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Hazard ratios of second primary malignancy after radioiodine for differentiated thyroid carcinoma: a large-cohort retrospective study

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Abstract

Introduction: The objective of this study is to evaluate the benefits of radioactive iodine (RAI) treatment and the risk of second primary malignancy (SPM) in RAI-treated patients.

Material and methods: The cohort for this analysis consisted of individuals diagnosed with a first primary differentiated thyroid carcinoma (DTC), reported by the Surveillance, Epidemiology, and End Results (SEER) database in 1988–2016. Overall survival (OS) difference was estimated by Kaplan-Meier curves and log-rank test, and hazard ratios (HR) were obtained by Cox proportional-hazards model to evaluate the association between RAI and SPM.

Results: Among 130,902 patients, 61,210 received RAI and 69,692 did not, and a total of 8604 patients developed SPM. We found that OS was significantly higher in patients who received RAI than in those who did not ($p < 0.001$). DTC survivors treated with RAI had increased risk of SPM in females ($p = 0.043$), particularly for SPM occurring in the ovary ($p = 0.039$) and leukaemia ($p < 0.0001$). The risk of developing SPM was higher in the RAI group than in the non-RAI group and the general population, and the incidence increased with age.

Conclusions: Increased risk of SPM occurs in female DTC survivors treated with RAI, which become more obvious with increasing age. Our research findings were beneficial to the formulation of RAI treatment strategies and the prediction of SPM for patients with thyroid cancer of different genders and different ages. **(Endokrynol Pol 2023; 74 (3): 260–270)**

Key words: *differentiated thyroid carcinoma; second primary malignant; radioactive iodine; cox proportional hazard model; hazard ratio*

Introduction

For the past 20 years, the incidence of thyroid cancer has been increasing in the world. In 2018, the number of new cases of thyroid cancer was about 586,000 in the world, ranking 9th among all cancers [1, 2]. The incidence of thyroid cancer has increased more than 300% over the past 4 decades in the United States [1–3]. Differentiated thyroid carcinoma (DTC), accounting for more than 90% of all thyroid cancers, has a 10-year overall survival (OS) exceeding 90% [4]; it is the most common endocrine malignancy, which consists of papillary and follicular thyroid cancers.

Surgery, radioactive iodine (RAI), and thyroid hormone-suppressive therapy is currently recognized as the standard treatment for patients with DTC [5]. With this approach, the survival time of most patients with thyroid cancer is excellent. RAI therapy plays an important role in reducing the risk of disease recurrence and tumour-related death, as well as good prognosis. Despite a favourable prognosis, the scope of treatment for many patients with thyroid cancer is controversial, including the extent of surgery as well as the use and dose of RAI therapy [6–8]. The side effects of RAI treatment are considered minimal, but RAI may cause some acute or chronic effects [5]. Moreover, the most important concern is whether RAI will benefit survival and increase potential risk of second primary malignancy (SPM) [9, 10]. Studies have shown that 19% of patients develop second malignancy after surviving a primary carcinoma [11]. The reasons include continued lifestyle, genetic susceptibility, and treatment modality (radiotherapy and chemotherapy) [12–14]. It is difficult to estimate the incidence of second primary ma-

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lignancies in patients with DTC after treatment with RAI because there are multiple factors that predispose the patients to SPM.

It has been reported that DTC survivors who received RAI treatment had increased risk of SPM [4, 15], and the SPM risk increased with increasing cumulative RAI activity [16, 17]. Some studies have also reported an increased incidence of SPM of certain organs for sensitivity to radioactivity [18, 19]. In contrast, another study suggested that the risk of second cancer was not related to RAI treatment [14]. Another study utilizing Surveillance, Epidemiology, and End Results (SEER) data included DTC patients for a total of 13 years from 1988 to 2001 (n = 18,882) and reported that RAI treatment was not associated with an increased risk of SPM [20]. Therefore, it is important to recognize the need for risk-benefit balance for DTC patients treated with RAI [21]. Previous studies using SEER tend to have a small sample size, short research time, or short follow-up time [4, 10]. In contrast, our study included DTC patients for nearly 30 years, with a longer period, more patients, and longer follow-up time.

This study aimed to determine whether there was a relationship between RAI treatment and the risk of developing SPM in DTC patients, whether gender was predicted by RAI treatment, and whether there was a relationship between RAI and non-radio-induced cancer. The effect of RAI treatment on OS was estimated by Kaplan-Meier curves. The relationship between the risk of SPM and some variables, including race, gender, age group, year of diagnosis, histological type, SEER stage, and tumour size, and whether to use RAI was assessed using the Cox proportional hazards regression model. This study is the largest study to date to analyse the all-cause and prognostic survival of RAI in DTC patients.

Material and methods

Data

The study population was from the SEER database of the United States National Cancer Institute (NCI). The SEER database collects cancer incidence data from population-based cancer registries covering a large proportion of the U.S. population. The SEER registries contain information on patient demographics, primary tumour site, tumour morphology, stage at diagnosis, treatment, and status. The SEER database is updated once a year to ensure high-quality data. The SEER*Stat software (SEER*Stat 8.3.9, available at https://seer.cancer.gov/seerstat/) was used to obtain information about patients' demographic, pathologic, and clinical characteristics.

