Original Article

Clinical Outcome by AMES Risk Definition in Japanese Differentiated Thyroid Carcinoma Patients

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OBJECTIVE: This study aimed to analyse whether age, metastasis, extrathyroidal invasion and size (AMES) risk definition is valuable for Japanese patients with differentiated thyroid carcinoma (DTC).
METHODS: Two hundred and fifteen Japanese DTC patients (43 men, 172 women; mean age, 51.0 years; mean follow-up, 102 months) treated surgically at our institutions between 1981 and 2001 were retrospectively analysed. Clinicopathological features were compared between high-risk and low-risk patients by AMES criteria. Various risk factors were also evaluated for each group of patients.
RESULTS: There were 57 high-risk and 158 low-risk patients. Recurrence and mortality rates were 43.9% and 24.6% in high-risk patients and 7.6% and 0.6% in low-risk patients, respectively ($p < 0.0001$). Disease-specific survival rates at 5, 10 and 15 years were 84.3%, 74.0% and 63.5% in high-risk patients and 100%, 100% and 98.3% in low-risk patients, respectively ($p < 0.0001$). Univariate analysis revealed that curative resection, local recurrence and distant metastasis were risk factors for mortality in the high-risk group. Multivariate analysis revealed that curative resection (hazard ratio [HR], 4.68; 95% confidence interval [CI], 1.23–17.83; $p = 0.024$) and distant metastasis (HR, 4.79; 95% CI, 1.24–18.40; $p = 0.023$) were significantly related to mortality in high-risk patients.
CONCLUSION: AMES can identify high-risk and low-risk Japanese patients. Distant metastasis and curative resection are prognostic factors for disease-specific death. [*Asian J Surg* 2007;30(2):102–7]

Key Words: AMES, differentiated thyroid carcinoma, prognostic factor

Introduction

The age, metastasis, extrathyroidal invasion and size (AMES) criteria have been used to identify high-risk and low-risk patients with differentiated thyroid carcinoma (DTC).[1–10] The rates of recurrence are 28% in high-risk patients and 14–46% in low-risk patients, and those for mortality are 4–8% and 1–2.4%, respectively.[1,2,4–6] Long-term survival rates range from 47% to 94% in high-risk patients, as compared with 96–100% in low-risk patients.[6,9,10] Various prognostic factors have been proposed for patients with DTC.[2–7, 9–18] The extent of thyroidectomy and lymph node dissection (LND) has been the major source of controversy. Other adjuvant therapies after surgery such as radioactive iodine (RI) therapy, extra beam radiation therapy (EBRT), and thyroid-stimulating hormone (TSH) suppression also remains controversial.

The aim of this study was to analyse whether AMES risk definition is valuable for Japanese DTC patients. Moreover, whether high-risk patients have prognostic factors was investigated. In Japan, RI ablation has been less frequently performed in clinical practice because RI treatment is

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restricted and can only be performed at a limited number of hospitals. Therefore, total or near total thyroidectomy followed by RI ablation is infrequent. We describe our experience with the AMES criteria for risk assessment in patients who underwent surgery for DTC and evaluated the prognostic factors related to recurrence or disease mortality.

Patients and methods

Clinical outcomes were retrospectively evaluated in 215 patients with DTC (43 men, 172 women; mean age, 51.0 years; mean follow-up, 102 months) treated surgically at Yokohama City University Hospital and Medical Center between 1981 and 2001. Patients were divided into high-risk and low-risk groups according to the AMES risk criteria,[1] as shown in Table 1, and the clinicopathological features were compared between the two groups. AMES risk definition has particularly been used in our clinical practice because the criteria are extremely straightforward. The clinicopathological features compared were age, gender, primary tumour size, pathology, extent of surgery, node dissection, lymph node metastasis (LNM), TSH suppression therapy, radiotherapies (RI and EBRT), recurrence, disease mortality and survival rates, as shown in Table 2. These features were also compared between patients with and without recurrence or disease-specific death according to risk group. In addition, prognostic factors for disease mortality in the high-risk group were evaluated in univariate and multivariate analyses. Curative resection in this study was defined as complete removal of tumour both macroscopically and microscopically regardless of the extent of surgery. Patients who underwent less total thyroidectomy were included in the curative resection group when there was no evidence of residual tumour after surgery. Node dissection in this study was therapeutic or prophylactic modified neck dissection (MND). Ipsilateral MND was node dissection in both central (pretracheal and paratracheal) compartment and ipsilateral lateral compartment. The frequency of LNM was defined as the number of patients with LNM including pathologically identified positive node divided by total number of patients.

