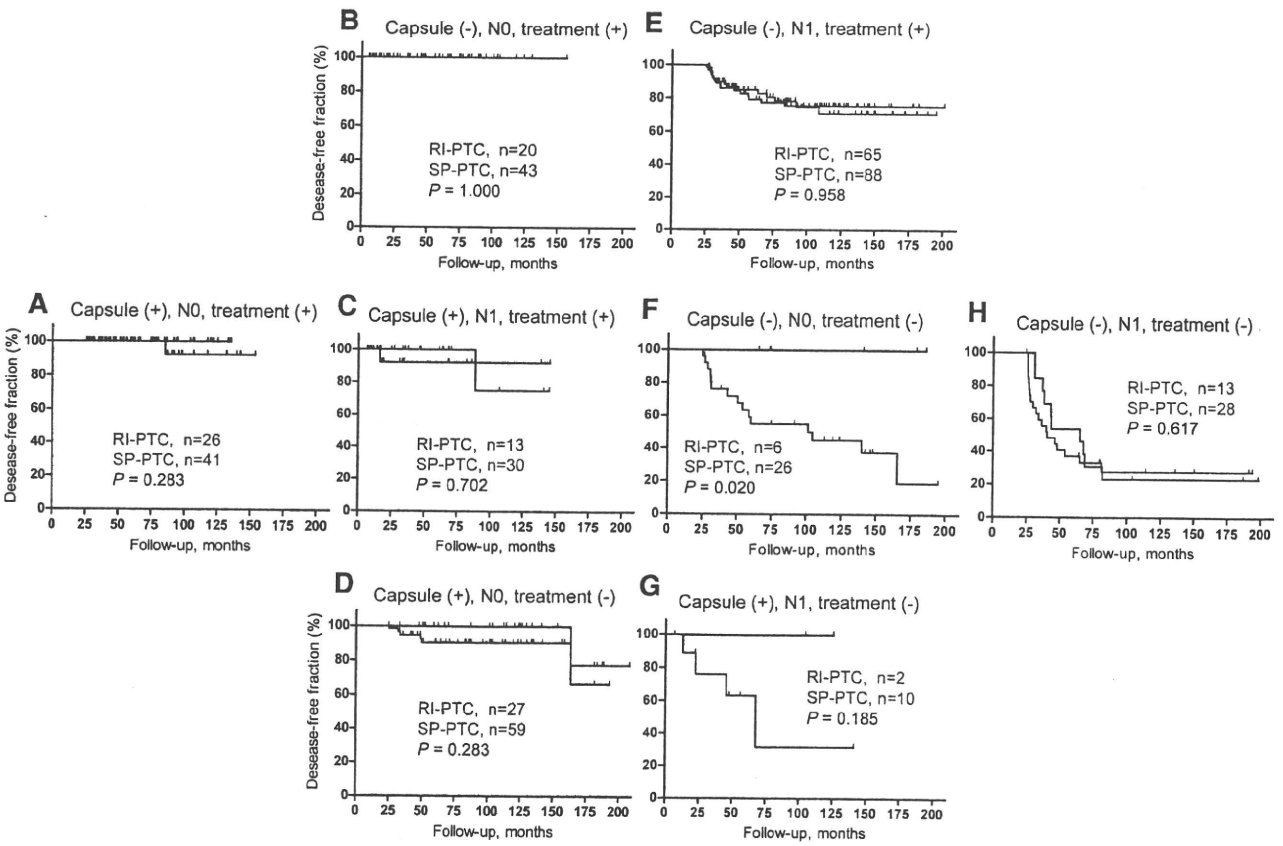

FIG. 2. Disease-free survival analyses of the effects of tumor capsule, nodal disease, and treatment adequacy in the RI-PTC and SP-PTC groups. The (+) or (−) signs in the graph titles indicate the presence or absence of tumor capsule or reflect the compliance of treatment with the Guidelines; N0 or N1 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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References

