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Prevalence of hypothyroidism among patients with breast cancer treated with radiation to the supraclavicular field: a single-centre survey

Yuichiro Kikawa,[1] Yasuhiro Kosaka,[2] Kazuki Hashimoto,[1] Eri Hohokabe,[1] Sayaka Takebe,[1] Ryo Narukami,[2] Takayuki Hattori,[2] Kazuhiro Ueki,[2] Kengo Ogura,[2] Toshiyuki Imagumbai,[2] Hironori Kato,[1] Masaki Kokubo[2]

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[1]Department of Breast Surgery, Kobe City Medical Center General Hospital, Kobe, Japan
[2]Department of Radiation Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

Correspondence to
Dr Yuichiro Kikawa; u-1ro@kcho.jp

ABSTRACT

Purpose We investigated the prevalence of hypothyroidism (HT) in patients with breast cancer who received radiation therapy to the supraclavicular (SC) field to evaluate the effect of radiation on thyroid.

Methods Between April 2007 and May 2016, consecutive patients with invasive breast cancer who received SC radiation were recruited. Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were measured between April and August 2016. On the basis of the radiation-planning CT images, thyroid volume was calculated and dose–volume parameters were estimated. The endpoints were the prevalence of HT as determined by high levels of TSH and low levels of fT4 in serum, and the prevalence of subclinical HT, determined by high-serum TSH and normal fT4.

Results Among the 68 consecutive patients, 26 were excluded from evaluation (10 patients died, 6 had a history of previous thyroid disease and 10 were lost to follow-up). One (2.4%) and six (14.3%) of these patients had HT and subclinical HT, respectively, with a mean TSH level of 8.27 µU/mL. By univariate analysis, a predictive factor of HT and subclinical HT was a thyroid volume $<8\,cm^3$ (OR 6.44, 95% CI 1.14 to 36.6; p=0.043). Multivariate analysis also showed an association between thyroid volume $<8\,cm^3$ and HT or subclinical HT (OR 18.48, 95% CI 1.48 to 230.86; p=0.024).

Conclusions The prevalence of HT in patients with breast cancer studied was relatively low. Although thyroid volume appeared to be a predictive marker of HT in this cohort, further prospective evaluation is needed.

Key questions

What is already known about this subject?

- Radiation-induced hypothyroidism (RIHT) is a common complication of head and neck cancer or Hodgkin disease treated with radiation to the thyroid region.
- In patients with breast cancer who received radiation therapy to the supraclavicular (SC) field, the results of published reports evaluating the effect of radiation on the thyroid are controversial.

What does this study add?

- To the best our knowledge, this is the first study in Japan to evaluate the prevalence and the risk factors of HT among patients with breast cancer treated with radiation to the SC field.
- We showed the prevalence of HT in Japanese patients with breast cancer treated with radiation to the SC region is relatively low compared with previous reports.
- Thyroid volume appeared to be a predictive marker of HT in this cohort.

How might this impact on clinical practice?

- Our analyses suggests that smaller thyroid volume is a possible predictive risk factor for HT, although further prospective evaluation is needed. Therefore, a careful follow-up might be necessary for patients with small thyroid volume.

INTRODUCTION

Radiation-induced hypothyroidism (RIHT) is a common complication of head and neck cancer or Hodgkin's disease following treatment with radiation to the thyroid region. The incidence of RIHT in these patients has been reported to be approximately 20%–50%[1] and about half of those occur within 5 years after receiving radiation therapy.[2] In patients with breast cancer who have lymph node metastasis, postoperative irradiation to the SC region is recommended.[3] However, radiation therapy (RT) to the supraclavicular (SC) field includes a part of the thyroid gland; therefore, there is concern about the effect on thyroid function in these patients. Smith *et al4* reported a cohort study based on the Surveillance, Epidemiology, and End Results database, which showed that there was no clear RIHT increase in patients with breast cancer over 65 years of age following radiation to the SC field. However, several other reports indicate that thyroid function is reduced because of irradiation to the SC region after breast surgery[5–7] and no conclusion has been obtained about RIHT among these patients. In Japan, reports of RIHT after breast surgery are also limited. The objective of this study was, therefore, to evaluate the prevalence and risk factors of RIHT in patients with breast cancer treated with radiation therapy to the SC region in Kobe City Medical Center General Hospital. This study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry managed by the National University Hospital Council of Japan (UMIN000022526).

