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Prognostic Value of Age and Distant Metastasis in Differentiated Thyroid Carcinoma Undergoing Salvage Surgery

HIDENORI SUZUKI, DAISUKE NISHIKAWA, SHINTARO BEPPU, HOSHINO TERADA, MICHI SAWABE and NOBUHIRO HANAI

Department of Head and Neck Surgery, Aichi Cancer Center, Nagoya, Japan

Abstract. *Aim: To investigate the association between survival outcomes and clinicopathological factors, including pathological restaging based on the UICC8th, among patients with recurrence differentiated thyroid carcinoma undergoing salvage surgery of local site. Patients and Methods: A total of 54 patients who underwent salvage surgery of local site for recurrence differentiated thyroid carcinoma were enrolled. The optimal cutoff ages at salvage surgery for predicting death and cancer-specific death were determined by receiver operating curve analysis. Overall and cancer-specific survivals were determined using log-rank test and Cox's proportional hazards model. Results: Univariate analysis showed that age and the presence of distant metastasis at salvage surgery were significantly associated with overall survival ($p=0.01$ and $p<0.05$, respectively) and cancer-specific survival ($p=0.02$ and $p=0.01$, respectively). The optimal cutoff age at salvage surgery for predicting the detection of both death ($p=0.01$) and cancer-specific death ($p=0.02$) was 65 years. Multivariate analysis showed that age ≥65 years and the presence of distant metastasis were significantly associated with shorter overall survival ($p<0.01$ and $p=0.03$, respectively) and shorter cancer-specific survival ($p<0.01$ and $p=0.01$, respectively). Conclusion: Older age and the presence of distant metastasis at salvage surgery of local site were identified as predictors for poor survival outcomes in recurrence differentiated thyroid carcinoma.*

Differentiated thyroid carcinoma generally has good overall survival (OS) and cancer-specific survival (CSS) following initial surgery (1-7). Total thyroidectomy with adjuvant radioactive iodine for differentiated thyroid carcinoma has been established as the standard-treatment strategy in Western countries, while non-total thyroidectomy such as hemithyroidectomy and subtotal thyroidectomy, has been widely utilized in Japan (1). Several countries have incorporated non-total thyroidectomy into guidelines due to less complication and equivable OS in comparison with total thyroidectomy, and non-total thyroidectomy increased widely (1-3).

Salvage surgery of local site in recurrence differentiated thyroid carcinoma, including completion thyroidectomy for distant recurrence after hemithyroidectomy, has remained challenging due to safety concerns (4-6). Moreover, predictor for CSS and OS after salvage surgery of local site in recurrence differentiated thyroid carcinoma are yet to be fully investigated (4). Pathological restaging based on the eighth edition of the Union for International Cancer Control (UICC8th) TNM Classification of Malignant Tumors has been widely used as a predictor of survival in various types of cancers, including differentiated thyroid carcinoma (7-9). We had also previously reported that pathological restaging based on UICC8th at initial surgery was a significant predictor for OS and CSS in 543 patients with papillary thyroid carcinoma (7).

Therefore, the present study investigated the association between survival outcomes and clinicopathological factors at salvage surgery, including pathological restaging based on the UICC8th, among patients who underwent salvage surgery of local site for differentiated thyroid carcinoma.

Patients and Methods

Patients. From September 2003 to May 2017, 57 patients with a history of thyroid carcinoma surgery underwent salvage surgery of local site with/without regional site for recurrence thyroid carcinoma at the Aichi Cancer Center Hospital. Among these 57 patients, two with anaplastic carcinoma and one with carcinoma showing thymus-like differentiation were excluded from the study. Thus, 54 patients who underwent salvage surgery of local site with/without regional site for recurrence differentiated thyroid carcinoma were ultimately enrolled. This retrospective study was

Correspondence to: Hidenori Suzuki, Department of Head and Neck Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Tel: +81 527626111 (ext. 3104), Fax: +81 527642944, e-mail: hi.suzuki@aichi-cc.jp

Key Words: Salvage surgery, differentiated thyroid carcinoma, age, distant metastasis, survival.