1. **Schneider AB, Ron E, Lubin J, Stovall M, Gierlowski TC** 1993 Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. J Clin Endocrinol Metab 77:362–369
2. **Acharya S, Sarafoglou K, LaQuaglia M, Lindsley S, Gerald W, Wollner N, Tan C, Sklar C** 2003 Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. Cancer 97:2397–2403
3. **Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice Jr JD** 1995 Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141:259–277
4. **Shibata Y, Yamashita S, Masyakin VB, Panasyuk GD, Nagataki S** 2001 15 years after Chernobyl: new evidence of thyroid cancer. Lancet 358:1965–1966
5. **Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voilleque P, Shakhtarin V, Parshkov E, Kulikov S, Lushnikov E, Abrosimov A, Troshin V, Romanova G, Doroschenko V, Proshin A, Tsyb A** 2004 Risk of thyroid cancer in the Bryansk Oblast of the Russian Federation after the Chernobyl Power Station accident. Radiat Res 162: 241–248
6. **Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goulko G, Hoshi M, Abrosimov A, Anoshko J, Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E, Lushnikov E, Maksioutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Piliptsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D** 2005 Risk of thyroid cancer after exposure to 131I in childhood. J Natl Cancer Inst 97:724–732
7. **Pacini F, Vorontsova T, Demidchik EP, Molinaro E, Agate L, Romei C, Shavrova E, Cherstvoy ED, Ivashkevitch Y, Kuchinskaya E, Schlumberger M, Ronga G, Filesi M, Pinchera A** 1997 Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab 82:3563–3569
8. **Williams ED, Abrosimov A, Bogdanova T, Demidchik EP, Ito M, LiVolsi V, Lushnikov E, Rosai J, Sidorov Y, Tronko MD, Tsyb AF, Vowler SL, Thomas GA** 2004 Thyroid carcinoma after Chernobyl latent period, morphology and aggressiveness. Br J Cancer 90:2219–2224
9. **Bogdanova TI, Zurnadzhy LY, Greenebaum E, McConnell RJ, Robbins J, Epstein OV, Olijnyk VA, Hatch M, Zablotska LB, Tronko MD** 2006 A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: pathology analysis of thyroid cancer cases in Ukraine detected during the first screening (1998–2000). Cancer 107:2559–2566
10. **Demidchik YE, Demidchik EP, Reiners C, Biko J, Mine M, Saenko VA, Yamashita S** 2006 Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. Ann Surg 243:525–532
11. **Spinelli C, Bertocchini A, Antonelli A, Miccoli P** 2004 Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients < or =16 years old. J Pediatr Surg 39:1500–1505
12. **Gow KW, Lensing S, Hill DA, Krasin MJ, McCarville MB, Rai SN, Zacher M, Spunt SL, Strickland DK, Hudson MM** 2003 Thyroid carcinoma presenting in childhood or after treatment of childhood malignancies: An institutional experience and review of the literature. J Pediatr Surg 38:1574–1580
13. **Furlan JC, Rosen IB** 2004 Prognostic relevance of previous exposure to ionizing radiation in well-differentiated thyroid cancer. Langenbecks Arch Surg 389:198–203
14. **Naing S, Collins BJ, Schneider AB** 2009 Clinical behavior of radiation-induced thyroid cancer: factors related to recurrence. Thyroid 19:479–485
15. **Dedov, II, Sviridenko N** 2001 [Iodine deficiency in the Russian Federation]. Vestn Ross Akad Med Nauk 3–12
16. **Thomas GA, Williams ED, Becker DV, Bogdanova TI, Demidchik EP, Lushnikov E, Nagataki S, Ostapenko V, Pinchera A, Souchkevitch G, Tronko MD, Tsyb AF, Tuttle M, Yamashita S** 2001 Creation of a tumour bank for post Chernobyl thyroid cancer. Clin Endocrinol (Oxf) 55:423
17. **Stepanenko VF, Voilleque PG, Gavrilin YI, Khrouch VT, Shinkarev SM, Orlov MY, Kondrashov AE, Petin DV, Iaskova EK, Tsyb AF** 2004 Estimating individual thyroid doses for a case-control study of childhood thyroid cancer in Bryansk Oblast, Russia. Radiat Prot Dosimetry 108:143–160
18. **Sobin LH, Wittekind Ch, eds.** 2002 International Union Against Cancer (UICC). TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss
19. **DeLellies RA, Lloyd RV, Heitz PU, Eng C, eds.** 2004 World Health organization classification of tumors. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press
20. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM** 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
21. **Stone M** 1998 Akaike's criteria. In: Armitage P Colton T, eds. In: Encyclopedia of Biostatistics. Chichester: John Wiley and Sons; A-Cox 123–124
22. **Farahati J, Demidchik EP, Biko J, Reiners C** 2000 Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. Cancer 88:1470–1476
23. **Lundgren CI, Hall P, Dickman PW, Zedenius J** 2006 Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 106:524–531
24. **Mazzaferri EL, Young RL** 1981 Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 70:511–518
25. **DeGroot LJ, Kaplan EL, McCormick M, Straus FH** 1990 Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71:414–424
26. **Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP,**