Inclusion and exclusion criteria

The baseline cohort for this analysis consisted of individuals diagnosed with a first primary thyroid cancer identified by International Classification of Diseases (ICD) code ICD-O-3:C73.9, reported to the SEER 18 database between 1988 and 2016. Considering the association between chemo patients and increased risk of SMP [13] and radiation therapies other than RAI that the SEER registries encode, such as beam radiation and radioactive interstitial implants, we excluded patients who were treated with both chemotherapy and RAI completely, and we excluded those who received radiation therapy other than RAI from the SEER database before extracting the data. Individuals were followed up through the developed second primary cancer, death, or the end of the study period.

The inclusion and exclusion criteria were outlined in Figure 1. A total of 37,935 people were excluded from our analysis due to one or more of the following 6 reasons:

- 1 — the study limited tumour histology to papillary and follicular thyroid cancer, defined as International Classification of Diseases for Oncology third edition histology codes 8052, 8130, 8260, 8330-8332, 8335, 8340–8344, and 8450 [15]. Patients with other histologic subtype from analysis were excluded (n = 10,870);
- 2 — patients whose survival time was missing were excluded (n = 598);
- 3 — patients diagnosed with SPM within 12 months of the thyroid cancer diagnosis were excluded (n = 1272) [22]
- 4 — the aim of this study was to evaluate the association between RAI and risk of second primary malignancy other than thyroid cancer; hence, patients with recurrent thyroid cancer were excluded (n = 335) [23]
- 5 — patients younger than 18 years of age were excluded (n = 1646);
- 6 — patients with missing data were excluded (n = 14,640).

Finally, 130,902 patients were included in total. Additional variables analysed were sex, race (white, black, and other [American Indian/AK Native, Asian/Pacific Islander]), age (< 45 years, 45–54 years, 55–64 years, and ≥ 65 years) [5, 24], year of diagnosis (1988–2016), SEER stage (localized, regional, and distant), tumour size (0–10 mm and > 10 mm), and RAI therapy (yes or no). The end point of the study was set as 31 December 2016. The enrolled DTC patients were divided into 2 cohorts: those who received RAI and those who did not.

Statistical analysis

The data were extracted with SEER*Stat software and imported into MATLAB (available at https://www.mathworks.com/). In the study, MATLAB software was used for processing data, deleting missing values, and quantifying data. Patients' clinicopathological characteristics were expressed as mean ± standard deviation (SD) for continuous variables, and number with percentage for categorical variables. The chi-square test was used to compare the differences of clinicopathological characteristics between patients who received RAI and those who did not. The chi-square test was performed using IBM SPSS software version 25.

In this study the OS difference was estimated by Kaplan-Meier curves and the log-rank test. Survival time was defined as the time after the diagnosis until death or last follow-up. In addition, a Cox proportional hazard model was performed to assess hazard ratios (HR) and 95% confidence interval (CI), with the occurrence of second primary cancer regarded as an outcome variable in the model. The endpoint was defined as the time from the date of DTC diagnosis to death or last follow-up or diagnosis date of the second malignancy, whichever came first. Univariate analyses were performed for each variable between patients who received RAI and those who did not. In this step, a total of 8 variables were evaluated including race, gender, age group, year of diagnosis, histological type, SEER stage, tumour size, and whether to use RAI. To explore whether each variable still had a higher HR value with statistical significance when other variables existed [25], we used 6 variables including race, age group, year of diagnosis, SEER stage, tumour size, and whether to use RAI in the adjusted Cox model for multivariable analyses. The statistical level of significance was set at $p < 0.05$, and all p value were 2 sided. All statistical analyses were performed using R 4.0.0 software, and the Cox proportional haz-