Table I. *Clinicopathological factors in 54 patients with differentiated thyroid carcinoma who underwent salvage thyroidectomy.*

Factor		Number
Gender	Male/Female	11/43
Age	Median±standard deviation (years)	62±13.9
Initial surgery	Total thyroidectomy/Non-total thyroidectomy	3/51
Duration from initial surgery	Median±standard deviation (years)	5.5±9.42
Local site	T0/T1/T2/T3/T4a	22/10/2/10
Regional site	N0/N1a/N1b	21/4/29
Distant metastasis	Presence/Absence	16/38
Pathology	Papillary/Follicular	50/4
Pathological T-restage (UICC8th)	rpT0/1/2/3/4a	28/10/0/7/9
Pathological N-restage (UICC8th)	rpN0,X/1a/1b	16/6/32
Surgical method for local site	Completion total thyroidectomy/Others	22/32
Surgical method for regional site	Neck dissection/Lymph node excision/Absence	38/5/11
Adjuvant therapy	Radioactive iodine/External radiation/Absence	12/1/41
Survival outcome	Cancer-specific death/Other death/Alive	10/2/42
Follow-up duration	Median±standard deviation (years)	5.30±3.45

UICC8th: Eighth edition of Union for International Cancer Control.

approved by the institutional review board of Aichi Cancer Center Hospital and carried out according to the Declaration of Helsinki. Pathological diagnoses included papillary carcinoma (n=50) and follicular carcinoma (n=4).

Clinicopathological factors. Initial surgery for local site included total thyroidectomy (n=3) and non-total thyroidectomy (n=51). The mean±standard deviation (SD) duration from initial surgery to salvage surgery was 8.26±9.42 years. Clinical TNM staging and pathological TNM restaging based on the UICC8th were previously described (7). Briefly, both pathological and intraoperative reports were used according to the eighth edition of the cancer staging manual of the American Joint Committee on Cancer and the UICC8th (7, 10, 11). Salvage surgery of local site included completion total thyroidectomy for crT0 (n=22) and total thyroidectomy with/without adjacent organs for crT1-4a (n=32). Among the included patients, 43 underwent salvage surgery for regional recurrence, that included neck dissection (n=38) and lymph node excision after initial neck dissection (n=5). Adjuvant therapy comprised radioactive iodine (n=12) and external radiation (n=1). Patients who developed locoregional recurrence tumor after salvage surgery underwent repeat salvage surgery as appropriate.

Statistical analysis. Survival time, determined as the number of days from the date of salvage surgery until an event (*i.e.*, death for OS and death from differentiated thyroid carcinoma for CSS) or last contact, were calculated using the Kaplan–Meier methods. The log-rank test and Cox's proportional hazards model were used for univariate survival analysis of categorical (gender, initial surgery, local recurrence, regional recurrence, distant metastasis, pathology, pathological T restaging, pathological N restaging, surgical method for regional recurrence, and adjuvant therapy) and continuous (age and duration from initial surgery) variables, respectively. The Mann-Whitney test was used to determine relationships between death and survival, as well as between cancer-specific death and other than cancer-specific death, according to age at salvage surgery. The optimal cutoff values age for predicting OS and CSS was determined using the area under the curve (AUC) of the receiver operating characteristic (ROC) (12). Patients were then categorized into two groups based on age (≥65 years old and <65 years old), after which differences between them were compared using the chi-square test, Fisher's exact test, the Mann-Whitney *U*-test, and the log-rank test. Multivariate survival analyses (OS and CSS) using a Cox's proportional hazards model determined the hazards ratio (HR) and 95% confidence interval (CI) for age (≥65 years old/<65 years old) and distant metastasis (presence/absence). All statistical analyses were carried out using the JMP software package (version 9; SAS: Cary, NC, USA), and a *p*-value values less than 0.05 was considered statistically significant.