Statistical analysis

Statistical analysis was performed with the use of Student's *t* test or the Mann–Whitney test, as appropriate. Frequencies were compared with the χ^2 test and Fisher's exact probability test. Disease-specific survival curves were assessed with the Kaplan–Meier method and compared with the use of the log-rank test. Univariate and multivariate analyses were used to evaluate the impact of prognostic factors on outcome. Multivariate regression analysis was performed with the use of a Cox proportional-hazards model on factors found to be significant in univariate analysis. Hazard ratios (HR) (95% confidence interval [CI]) were calculated for significant prognostic factors. Differences were considered statistically significant when p values were < 0.05. Statistical analyses were performed with StatView-J, version 5.0 (SAS Institute Inc., Cary, NC, USA).

Table 1. High-risk and low-risk patients according to the age, metastasis, extrathyroidal invasion and size (AMES) risk criteria

High-risk group ($n = 57$)	
Younger patients (men ≤ 40, women ≤ 50)	2 (3.5%)
PTC with distant metastasis	2
Older patients (men > 40, women > 50)	55 (96.5%)
PTC with	
(a) Extrathyroid invasion	42
(b) Distant metastasis	2
(c) Primary tumour (≥ 5 cm)	
(a) and (b)	4
(a) and (c)	2
(a), (b) and (c)	1
FTC with	
(a) Wide invasion	2
(b) Distant metastasis	
(c) Primary tumour (≥ 5 cm)	
(a) and (b)	1
(a) and (c)	1
Low-risk group ($n = 158$)	
Younger patients (men ≤ 40, women ≤ 50)	81 (51.3%)
without distant metastasis	
PTC	74
FTC	7
Older patients (men > 40, women > 50)	77 (48.7%)
primary tumour (< 5 cm) without distant metastasis	
PTC without extrathyroid invasion	72
FTC with minimal invasion	5

PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma.

Results

Patient characteristics and clinicopathological data are summarized in Table 2. There were 57 (26.5%) high-risk and 158 (73.5%) low-risk patients. The high-risk group had 53 papillary thyroid carcinomas (PTCs) and four follicular

Table 2. Patient characteristics and clinicopathological data

	High-risk group ($n = 57$)	Low-risk group ($n = 158$)	p
Mean age (yr)	59.3	48.0	$p < 0.0001$
Gender (M:F)	12:45	31:127	NS
Mean size (cm)	3.9	2.2	$p < 0.0001$
Pathology			
Papillary	53 (93.0%)	146 (92.4%)	NS
Follicular	4 (7.0%)	12 (7.6%)	NS
Extent of surgery			
Lobectomy	28 (49.1%)	100 (63.3%)	NS
Subtotal/total	29 (50.9%)	58 (36.7%)	NS
Node dissection	47 (82.5%)	93 (58.9%)	$p = 0.0012$
LNM	36/47 (76.6%)	67/93 (72.0%)	NS
TSH suppression	55 (96.5%)	89 (56.3%)	$p < 0.0001$
Radiotherapy	8 (14.0%)	3 (1.9%)	$p = 0.0014$
RI	5 (8.8%)	2 (1.3%)	$p = 0.0152$
EBRT	3 (5.3%)	1 (0.6%)	NS
Recurrence	25 (43.9%)	12 (7.6%)	$p < 0.0001$
Local	8	6	
Distant	9	4	
Local + distant	8	2	
Mortality rate	14 (24.6%)	1 (0.6%)	$p < 0.0001$
Survival rates			
5 yr	84.3%	100.0%	$p < 0.0001$
10 yr	74.0%	100.0%	
15 yr	63.5%	98.3%	

LNM was analysed in 47 (82.5%) high-risk and 93 (58.9%) low-risk patients who underwent systematic LND (ipsilateral or bilateral MND). NS = not significant; LNM = lymph node metastasis; TSH = thyroid-stimulating hormone; RI = radioiodine; EBRT = extra beam radiation therapy.

thyroid carcinomas (FTCs), and the low-risk group had 146 PTCs and 12 FTCs. Subtotal or total thyroidectomy was performed in 50.9% of the high-risk patients and 36.7% of the low-risk patients. Systematic LND was done in 47 (82.5%) high-risk patients and 93 (58.9%) low-risk patients. The level of TSH was sufficient for suppression therapy in 55 (96.5%) high-risk patients and 89 (56.3%) low-risk patients. RI therapy and EBRT were performed in five (8.8%) and three (5.3%) high-risk patients and in two (1.3%) and one (0.6%) low-risk patients, respectively.