Johnston DA, Ordonez NG 1992 The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab 75:714–720
27. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, Sturgeon C 2007 Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 246:375–381; discussion 381–374
28. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A 2006 Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. World J Surg 30:780–786
29. Toniato A, Boschin I, Casara D, Mazzarotto R, Rubello D, Pelizzo M 2008 Papillary thyroid carcinoma: factors influencing recurrence and survival. Ann Surg Oncol 15:1518–1522
30. Machens A, Holzhausen HJ, Dralle H 2005 The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. Cancer 103:2269–2273
31. Ito Y, Hirokawa M, Uruno T, Kihara M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A 2008 Biological behavior and prognosis of encapsulated papillary carcinoma of the thyroid: experience of a Japanese hospital for thyroid care. World J Surg 32:1789–1794
32. Miccoli P, Minuto MN, Ugolini C, Panicucci E, Massi M, Berti P, Basolo F 2008 Papillary thyroid cancer: pathological parameters as prognostic factors in different classes of age. Otolaryngol Head Neck Surg 138:200–203
33. Lupi C, Giannini R, Ugolini C, Proietti A, Berti P, Minuto M, Materazzi G, Elisei R, Santoro M, Miccoli P, Basolo F 2007 Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. J Clin Endocrinol Metab 92:4085–4090

Hot Thyroidology

Chernobyl Thyroid Cancer 25 years after: in search of a molecular radiation signature

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ABSTRACT

Chernobyl accident, the worst technogenic catastrophe involving massive radiation release into the environment, will soon reach the 25th anniversary. Its major internationally recognized health consequence is thyroid cancer among the individuals affected by radioiodines at early ages. The largest in the world and unique series of radiation-induced thyroid malignancies has been a subject of investigations in many different aspects of sciences for decades. Here we review the results of investigations aimed at the elucidation of the "radiation signature", a molecular classifier that could help discriminating between radiation-induced and sporadic tumors. The attempts to determine such employ a large variety of techniques, including measurements of DNA copy number variation on microarrays, differential gene expression profiling, proteomics, immunohistochemistry and genotyping of selected target genes or of the whole genome. From the point of view of study design and result interpretation, they could be broadly subdivided into those exploring molecular differences occurring after exposure to different etiological factors (i.e. radiation or other), thus looking for the damage pattern, and the ones seeking the markers of susceptibility to different etiological forms of thyroid cancer. There have been certain advances in both lines of investigations suggestive that establishment of the discriminative molecular signature is plausible. However, studies are far of being accomplished and require further efforts in following-up and investigating the Chernobyl cohort. Possible solutions to create comprehensive molecular concept will likely be integrative approaches combing clinico-pathological and extensive molecular data, and in-depth bioinformatic analyses.

Key-words: Chernobyl accident, thyroid cancer, molecular marker, genomics, gene expression, genetic association study

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