Results

Clinicopathological factors and survival outcomes. Clinicopathological factors are presented in Table I. Accordingly, patients had a median±SD of age of 62±13.9 years (range=23-83) at salvage surgery. At the end of the study, the median±SD duration of follow-up duration was 5.30±3.45 years for all patients, 5.99±3.50 years for the 42 patients who survived, 4.03±2.92 years for the 12 patients who died of any cause, 4.25±2.96 years for the 10 patients who died due to differentiated thyroid carcinoma. The 3-, 5-, 10-year OS rates were 92.2%, 82.1%, 72.3%, while the 3-, 5-, 10-year CSS rates were 93.9%, 86.1%, 75.7%, respectively. Univariate analyses of OS and CSS are presented in Table II. Accordingly, age and the presence of distant metastasis were significantly associated with OS (p=0.01 and p<0.05, respectively) and CSS (p=0.02 and p=0.01, respectively).

Age and survival outcomes. The relationships between death and survival, as well as between cancer-specific death and other than cancer-specific death, according to age at salvage surgery are presented in Figure 1. Patients who died at last contact were significantly older at salvage surgery than those who survived

Table II. *Univariate survival analysis in 54 patients with differentiated thyroid carcinoma.*

Factor		*p*-Value	
		OS	CSS
Gender	Male/Female	0.26[a]	0.12[a]
Age	Continuous viable	0.01[b]	0.02[b]
Initial surgery	Total thyroidectomy/Non-total thyroidectomy	0.31[a]	0.16[a]
Duration from initial surgery	Continuous viable	0.64[b]	0.95[b]
Local site	T0/T1-4a	0.31[a]	0.20[a]
Regional site	N0/N1a/N1b	0.71[a]	0.22[a]
Distant metastasis	Presence/Absence	<0.05[a]	0.01[a]
Pathology	Papillary/Follicular	0.24[a]	0.28[a]
Pathological T-restage (UICC8th)	rpT0/1/2/3/4a	0.52[a]	0.44[a]
Pathological T4-restage (UICC8th)	rpT0-3/4a	0.28[a]	0.59[a]
Pathological N-restage (UICC8th)	rpN0,X/1a/1b	0.80[a]	0.61[a]
Surgical method for local site	Completion total thyroidectomy/Others	0.31[a]	0.20[a]
Surgical method for regional site	Presence/Absence	0.50	0.49[a]
Adjuvant therapy	Presence/Absence	0.61[a]	0.92[a]

OS: Overall survival, CSS: cancer-specific survival. [a]Log-rank test, [b]Cox proportional hazards model.

Table III. *Associations between clinicopathological factors and age at salvage thyroidectomy in 54 patients with differentiated thyroid carcinoma.*

Factor		Age≥65 (n=24)	Age<65 (n=30)	*p*-Value
Gender	Male/Female	5/19	24/6	1.00[a]
Initial surgery	Total thyroidectomy/Non-total thyroidectomy	1/23	2/28	1.00[b]
Age	Median±SD (years)	71±5.18	55.5±11.1	<0.01[c]
Duration from initial surgery	Median±SD (years)	7±12.0	4±6.06	0.08[c]
Primary site	Presence/Absence	10/14	11/19	0.78[a]
Regional site	N0/N1	6/18	15/15	0.09[a]
Distant metastasis	Presence/Absence	7/17	9/21	1.00[a]
Pathology	Papillary/Follicular	24/0	26/4	0.12[b]
Pathological T-restage on UICC8th	rpT0-3/4a	17/7	28/2	0.06[b]
Pathological N-restage on UICC8th	rpN0,X/1	6/18	10/20	0.56[a]
Surgical method for local site	Completion total thyroidectomy/Others	14/10	18/12	1.00[a]
Surgical method for regional site	Presence/Absence	18/6	25/5	0.51[a]
Adjuvant therapy	Presence/Absence	3/21	10/20	0.11[b]
Overall survival	Death/Alive	10/14	2/28	0.01[d]
Cancer-specific survival	Cancer-specific death/Others	9/15	1/29	<0.01[d]
Follow-up duration	Median±SD (years)	5.56±3.67	5.13±3.32	0.94[c]

UICC8th: Eighth edition of Union for International Cancer Control, SD: standard deviation. [a]Chi-square test, [b]Fisher's exact test, [c]Mann-Whitney's test, [d]Log-rank test.