Recurrence occurred in 43.9% of high-risk patients and 7.6% of low-risk patients ($p < 0.0001$). Mortality rates were 24.6% (14/57) in the high-risk group and 0.6% (1/158) in the low-risk group ($p < 0.0001$). Kaplan–Meier curves of disease-specific survival significantly differed between the two groups ($p < 0.0001$), as shown in Figure A. Survival rates at 5, 10 and 15 years were 84.3%, 74.0% and 63.5% in the high-risk group and 100%, 100% and 98.3% in the low-risk group, respectively.

Table 3 compares the clinicopathological features of patients with and without recurrence or disease-specific death in high-risk patients. Gender and curative resection were significantly related to recurrence. Subtotal or total thyroidectomy was performed more in a higher proportion of high-risk patients with recurrence than in those without recurrence. Pathology and TSH suppression therapy had no influence on clinical outcome. Radiotherapy could not be evaluated concerning the relation to recurrence or disease mortality in high-risk patients because only a small number of patients received RI therapy, EBRT, or both.

As shown in Tables 3 and 4, and Figures B, C and D, univariate analysis and Kaplan–Meier survival curves

Table 3. Univariate risk factor analysis of recurrence or disease-specific death in AMES high-risk patients ($n = 57$)

	Recurrence			Disease-specific death		
	(+) (n = 25)	(−) (n = 32)	p	(+) (n = 14)	(−) (n = 43)	p
Mean age (yr)	61.0	57.8	NS	62.9	58.0	NS
Gender (M:F)	9:16	3:29	0.014	3:11	9:34	NS
Mean size (cm)	4.2	3.5	NS	4.3	3.7	NS
Extent of surgery			0.033			NS
Lobectomy	8 (32.0%)	20 (62.5%)		5 (35.7%)	23 (53.5%)	
Subtotal/total	17 (68.0%)	12 (37.5%)		9 (64.3%)	20 (46.5%)	
LNM	17/19 (89.5%)	19/28 (67.9%)	NS	9/10 (90.0%)	27/37 (73.0%)	NS
Curative resection	18 (72.0%)	31 (96.9%)	< 0.001	8 (57.1%)	41 (95.3%)	0.0017
Local recurrence			NA	8 (57.1%)	8 (18.6%)	0.0143
Distant metastasis			NA	10 (71.4%)	7 (16.3%)	0.0003

LNM = lymph node metastasis; NS = not significant.

Table 4. Risk factor analysis of disease-specific death in AMES high-risk patients ($n = 57$)

	Survival curves (Kaplan–Meier)		Multivariate analysis	
	p	HR	95% CI	p
Curative resection	< 0.0001	4.68	1.23–17.83	0.024
Local recurrence	= 0.0110	2.2	0.70–6.92	0.178
Distant metastasis	< 0.0001	4.79	1.24–18.40	0.023

HR = hazard ratio; CI = confidence interval.

showed that curative resection, local recurrence, and distant metastasis were significantly related to disease mortality in high-risk patients. Multivariate analysis showed that curative resection (HR, 4.68; 95% CI, 1.23–17.83; $p = 0.024$) and distant metastasis (HR, 4.79; 95% CI, 1.24–18.40; $p = 0.023$) had statistical significance.

Discussion

AMES risk definition has identified high-risk and low-risk patients with DTC.[1–10] Our study also revealed significant differences between the two groups. In previous studies (including our results), rates of recurrence and mortality have ranged from 28% to 44% and 14–46% in high-risk patients, as compared with 4–8% and 0.6–2.4% in low-risk patients.[1,2,4–6]

Various risk factors have been studied in DTC patients.[2–7,9–18] Age and tumour size had no impact on outcome in our high-risk patients. Male gender was statistically associated with recurrence. Node dissection and TSH suppression were more commonly performed in high-risk patients than in low-risk patients; however, we could not find any significant impact on the clinical results.

Curative resection and distant metastasis were significantly related to disease-specific death in high-risk patients, consistent with the results of previous investigations.[2] In this study, curative resection was less frequently performed in high-risk patients who developed recurrence or death from disease than in those who did not (72.0% *vs.* 96.9% for recurrence, 57.1% *vs.* 95.3% for death). Multivariate analysis revealed that curative resection (HR, 4.68; 95% CI, 1.23–17.83; $p = 0.024$) and distant metastasis (HR, 4.79; 95% CI, 1.24–18.40; $p = 0.023$) were risk factors for disease mortality in high-risk patients. Thus, high-risk patients likely to have poor prognosis can be predicted by risk factor analysis and then assigned appropriate treatment