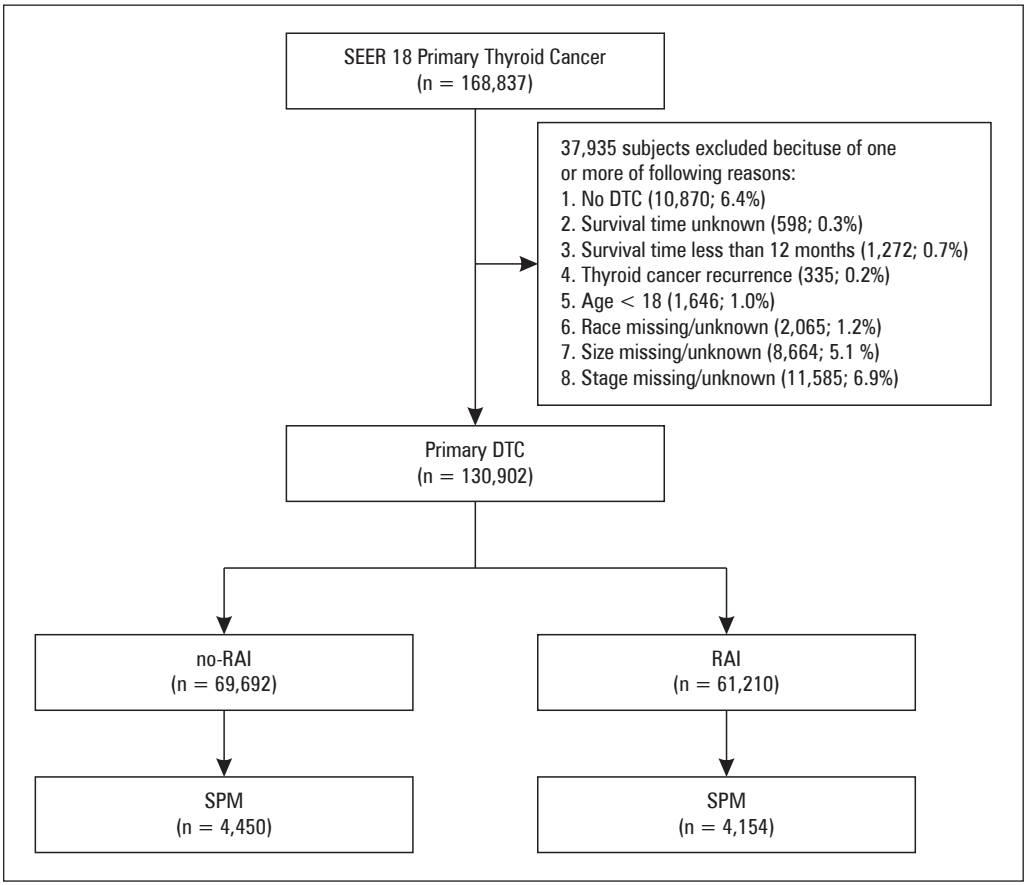

Figure 1. *Inclusion and exclusion criteria for first primary thyroid cancer and second primary cancer in Surveillance, Epidemiology, and End Results (SEER) data, 1988–2016. DTC — differentiated thyroid carcinoma; RAI — radiation iodine*

ard model was conducted using the "Survival" package (R Project, version: 3.6.2, available at https://cran.r-project.org/mirrors.html).

Results

Clinicopathological characteristics

The clinicopathological characteristics of the study population are shown in Tab. 1. A total of 130,902 DTC patients were enrolled during the period 1988–2016. Among these patients, 61,210 received RAI and 69,692 did not; 102,773 (78.5%) were female and 28,129 (21.5%) were male. Statistically significant differences were found in gender, race, age, year of diagnosis, SEER stage, histological type, tumour size, and vital status. The median duration of follow-up of all patients with DTC was 79 months, in RAI therapy patients it was 85 months, and in non-RAI therapy patients it was 72 months. The median time of SPM development for

Table 1. ***Clinicopathological characteristics of differentiated thyroid carcinoma (DTC) patients with radiation iodine (RAI) or without RAI***

Variables	First Primary (n = 130,902)		RAI (n = 61,210)		non-RAI (n = 69,692)		p-value	SPM (n = 8604)		RAI SPM (n = 4154)		non-RAI SPM (n = 4450)		p-value
	N	%	N	%	N	%		N	%	N	%	N	%	
Gender														
Male	28,129	21.5	14,605	23.9	13,524	19.4	< 0.001	2322	27	1228	29.6	1094	24.6	< 0.001
Female	102,773	78.5	46,605	76.1	56,168	80.6		6282	73	2926	70.4	3356	75.4	
Race														
White	107,622	82.2	50,130	81.9	57,492	82.5		7240	84.1	3437	82.7	3803	85.4	
Black	8379	6.4	3248	5.3	5131	7.4	< 0.001	533	6.2	223	5.4	310	7.0	< 0.001
Other	14,901	11.4	7832	12.8	7069	10.1		831	9.7	494	11.9	337	7.6	

Table 1. *Clinicopathological characteristics of differentiated thyroid carcinoma (DTC) patients with radiation iodine (RAI) or without RAI*

Variables	First Primary (n = 130,902)		RAI (n = 61,210)		non-RAI (n = 69,692)		p-value	SPM (n = 8604)		RAI SPM (n = 4154)		non-RAI SPM (n = 4450)		p-value
	N	%	N	%	N	%		N	%	N	%	N	%	
Age [y]														
< 45	56,395	43.1	28,661	46.8	27,734	39.8		1937	22.5	1007	24.3	930	20.9	
45–54	32,037	24.5	14,901	24.3	17,136	24.6	< 0.001	2198	25.5	1113	26.8	1085	24.4	< 0.001
55–64	23,684	18.1	10,184	16.7	13,500	19.4		2260	26.3	1060	25.5	1200	27.0	
≥ 65	18,786	14.3	7464	12.2	11,322	16.2		2209	25.7	974	23.4	1235	27.7	
Year of diagnosis														
1988–1996	9758	7.5	4566	7.5	5192	7.4		1,587	18.4	735	17.7	852	19.2	
1997–2006	37,170	28.4	18,515	30.2	18,655	26.8	< 0.001	4031	46.9	1974	47.5	2057	46.2	0.198
2007–2016	83,974	64.2	38,129	62.3	45,845	65.8		2986	34.7	1445	34.8	1541	34.6	
Stage														
Localized	91,496	69.9	33,013	53.9	58,483	83.9		6074	70.6	2335	56.2	3739	84.0	
Regional	37,582	28.7	26,930	44.0	10,652	15.3	< 0.001	2387	27.7	1711	41.2	676	15.2	< 0.001
Distant	1,824	1.4	1267	2.1	557	0.8		143	1.7	108	2.6	35	0.8	
Histological														
FTC	124,557	95.2	57,933	94.6	66,624	95.6	< 0.001	8077	93.9	3872	93.2	4205	94.5	0.013
PTC	6,345	4.8	3277	5.4	3068	4.4		527	6.1	282	6.8	245	5.5	
Tumour size														
0–10 mm	51,747	39.5	13,586	22.2	38,161	54.8	< 0.001	3542	41.1	1042	25.1	2500	56.2	< 0.001
> 10 mm	79,155	60.5	47,624	77.8	31,531	45.2		5062	58.9	3112	74.9	1950	43.8	
Vital status														
Alive	121,725	93.0	57,248	93.5	64,477	92.5	< 0.001	6168	71.6	3005	72.4	3163	71.1	0.194
Overall death	9177	7.0	3962	6.5	5215	7.5		2436	28.4	1149	27.6	1287	28.9	
Cancer-specific death	1776	1.4	1051	1.7	725	1.0	< 0.001	238	2.7	152	3.6	86	1.9	< 0.001
Median follow-up (months) (IQR)	79 (34–137)		85 (41-141)		72 (29–133)			128 (81–183)		126.5 (82–182)		129 (79–183)		