(p=0.02). Moreover, those who succumbed to cancer-specific death at last contact were significantly older at salvage surgery than those with other than cancer-specific death (p=0.03). ROC curves showing the relationship between death and survival, as well as between cancer-specific death and other than cancer-specific death, according to age at salvage surgery are presented in Figure 2. Accordingly, the optimal cutoff age at salvage surgery for predicting death (p=0.01; AUC=0.73) and cancer-specific death (p=0.02; AUC=0.72) was 65 years old.

Clinicopathological factors and age. Associations between clinicopathological factors and age (age ≥65/age <65) are detailed in Table III. Accordingly, log rank test showed that patients ≥65 years old had significantly associated with shorter OS (p=0.01) and CSS (p<0.01) than those <65 years old.

Multivariate survival analysis. Results of multivariate survival analyses are presented in Table IV. Accordingly, age ≥65 years old and the presence of distant metastasis were

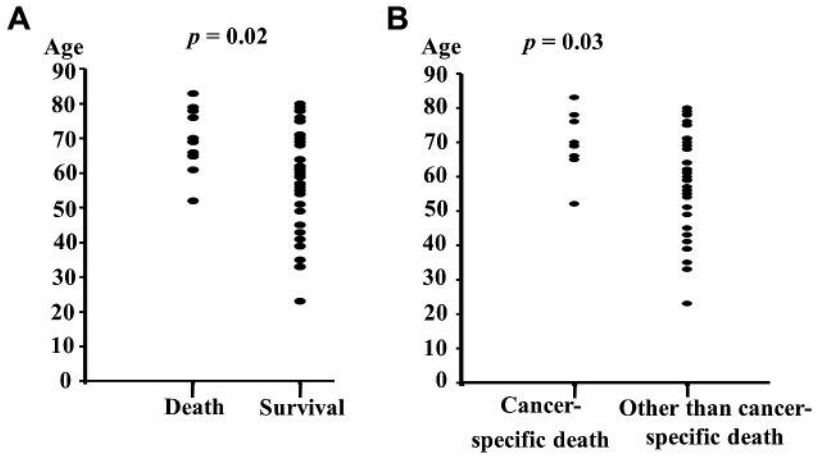

Figure 1. *The Mann-Whitney test was used to determine the relationships (A) between death and survival (p=0.02) and (B) between cancer-specific death and other than cancer-specific survival (p=0.03) according to age at salvage surgery.*

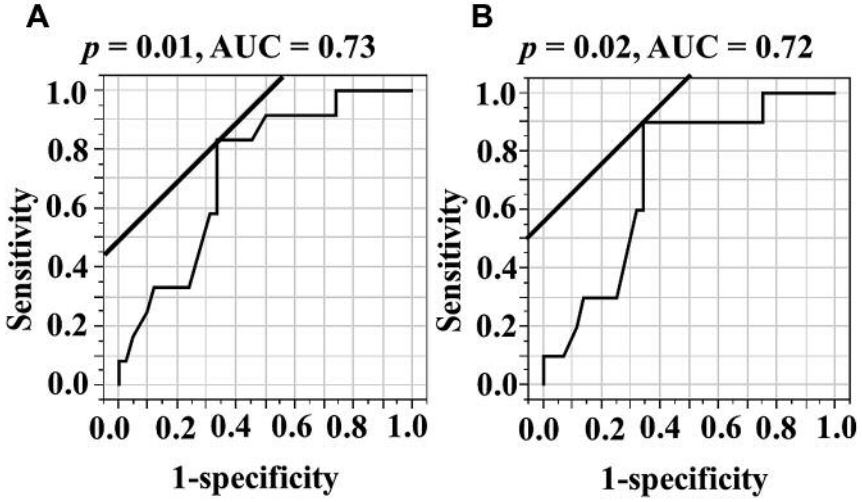

Figure 2. *Receiver-operating characteristic curves for the age at salvage surgery showing the relationships (A) between death and survival (p=0.01, AUC=0.73) and (B) cancer-specific death and other than cancer-specific survival (p=0.02, AUC=0.72).*