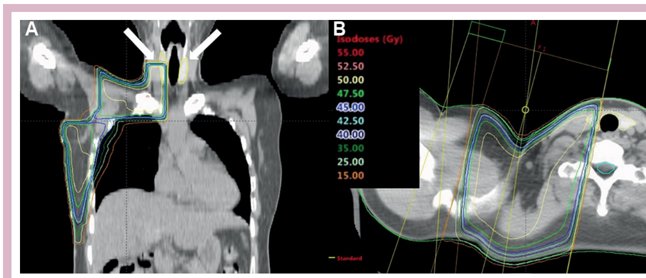

Figure 1 (A) Coronal radiation dosimetric plan used in the CT-based radiation therapy technique. The thyroid gland is indicated by the arrows. (B) Axial radiation dosimetric plan for the supraclavicular field.

PATIENTS AND METHODS

Patient recruitment and sampling

This is a single-centre survey of the prevalence of hypothyroidism among patients with breast cancer. Between April 2007 and May 2016, consecutive patients with invasive breast cancer who received unilateral SC radiation therapy in Kobe City Medical Center General Hospital were recruited. We obtained written informed consents from these patients and each provided a blood sample within the period of April to August 2016. Patients with a history of thyroid disease or those who had undergone thyroid surgery before receiving irradiation and those who took oral thyroid hormone were excluded from the study population. Thyroid-stimulating hormone (TSH), free thyroxine (fT4), antithyroglobulin antibody (TgAb) and antithyroid peroxidase antibody (TPOAb) were measured in the blood samples. The reference range of TSH is 0.50–5.00 µU/mL and that of fT4 is 0.09–1.70 ng/dL. Positive values of TgAb and TPOAb are 28 IU/mL and 16 IU/mL or more, respectively. We also asked the patients about their family history of thyroid disease and any previous history of type 1 diabetes and rheumatoid arthritis that could affect thyroid function. Furthermore, we examined each patient's history of chemotherapy and hormone therapy from their medical records. Based on the radiation planning CT images of each patient, the volume of the thyroid gland was calculated and dose–volume parameters were estimated. The primary endpoint was the prevalence of HT as determined by a high serum level of TSH and low serum level of fT4. Secondary endpoint included the prevalence of subclinical HT as determined by high serum level of TSH and normal level of fT4.

Radiation therapy to the SC lymph node region and breast (or chest wall)

RT to the SC area was performed by a 'half-field technique'. Non-opposing anterior and posterior beams to the SC area above the isocentre were used, sparing the spinal canal and humeral head. The upper end of the radiation field is the caudal end of the cricoid cartilage. A 4 or 6 Megavolt (MV) photon beam is delivered anteriorly and a 10 MV photon beam is delivered posteriorly. RT to the breast o r chest wall located below the isocentre is also performed by 4 or 6 MV non-opposing portal irradiation. The thyroid gland is included in the upper side of the radiation field (figure 1A, B).

Volume calculation of the thyroid gland

The outline of the thyroid was easily contoured based on the CT image and the thyroid volume could then be calculated automatically (figure 2).

Estimation of the dose–volume parameters

The dose–volume parameters were estimated based on the tissue-specific dose–volume histogram (figure 3a, b). The thyroid volume percentage that received radiation doses of 30, 40 or 50 Gy are expressed as V30, V40 and V50, respectively.