p-values are based on χ^2 test. Statistically significant p-value < 0.05. SPM — second primary malignant; SD — standard deviation; PTC — papillary thyroid cancer; FTC — follicular thyroid cancer; IQR — interquartile range

all cases, cases with RAI treatment, and cases without RAI treatment was 128 months, 126.5 months, and 129 months, respectively.

Prognostic impact of RAI on OS

During the study period, 9177 (7.01%) patients died, 3962 (3.03%) patients received RAI, and 5215 (3.98%) did not receive RAI. The OS for patients received RAI was significantly higher than those who did not (see Fig. 2A, log-rank test, both $p < 0.001$). Gender group analysis demonstrated that RAI had a significant impact on the OS, and the OS among females was significantly higher than for males (see Fig. 2BC, log-rank test, both $p < 0.001$).

Prognostic impact of RAI on CSM

More of those who received RAI died of thyroid cancer compared to those who did not receive RAI (1.6% *vs.* 1.0%, $p < 0.001$). Thyroid cancer-specific mortality (CSM) by RAI usage is provided in Table 2. CSM was higher in males treated with RAI than in males not treated with RAI [3% (n = 444) *vs.* 1.9% (n = 258), $p < 0.001$], and a consistent result was also observed in females, race subgroups, age subgroups, 1988-1996 Y, 1997-2006 Y, localized, FTC, and 0-10 mm subgroups. RAI was associated with reduced CSM value in patients with regional [RAI: 2.2% (n = 592), non-RAI: 2.6% (n = 279), $p = 0.015$] and distant [RAI: 21.2% (n = 269), non-RAI: 31.1% (n = 173), $p < 0.001$].

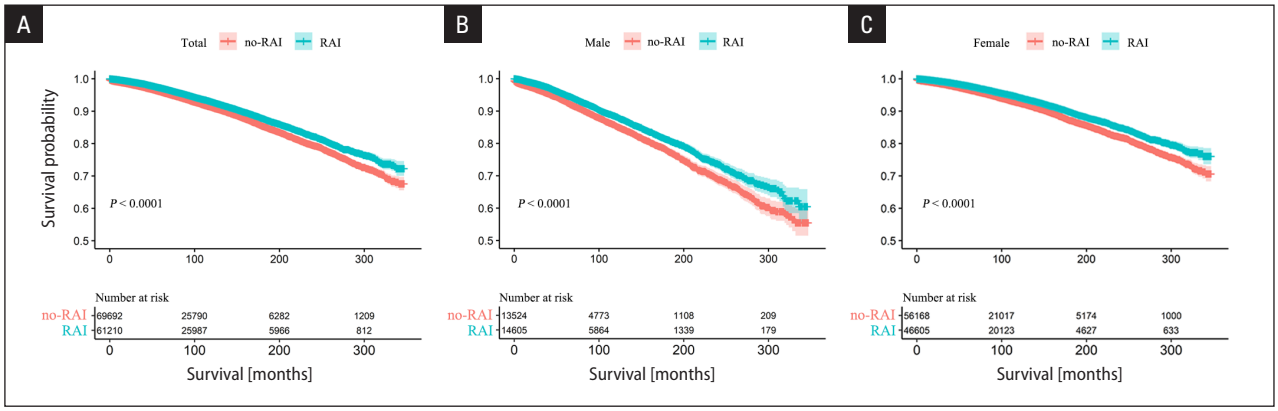

Figure 2. *Overall survival difference for differentiated thyroid carcinoma (DTC) patients according to treatment.* **A.** *Total overall survival;* **B.** *Male overall survival;* **C.** *Female overall survival. RAI — radiation iodine*

Table 2. ***Thyroid cancer specific mortality by radiation iodine (RAI) usage***

Variables	RAI (%)	non-RAI (%)	p-value
Gender			
Male	444 (3.0)	258 (1.9)	< 0.001
Female	607 (1.3)	467 (0.8)	< 0.001
Race			
White	825 (1.6)	569 (1.0)	< 0.001
Black	69 (2.1)	56 (1.1)	< 0.001
Other	157 (2.0)	100 (1.4)	0.006
Age [y]			
< 45	94 (0.3)	42 (0.2)	< 0.001
45–54	194 (1.3)	110 (0.6)	< 0.001
55–64	290 (2.8)	142 (1.0)	< 0.001
≥ 65	473 (6.3)	431 (3.8)	< 0.001
Year of diagnosis			
1988–1996	295 (6.5)	191 (3.7)	< 0.001
1997–2006	512 (2.8)	279 (1.5)	< 0.001
2007–2016	244 (0.6)	255 (0.6)	0.116
Stage			
Localized	190 (0.6)	273 (0.5)	0.026
Regional	592 (2.2)	279 (2.6)	0.015
Distant	269 (21.2)	173 (31.1)	< 0.001
Histological			
FTC	902 (1.6)	604 (0.9)	< 0.001
PTC	149 (4.5)	121 (3.9)	0.234
Tumour size [mm]			
0–10	102 (0.8)	141 (0.4)	< 0.001
>10	949 (2.0)	584 (1.9)	0.160

p-values are based on univariate analysis of Cox proportional hazard model. Statistically significant p-value < 0.05. HR — hazard ratio; PTC — papillary thyroid cancer; FTC — follicular thyroid cancer