significantly associated with shorter OS (HR=7.37, 95%CI=1.91-48.5, $p<0.01$ and HR=3.76, 95%CI=1.14-12.5, $p=0.03$, respectively) and shorter CSS (HR=14.9, 95%CI=2.70-280.2, $p<0.01$, and HR=6.54, 95%CI=1.76-28.3, $p=0.01$, respectively). Kaplan-Meier curves of OS and CS are presented in Figure 3.

Discussion

Univariate and multivariate survival analyses employed in the present study showed that age ≥65 years and presence of distant metastasis were significantly associated with shorter OS and CSS among patients who underwent salvage surgery of local site for recurrence differentiated thyroid carcinoma. Hemithyroidectomy for differentiated thyroid carcinoma at initial surgery, which promotes less complications compared to total thyroidectomy while having comparable OS, had increased to 10-fold after the release of the American Thyroid Association guidelines (2). Although one study showed that hemithyroidectomy results in significantly more local recurrence than total thyroidectomy with/without radioactive iodine (12), an increase in the number of salvage surgery of local recurrence may be expected in the future (2). Distant metastasis has been the strongest predictor of survival outcomes (OS and CSS) among patients with differentiated thyroid carcinoma (14, 15). Accordingly, Adam *et al*. reported that the presence of distant metastasis was significantly associated with shorter OS in 61,775

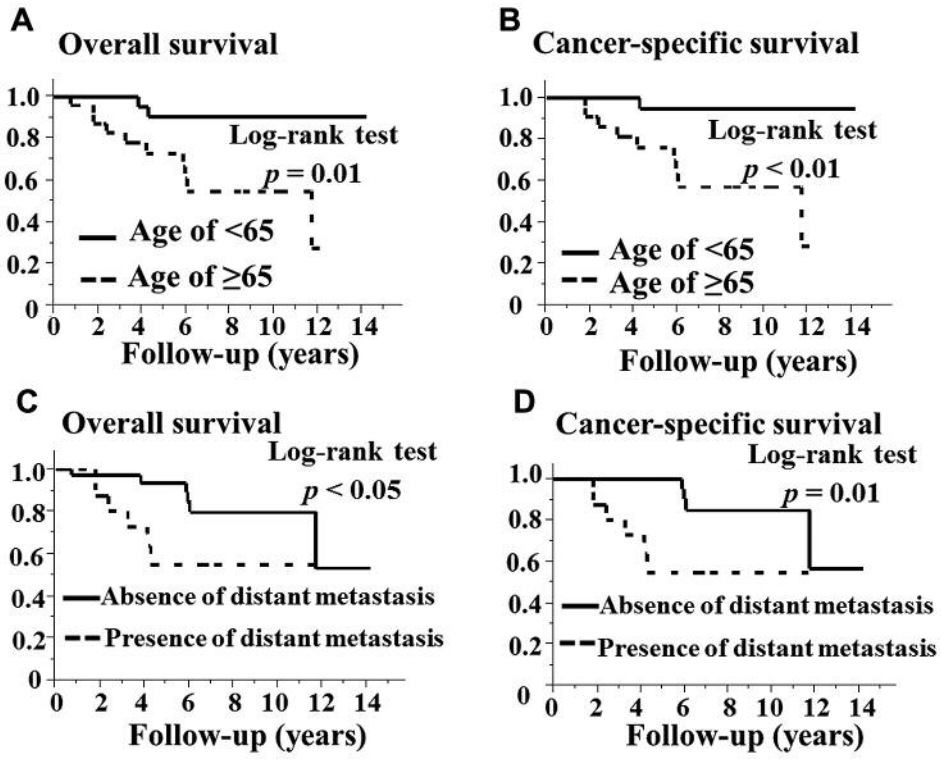

Figure 3. *Kaplan-Meier curves for the cumulative probability of overall survival (OS) and cancer-specific survival (CSS) among 54 patients with recurrence differentiated thyroid carcinoma using the log-rank test. Patients ≥65 years old at salvage surgery exhibited significantly poorer (A) OS (p=0.01) and (B) CSS (p<0.01) than those <65 years old. Similarly, patients with the presence of distant metastasis exhibited significantly poorer (C) OS (p<0.05) and (D) CSS (p=0.01) than those without distant metastasis.*