Statistical analysis

Age, V30, V40 and V50 are presented as continuous variables as mean and SD. Thyroid volume and time from radiation (months) are presented as median and range. Categorical variables that can affect hypothyroidism were defined as follows: age >65-year old or ≤65-year old, Ab positive or negative, months from RT <12 months, 12–60 months or >60 months, V30 >50% or≤50% and thyroid volume <8 cm^3 or ≥8 cm^3. (The cut-off volume of thyroid was based on the report by Chyan *et al*[8]). Unadjusted associations between RIHT (subclinical HT + HT) and categorical variables were calculated by Fisher's exact test, and multivariate analysis was performed with the logistic regression method to obtain the ORs and 95% CIs. Statistical significance was set at p<0.05 and SPSS V.23 was used for analyses.

RESULTS

A total of 68 consecutive patients were screened. Among these patients, 26 were excluded from evaluation (10 patients died, 6 had a history of previous thyroid disease and 10 were lost to follow-up) and blood samples were taken from the remaining 42 patients (figure 4). The prevalence of HT was 2.4% and that of subclinical HT was 14.3%. Figure 5 shows the event chart of HT and subclinical HT and the time from the end of RT to the day of the survey. The median period from receiving RT to the investigation of HT in patients was 30 months.

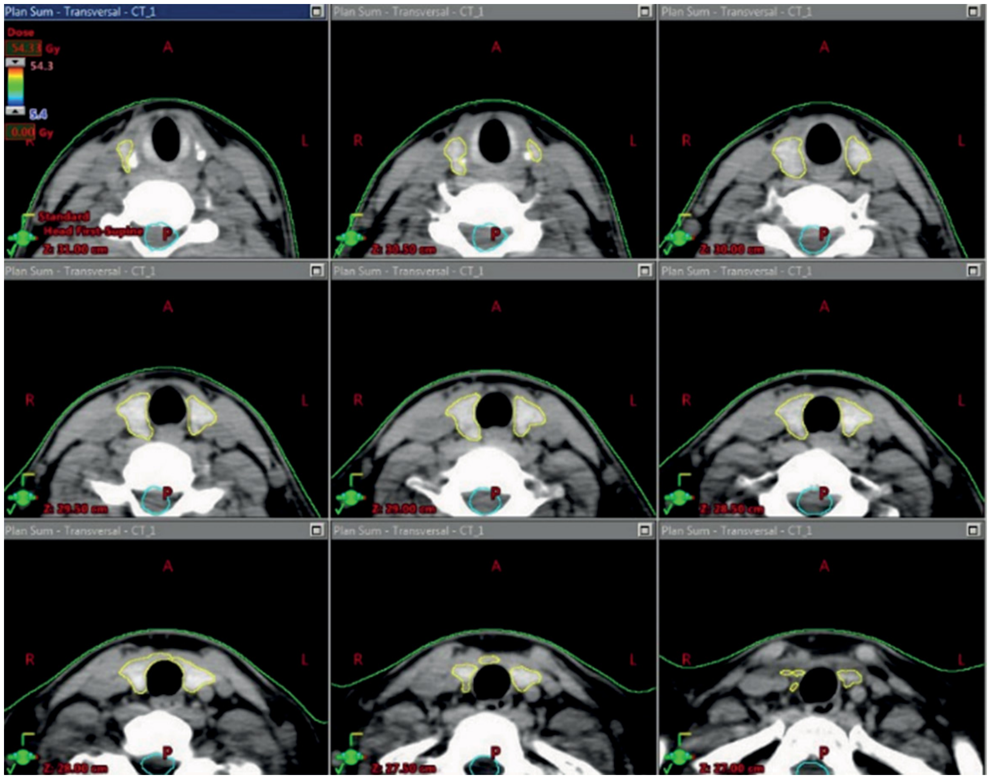

Figure 2 Axial view of the thyroid. The thyroid gland is shown outlined in yellow.