Univariate analysis

We performed a univariate Cox regression model to estimate the HRs for different variables including demographic characteristics, histological type, SEER stage, tumour size, and whether using RAI, with the endpoint defined as the time from the date of DTC diagnosis to diagnosis date of the second malignancy (see Tab. 3). In univariate Cox regression analyses, most of the variables showed statistical significance ($p < 0.05$), except for histological type. In both male and female groups, patients older than 65 years had the highest HR value, and the most recent period (2007 to 2016) had the highest elevation; the HR regional value was lower than that of the localized value. In the female group, HR of the black participants were higher than that of the white participants, other races' HRs were lower than that of the whites, and the use of RAI was a significant predictor of SPM, whereas in the male group, HR value among black persons and therapy were not significant.

Multivariable analysis

In multivariable Cox regression analyses (see Fig. 3), a significant difference was found between the RAI and non-RAI groups. Receiving RAI treatment was a significant predictor of SPM in the female group of DTC survivors. Furthermore, adjusted HR increased with age for both males and females and the group over 65 years old, and still showed the highest HR value among all variables – the same as the result of univariate analysis. The adjusted HR of tumours larger than 10 mm and other races was lower than the reference, both in males and females. Moreover, we observed that there was no significant difference between the year of diagnosis and SEER stage in

Table 3. ***Univariate survival analysis for demographic, histological type, tumour size, and therapy***

Variables	Male		Female	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Race				
White	Reference		Reference	
Black	1.14 (0.94–1.37)	0.190	1.11 (1.00–1.22)	0.049
Other	0.80 (0.69–0.94)	0.005	0.87 (0.81–0.95)	0.001
Age [y]				
< 45	Reference		Reference	
45–54	3.13 (2.72–3.61)	< 0.001	2.23 (2.09–2.39)	< 0.001
55–64	5.78 (5.05–6.63)	< 0.001	3.57 (3.33–3.83)	< 0.001
≥ 65	8.99 (7.84–10.31)	< 0.001	4.92 (4.58–5.29)	< 0.001
Year of diagnosis				
1988–1996	Reference		Reference	
1997–2006	1.14 (1.00–1.29)	0.045	1.26 (1.17–1.37)	< 0.001
2007–2016	1.23 (1.07–1.42)	0.003	1.49 (1.36–1.63)	< 0.001
Stage				
Localized	Reference		Reference	
Regional	0.85 (0.78–0.93)	< 0.001	0.93 (0.88–0.99)	0.021
Distant	1.20 (0.94–1.53)	0.141	1.10 (0.88–1.39)	0.392
Histological				
FTC	Reference		Reference	
PTC	1.07 (0.92–1.25)	0.38	1.02 (0.92–1.14)	0.665
Tumour size				
0–10 mm	Reference		Reference	
> 10 mm	0.78 (0.72–0.85)	<0.001	0.84 (0.80–0.88)	< 0.001
Therapy				
Non-RAI	Reference		Reference	
RAI	0.93 (0.86–1.02)	0.116	0.95 (0.91-1.00)	0.048

p-values are based on univariate analysis of Cox proportional hazard model. Statistically significant p-value < 0.05; HR — hazard ratio; CI — confidence interval; PTC — papillary thyroid cancer; FTC — follicular thyroid cancer; RAI — radiation iodine

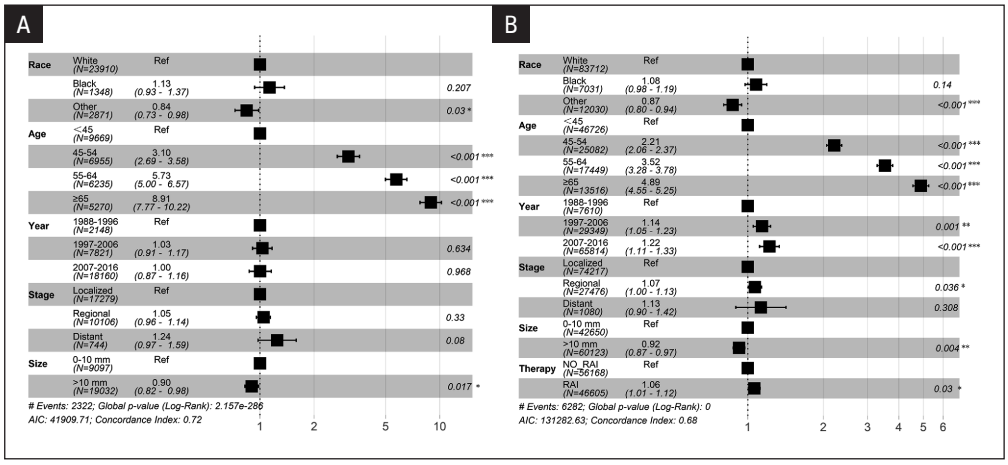

Figure 3. *Hazard ratio (HR) difference for differentiated thyroid carcinoma (DTC) patients according to treatment (*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001).* **A.** *Male HR value in multivariable Cox regression analysis;* **B.** *Female HR value in multivariable Cox regression analysis*

the male group, while the HR values in 1997–2008 and 2009–2016 were 1.14 versus 1.22, respectively, ($p < 0.001$), and the adjusted HR of the SEER stage was higher in patients with regional disease as compared to localized (adjusted HR = 1.07, p = 0.036) in the female group. In the multivariable analysis, we further verified the result that RAI treatment was a significant predictor of SPM for females.