Table IV. *Multivariate analysis in 54 patients with differentiated thyroid carcinoma.*

Factor	Overall survival			Cancer-specific survival		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (≥65/<65)	7.37	1.91-48.5	<0.01	14.9	2.70-280.2	<0.01
Distant metastasis (Presence/Absence)	3.76	1.14-12.5	0.03	6.54	1.76-28.3	0.01

HR: Hazards ratio, 95%CI: 95% confidence interval.

patients with papillary thyroid carcinoma who underwent 54,926 total thyroidectomy and 6,849 non-total thyroidectomy as initial treatment (14), while Patron *et al*. reported that distant metastasis after initial surgery was a significant predictor of death following univariate and multivariate analyses in 201 patients with N0M0 differentiated thyroid carcinoma (15). The findings of the present study showed a significant association between the presence of distant metastasis and shorter survival outcomes (OS and CSS), which are consistent with those presented in previous studies (14, 15).

Salvage surgery of local site for recurrence differentiated thyroid carcinoma, including completion thyroidectomy for lymph node and distant recurrence has been considered as a more aggressive and challenging treatment given its higher complication rates compared to initial surgery (3-6). Older age had also been reported as a predictor of survival outcomes, such as CSS, after recurrence differentiated thyroid carcinoma (5, 16). Accordingly, Uchida *et al*. reported that among 86 patients who underwent salvage surgery for local recurrence, those ≥45 years old at reoperation had shorter CSS than those <45 years old after univariate and multivariate analyses (5).

Moreover Ito *et al*. reported that among 105 patients with distant recurrence of papillary thyroid cancer, those <55 years old at recurrence had significantly longer CSS than those ≥55 years old (16). The findings of the present study showed that a significant association between older age and shorter survival outcomes, which are consisted with those reported in previous studies (5, 16). Moreover, given that the cutoff for continuous variable can be determined using the lowest *p*-value, median, and ROC analysis, we utilized ROC analysis, the most frequent and reasonable method, to calculate cutoff values as described a previous meta-analysis using continuous variables (17).

The results of the present study suggested that age ≥65 years and distant metastasis were adequate to identify patients with differentiated thyroid carcinoma who had shorter OS and CSS and needed close follow-up following salvage surgery of local site.

Amit *et al*. and our group reported that pathological restaging based on the UICC8th in differentiated thyroid carcinoma was a significant predictor of survival outcomes (7, 8). To the best of our knowledge, the association between survival outcomes and UICC8th restaging upon salvage surgery had not be fully investigated, which we believe, merits further study. Restaging of T and N classifications was not identified as significant of predictor for survival in the present study, which may have been attributed to the small sample size. The limitations of this study included its small sample and retrospective design. Therefore, prospective studies involving larger samples would yield more valuable results.

Moreover, predictors such as Mts1 up-regulation for cases with initial surgery in thyroid cancer had been researched immunohistochemically and radiologically (18-20), and we believe that detailed research for predictors of cases with salvage surgery will be needed in the future.

Conclusion

Univariate and multivariate survival analyses employed in the present study demonstrated that age ≥65 years and the presence of distant metastasis among patients who underwent salvage surgery of local site for recurrence differentiated thyroid carcinoma were significantly associated with shorter OS and CSS.

Conflicts of Interest

All Authors declared that they have no conflicts of interest in regard to this study.

Authors' Contributions

H.S. conceived, designed and performed the study; H.S., D.N., S.B., H.T., M. S., and N.H. recruited patients; H.S. contributed materials, statistical analysis, writing. All Authors state they significantly participated in the creation for the study, approved the final article.

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