The characteristics of patients with HT or subclinical HT (TSH high, n=7) and those without (TSH normal, n=35) are listed in table 1. The mean values of TSH were 8.27 µU/mL (3.00 SD) in the HT + subclinical HT group and 2.55 µU/mL (1.45 SD) in the non-HT group. Regarding the dose–volume parameters, there was no significant difference between the two groups. There were no patients with a previous history of type 1 diabetes or rheumatoid arthritis.

Univariate analysis indicated that thyroid volume <8 cm^3 was significantly associated with high levels of TSH (OR 6.44, 95% CI 1.14 to 36.6; p=0.043). However, age, dose–volume parameters, TgAb positivity or TPOAb positivity and follow-up time were not associated with high TSH (table 2). By multivariate analysis, thyroid volume <8 cm^3 was also associated with high TSH (OR 18.48, 95% CI 1.48 to 230.86; p=0.024) (table 3).

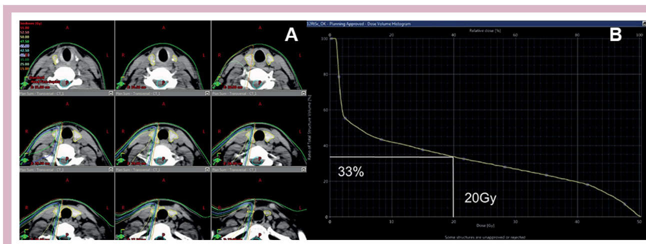

Figure 3 (**A**) Coloured lines show the isodose areas. (**B**) Dose–volume histogram. In this patient, V20 was estimated to be 33%. V20, thyroid volume percentage that received radiation doses of 20Gy.

DISCUSSION

The prevalence of HT in patients with breast cancer in our institution after irradiation to the SC region was 2.4%, which was less than that previously reported (6%–18%).[4 5 7 9] In addition, thyroid volume <8 cm^3 was identified as an independent possible risk factor for HT or subclinical HT in both univariate and multivariate analyses. Chyan *et al*[8] showed that the incidence of HT in

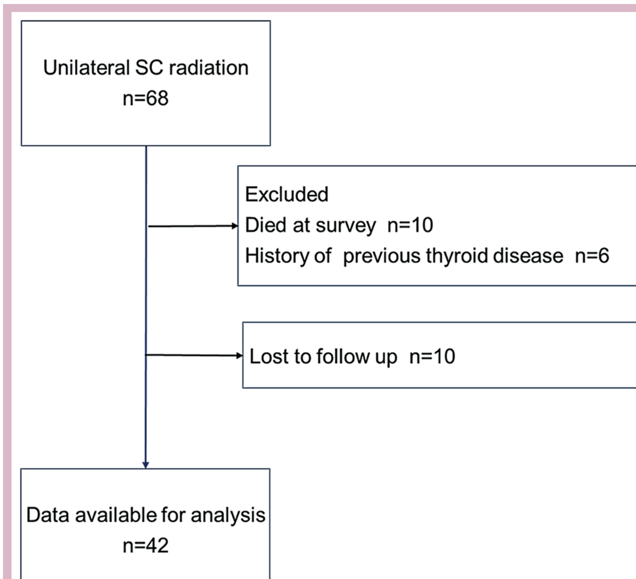

Figure 4 Study cohort flow diagram. SC supraclavicular.