Incidence of SPM

A total of 8604 patients developed SPM after a primary thyroid cancer. Among them, 2322 (27%) patients were male and 6282 (73%) patients were female. Table 4 presents the distribution of the different second primary malignancy sites. In the males, the incidence of all malignancy in the RAI group and non-RAI group were 8.41% (n = 1228) and 8.09% (n = 1,094); whereas in females the RAI group and non-RAI group were 6.27% (n = 2,926) and 5.97% (n = 3356). The incidence of SPM in females was lower than in the male group (see Fig. 4A, $p < 0.05$). In terms of different types of SPM, the most common sites were in the cecum and rectum, lung and bronchus, melanoma of the skin, breast, prostate, kidney and renal pelvis, and haematopoietic system, both in the RAI and non-RAI group. The incidence of prostate cancer was highest among SPM in the male group, and the incidence of RAI and non-RAI were 2.43% (n = 355) and 2.58% (n = 349), respectively, followed by melanoma of the skin. In females, the incidence of breast cancer group was highest among SPM, and the RAI group had a higher incidence (2.32%, 1,081) than the non-RAI group (2.27%, 1,276). In particular, DTC survivors treated with RAI in the female group had increased risk of SPM compared to the non-RAI group in certain types of malignancies, including ovarian cancer (0.17% *vs.* 0.12%, 80 *vs.* 69, p = 0.039) and leukaemia (0.22% *vs.* 0.12%, 104 *vs.* 68, $p < 0.001$), which showed greater sensitivity to radioactivity.

The incidence of SPM increased with age both in the RAI group and in the non-RAI group, and incidence in the RAI group in all age subgroups demonstrated higher incidence than the non-RAI group. There were statistically significant differences among age subgroups of 41–50, 51–60, 61–70, and > 70 years of age between the RAI group and the non-RAI group (see Fig. 4B). The incidence of SPM increased with age in both females and males, and the incidence of SPM in men was higher than in women over 40 years old (see Fig. 4C–D). There were statistically significant differences in age subgroups of only 61–70 years for the male group and age subgroups of 41–50, 61–70, and > 70 years for the female group.

Discussion

In the current study, a retrospective large cohort analysis based on SEER was performed, and the risk of SPM after DTC was analysed in a series of 130,902 patients treated over almost 30 years, among whom 61,210 received RAI. We found that the use of RAI for DTC patients could increase OS, and the OS of females was significantly higher than for males. The result of this study was consistent with a previous National Cancer Database (NCDB) study which suggested that RAI was associated with improved OS in patients with DTC [26]. Moreover, a large number of studies indicate that RAI treatment could reduce the risk of recurrence of thyroid cancer and improve the survival for intermediate-risk, well-differentiated thyroid carcinoma patients [10, 27, 28]. Wang et al. proposed several factors to explain these different results, including racial differences,

Table 4. *The distribution of the different second primary malignancy sites*

Second primary site	Male					Female				
	RAI (14,605)		non-RAI (13,524)			RAI (46,605)		non-RAI (56,168)		
	N	%	N	%	p	N	%	N	%	p
Salivary gland	10	0.07	7	0.05	0.564	25	0.05	18	0.03	0.090
Other oral cavity and pharynx	26	0.18	23	0.17	0.864	23	0.05	21	0.04	0.351
Digestive system										
Stomach	15	0.10	24	0.18	0.095	31	0.07	32	0.06	0.530
Cecum and rectum	78	0.53	67	0.50	0.638	195	0.42	225	0.40	0.633
Liver	16	0.11	9	0.07	0.224	22	0.05	16	0.03	0.118
Others	60	0.41	38	0.28	0.063	100	0.21	129	0.23	0.627
Respiratory system										
Lung and Bronchus	98	0.67	90	0.67	0.936	245	0.53	284	0.51	0.658
Others	8	0.05	5	0.04	0.484	8	0.02	14	0.02	0.402
Skin excluding basal and squamous										
Melanoma of the skin	137	0.94	120	0.89	0.638	203	0.44	260	0.46	0.539
Others	6	0.04	9	0.07	0.359	11	0.02	8	0.01	0.269
Breast	4	0.03	4	0.03	-	1,081	2.32	1276	2.27	0.566
Female genital system										
Ovary	–	–	–	–	–	80	0.17	69	0.12	0.039
Corpus uteri	–	–	–	–	–	158	0.34	185	0.33	0.767
Others	–	–	–	–	–	54	0.12	76	0.14	0.393
Male genital system										
Prostate	355	2.43	349	2.58	0.461	–	–	–	–	–
Others	10	0.07	5	0.04	0.250	–	–	–	–	–
Urinary system										
Kidney and renal pelvis	94	0.64	67	0.50	0.097	102	0.22	126	0.22	0.872
Others	73	0.50	66	0.49	0.872	41	0.09	52	0.09	0.819
Brain and other nervous system										
Brain	20	0.14	16	0.12	0.655	32	0.07	38	0.07	0.940
Other nervous system	16	0.11	25	0.18	0.101	120	0.26	120	0.21	0.141
Other endocrine excluding thyroid	18	0.12	14	0.10	0.617	33	0.07	37	0.07	0.753
Haematopoietic system										
Lymphoma	59	0.40	62	0.46	0.500	118	0.25	121	0.22	0.203
Leukaemia	55	0.38	31	0.23	0.025	104	0.22	68	0.12	< 0.0001
Myeloma	11	0.08	17	0.13	0.184	27	0.06	49	0.09	0.088
Others	59	0.40	46	0.34	0.373	113	0.24	132	0.24	0.788
Total	1,228	8.41	1,094	8.09	0.332	2,926	6.27	3,356	5.97	0.043