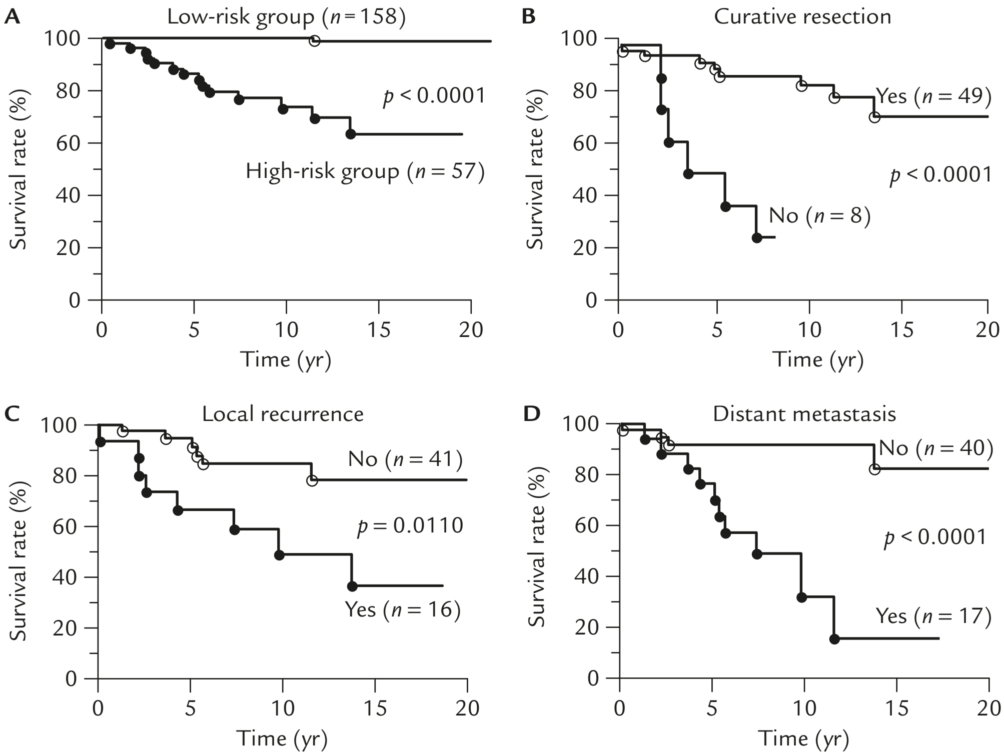

Figure. (A) Kaplan–Meier curves of disease-specific survival for AMES high-risk ($n = 57$) and low-risk ($n = 158$) patients. (B–D) Kaplan–Meier curves of disease-specific survival for AMES high-risk patients ($n = 57$) according to three prognostic factors (curative resection, local recurrence and distant metastasis) indicated in univariate analysis.

strategies. In particular, curative resection is a more important risk factor that can be evaluated at the time of surgery. Local recurrence and distant metastasis are risk factors that have usually been found in the follow-up period. Therefore, complete resection is considered essential to prevent adverse prognosis when primary cancers present with extrathyroidal invasion to adjacent neck structures. To the contrary, we could not find any risk factors for low-risk patients.

There has been an unusual dilemma pertaining to RI treatment. Radiotherapy (RI therapy, EBRT or both) contribute to improved survival in patients who undergo incomplete resection.[2] RI therapy for distant metastasis is also considered to decrease disease mortality.[2,13,17,18] We reviewed our experience without RI ablation as adjuvant therapy because of the different background to use radioiodine. In Japan, RI treatment is restricted and can be performed at a limited number of hospitals only. RI ablation is therefore not routinely performed after initial surgery. Japanese patients usually receive RI therapy when distant metastasis is visually detected on chest X-ray or computed tomography. In this study, only 8.8% of high-risk patients received therapeutic RI treatment. We therefore cannot delineate the effect of RI treatment on our clinical outcomes. Our results showed relatively high recurrence and mortality rates but this may be due to selection bias in patients referred to us because our institution has contributed as a tertiary teaching hospital. Moreover, poor clinical outcomes are likely to be attributed to the less frequent application of RI treatment. We consider that more frequent use of RI may improve the outcome in our high-risk patients. This issue needs to be considered in our present and future practice.

In conclusion, AMES risk definition can distinguish high-risk patients from low-risk patients. Our findings suggest that the curability of primary tumour resection and distant metastasis are significantly associated with disease mortality. We conclude that AMES is valuable for Japanese patients with DTC and both curative resection and distant metastasis are prognostic factors for death from disease in AMES high-risk patients.

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