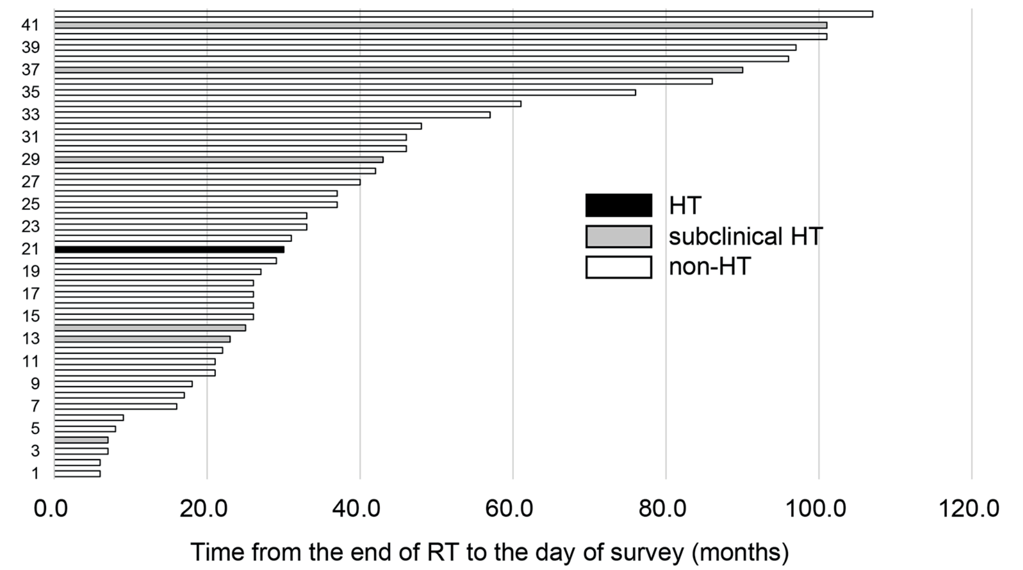

Figure 5 Event chart of hypothyroidism (HT). The prevalence of HT was 2.4% and that of subclinical HT was 14.3%. RT, radiation therapy.

patients with oropharyngeal cancer who were treated with RT to the neck decreased when the initial thyroid volume was 8 cm^3 or more. On the basis of that study, we also set the threshold to 8 cm^3. Similarly, there are several reports that small thyroid volume can become a risk factor for HT,[9–12] and it is considered that the smaller the volume of the thyroid that is not affected by radiation, the higher the risk of HT.

The threshold for direct thyroid radiation damage varies, according to previous reports. Cella *et al*[13] regarded V30 >62.5% as indicating a risk of HT in Hodgkin's lymphoma and Akgun *et al*[12] emphasised V30

Table 1 Patient characteristics

		TSH high (n=7)	TSH normal (n=35)
Age at survey, years	Mean (SD)	61.3 (11.7)	58.1 (11.4)
Age group, years	n (%)		
≤65		5 (71.4)	30 (85.7)
>65		2 (28.6)	5 (14.3)
TSH level, µU/mL	Mean (SD)	8.27 (3.00)	2.55 (1.45)
V30, %	Mean (SD)	30.1 (22.4)	36.0 (20.5)
V40, %		25.3 (20.2)	31.5 (21.0)
V50, %		4.0 (7.2)	13.2 (15.3)
Thyroid volume cm^3	Median (range)	6.2 (5.6–21.4)	10.0 (5–22.5)
<8 cm^3	n (%)	4 (57.1)	6 (17.1)
≥8 cm^3		3 (42.9)	29 (82.9)
Months from radiation	Median (range)	30.0 (7.0–101.0)	31.0 (6.0–107.0)
<12 months	n (%)	1 (14.3)	6 (17.1)
12–60 months		4 (57.1)	22 (62.9)
>60 months		2 (28.6)	7 (20.0)
TgAb(+) or TPOAb(+)	n (%)	4 (57.1)	9 (25.1)
History of chemotherapy	n (%)	7 (100)	33 (94.2)
History of endocrine therapy	n (%)	5 (71.4)	28 (80.0)
Family history of thyroid disease	n (%)	0 (0)	3 (8.6)

TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody; TSH, thyroid-stimulating hormone; V30, thyroid volume percentage that received radiation doses of 30Gy; V40, thyroid volume percentage that received radiation doses of 40Gy; V50, thyroid volume percentage that received radiation doses of 50Gy.