p-values are based on chi-square test. Statistically significant p-value < 0.05. RAI — radiation iodine

length of follow-up, and different treatment protocols, which might have an important impact on the recurrence rate of thyroid cancer and survival [10]. Overall, RAI is a key component of postoperative treatment of thyroid cancer, which can destroy thyroid cancer tissue by producing high-energy β-rays, remove latent foci, remove postoperative residual thyroid tissue such as metastatic or unresectable lesions, and reduce recurrence of thyroid cancer and improve the OS.

However, focusing just on thyroid cancer CSM, we found that a larger proportion of patients who received RAI specifically died of their thyroid cancer compared to non-RAI individuals [1.7% (n = 1,051) *vs.* 1.0% (n = 725), $p < 0.001$]. This result was consistent with a previous

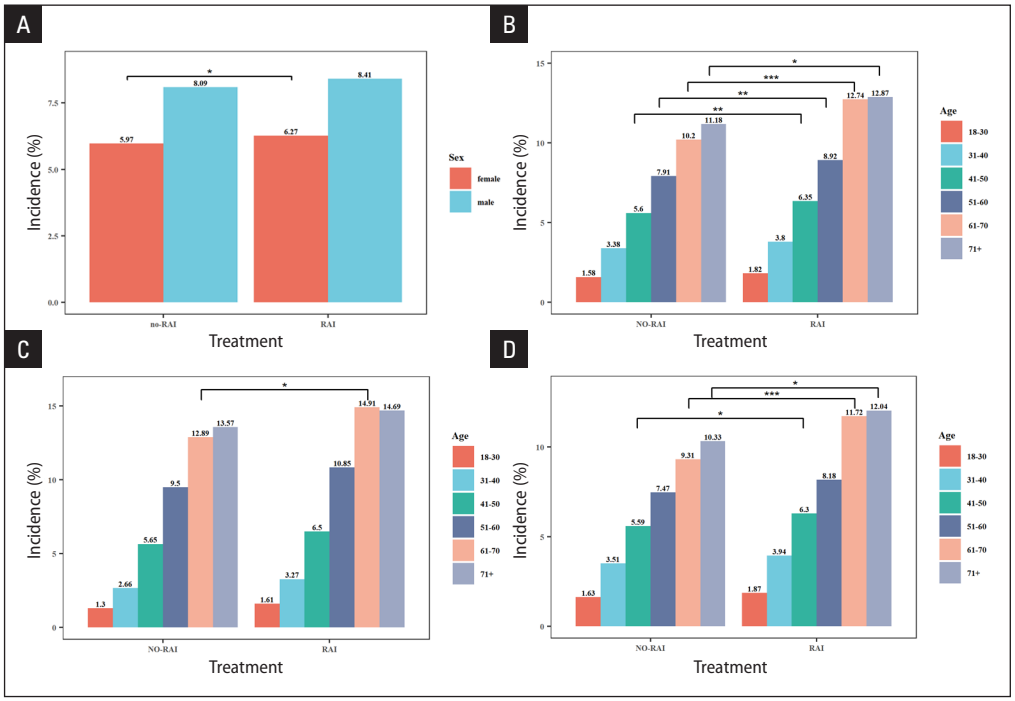

Figure 4. *Second primary malignant (SPM) incidence difference for differentiated thyroid carcinoma (DTC) patients according to treatment (*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001).* **A.** *SPM incidence difference in gender subgroups;* **B.** *SPM incidence difference in age subgroups;* **C.** *Male SPM incidence difference in age subgroups;* **D.** *Female SPM incidence difference in age subgroups. RAI — radiation iodine*

SEER study that showed a negative CSM association in patients with T1a disease [29]. Du et al. showed that the mortality of thyroid cancer increased both in intermediate-term (1–10 years) and long-term (10 years) survivors after RAI, while the mortality reduced in short-term (≤ 1 year) survivors, which is possibly due to the association between radiation exposure and thyroid cancer in a dose-dependent manner [30]. We excluded SPM diagnosed within 12 months of the thyroid cancer diagnosis, which may be another important cause. In addition, patients in the RAI group with regional or distant stage had lower CSM compared to those in the non-RAI group, especially in patients with distant metastatic thyroid cancer. These results indicate that RAI treatment may improve thyroid CSM, it was consistent with previous studies [31, 32]. We found that the mortality rate after RAI treatment was higher than that of non-RAI in all subgroups except for regional and distant metastasis. We speculate that this may be because DTC patients treated with RAI were more inclined to be high risk and intermediate risk.

In addition to the above aspects of survival, previous studies have found that RAI treatment was associated with a higher risk of SPM [4, 33, 34], which is a clinical concern regarding risks of adverse effects from this treatment. Several studies showed that primary thyroid cancer survivors treated with RAI were at increased risk of developing SPMs than those who did not receive RAI [15, 23, 35, 36], and a linear correlation was found between the risk of SPM and the RAI. RAI under a standard activity of 3.7 GBq (100 mCi) will induce in excess of 53 solid cancers and 3 leukaemias every 10 years in 10,000 patients [17]. The 2015 ATA Management Guidelines indicated that the risk of SPM increased significantly when patients received high-dose cumulative activity greater than 600 mCi, suggesting a dose–effect relationship [5]. In Iran, 973 patients followed for a median of 6 (3–26) years did not show significantly increased overall rate of SPM after a 3-year interval from the first RAI treatment, but a cumulative dose of RAI more than 40 GBq (1.08 Ci) considerably increased the risk of SPM [37]. The risk of SPM may be radically increased in patients with high cumulative activities. In contrast, Berthe et al. suggested that the risk of second cancer was not related to RAI treatment [14]. One study utilizing SEER data reported that RAI treatment was not associated with an increased risk of SPM; it was not statistically significant on multivariable analysis between RAI and SPM [20].

It was found that the HR value was higher in female patients with DTC after treatment with RAI after adjusting for different covariates. The HR value increased with the year of diagnosis in the multivariable analysis. The reason for this finding might have been due to their lifestyle exposures, including frequent use of imaging modalities [e.g. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT or CT)] and cosmic radiation, and ge-

netic predisposition. In addition, our results suggested that the incidence of SPM after treatment appeared to increase steadily with the age of DTC patients. Age was an important risk factor for SPM, and mean age of RAI patients was less than that of non-RAI patients (46.44 *vs*. 49.15). Thus, a recommendation of lifelong follow-up of DTC survivors could be made. We found that the adjusted HR of SEER stage was higher in patients with regional disease as compared to those with localized disease.

Our study suggested the following:

— the most common SPM were colorectal (e.g. cecum and rectum), lung and bronchus, melanoma of the skin, breast, kidney, and renal pelvis both in RAI and non-RAI groups, which is in agreement with the results of other studies [4, 12, 14, 15, 38, 39];
— DTC survivors treated with RAI in the female group had a significantly increased risk of developing SPM, which mainly included ovarian cancer and leukaemia, when comparing with cases without RAI therapy. Although the 2015 American Thyroid Association (ATA) Management Guidelines indicated an increased risk of leukaemia due to RAI treatment, the absolute increase in the risk of other malignancies was considered small. In this study, the number of developing SPM was largest in breast, prostate, melanoma of the skin, lung and bronchus, and colorectal cancers, which may be due to the use of RAI treatment and other factors such as genetic susceptibility of DTC patients, lifestyle, and environmental exposures that we did not include in analyses. In addition, this result was consistent with a previous report that suggested that female breast cancer was the most diagnosed cancer throughout the world, ranking first among all cancers, closely followed by lung, prostate, and colorectal cancer [2]. A previous study showed that lifestyle interventions after treatment, such as quitting smoking or regular exercise, may help to reduce the incidence of SPM [40].

We identified moderate evidence that the first primary thyroid cancer survivors were at increased risk of developing malignancies in the ovaries and haematopoietic system. This was consistent with a previous study that suggested that RAI was associated with increased risk of second cancer in the female reproductive system [14]. Sandeep et al. found that there was a 59% increased risk of developing ovarian cancer in comparison with the general population [18]. A previous study showed that acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) were complications of cytotoxic therapy [41]. Another study showed that the majority of patients with AML after treatment with RAI harboured high-risk cytogenetic abnormalities like therapy-related myeloid leukemia (t-AML)/treatment-related MDS arising after other cytotoxic anticancer treatments [42]. In most patients this occurred 3 to 10 years after radiation or chemotherapy and was associated with loss of chromosomes 5 or 7 and TP53 gene mutation, which increased the risk that cells would harbour leukaemia-causing genetic defects.

Our study has several limitations. The first and most important limitation is that our study is retrospective, intrinsic selection biases exist, and although the SEER database is updated once a year, there may be coding errors and incomplete variables. Second, the SEER database is unable to obtain details about the dose and duration of RAI therapy for DTC survivors; thus, we could not calculate the correlation between the dosage and the incidence of SPM. Third, the SEER database does not record certain information on the patient's clinical characteristics, such as postoperative biochemical data (e.g. thyroglobulin, thyroid-stimulating hormone, and thyroxine levels) and whole-body scanning. Fourth, it is also important to adjust for other risk factors for various SPM, such as lifestyle-related factors (e.g. family history, obesity, smoking, alcohol, consumption of red meat or processed meat), but these factors are not recorded in the SEER database.

Conclusion

RAI treatment was a risk factor for SPM in female DTC patients, and there was significant increase in the risk of SPM in radiation-sensitive organs. Gender, age, disease stage, and RAI therapy may all play important roles as predictors for the development of SPM in DTC survivors. Therefore, we recommend regular cancer screening for female DTC survivors.

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