Table 2 Univariate analysis

	OR	95% CI Lower	Upper	p-Value
>65-year old versus 65-year old≥	2.40	0.36	15.9	0.579
Ab(+) versus Ab(–)	3.85	0.72	20.6	0.176
V30 >50% versus ≥50%	0.42	0.04	3.92	0.654
Thyroid volume <8 cm^3 (vs ≤8)	6.44	1.14	36.6	0.043
Months from RT ≥60 (vs 12–60)	1.64	0.25	10.9	0.627
Months from RT ≤12 (vs 12–60)	1.15	0.11	12.6	1.000

Ab, antibody (antithyroglobulin antibody and/or thyroid peroxidase antibody); RT, radiation therapy.

as a predictor of RIHT. Tunio *et al*[9] considered V30 >50% as a risk factor of HT for breast cancer after RT to the SC area; therefore, we also analysed the association of V30 >50% with HT. However, there was no clear relationship between the two in our study.

Regarding the onset of RIHT, the median time to the development of HT is reported to be 1.4–1.8 years after RT.[14 15] We subdivided the time from the end of RT to the day of survey into periods of <12 months, 12–60 months and >60 months for analysis and could not show any significant association between the elapsed time and HT.

As limitations of our study, we recognise the following. First, the sample size is small. Second, there are missing data (10 patients died and 10 were lost to follow-up). Third, the baseline data before irradiation and the timing of the event are unknown due to the cross-sectional nature of the study. Therefore, the actual association between RT and high TSH is unclear. Moreover, the clinical importance of subclinical HT is unknown and it would be necessary to follow these patients carefully to ascertain whether fT4 decreases in the future.

In this study, HT and subclinical HT were combined and analysed together because there was only one case of HT. As results of univariate and multivariate analyses, smaller thyroid volume was a possible predictive risk factor for HT and subclinical HT. As discussed above, this is consistent with previous reports. Therefore, a careful follow-up might be necessary for patients with small thyroid volume.

Regarding the prevention of RIHT, irradiation of the SC area sparing the thyroid gland is indicated, although there is concern that this may result in insufficient irradiation and increased recurrence. Recently, the usefulness of intensity-modified radiotherapy (IMRT) has also been reported in postoperative breast cancer as a method of reducing the irradiation dose to normal tissue.[16 17] IMRT may help reduce the dose to the thyroid gland without reducing the treatment dose to the SC region. However, generalisation is difficult from the viewpoint of cost-effectiveness at the present time.

Table 3 Multivariate analysis

	OR	95% CI lower	Upper	p-Value
>65 year old versus 65 year old≥	2.40	0.15	39.28	0.538
Ab(+) versus Ab(–)	12.39	0.97	158.1	0.053
V30 >50% versus ≥ 50%	0.068	0.001	3.79	0.190
Thyroid volume <8 cm^3 (vs ≤8)	18.48	1.48	230.86	0.024
Months from RT ≥60m (vs 12–60)	2.97	0.20	37.34	0.459
Months from RT ≤12m (vs 12–60)	1.42	0.58	34.63	0.831

Ab, antibody (antithyroglobulin antibody and/or thyroid peroxidase antibody); m, months; RT, radiation therapy.

CONCLUSION

The prevalence of HT in Japanese patients with breast cancer treated with radiation to the SC region is relatively low compared with previous reports. Although thyroid volume appeared to be a predictive marker of HT in this cohort, a further prospective study that evaluates the serial TSH / fT4 before and after radiation is needed.

Contributors YK planned, analysed and submitted the study. YK evaluated the radiological findings. KH recruited patients of this study. EH recruited patients of this study. ST recruited patients of this study. RN evaluated the radiological findings. TH evaluated the radiological findings. KU, KO and TI evaluated the radiological findings. HK recruited patients of the study. MK advised the study design. All investigators finally approved the manuscript.

Competing interests None declared.

Ethics approval Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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