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Comparison of prognostic scoring systems in follicular thyroid cancer

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ABSTRACT

INTRODUCTION Many studies have addressed the accuracy of prognostic scoring systems in the treatment of differentiated thyroid cancers as a whole but few have addressed this issue in patients with follicular thyroid cancer (FTC) alone. The aim of this study was to establish the accuracy of the various scoring systems in determining the overall and disease free survival of FTC patients in Singapore.

METHODS Retrospective review was undertaken of 82 patients with FTC treated at a single tertiary institution between January 2000 and December 2014. Demographic, clinical, pathological and treatment outcomes were analysed. Prognostic scoring systems evaluated for the cohort included TNM (Tumour, Nodes, Metastases), AGES (Age, Grade, Extent, Size), MACIS (Metastases, Age, Completeness of resection, Invasion, Size), AMES (Age, Metastases, Extent, Sex) and EORTC (European Organisation for Research and Treatment of Cancer). Statistical analysis was performed by plotting Kaplan–Meier survival curves and using the Cox proportional hazards model.

RESULTS There were 29 male and 53 female patients with a mean age of 48 years. The mean follow-up duration was 88 months and there were 7 deaths (9%). The ten-year overall survival rate was 90%. Factors predictive of survival on univariate analysis were age, size of tumour, invasiveness, completeness of resection, metastasis, external beam radiotherapy, and risk scores using the AGES and MACIS scoring systems ($p<0.05$). On multivariate analysis, AGES and MACIS provided the best prognostic information.

CONCLUSIONS MACIS is the best prognostic scoring system currently available for FTC and it is superior to other scoring systems in term of guiding management. The scoring systems require further development to accommodate variations in clinical practice globally and to improve the prognostic accuracy.

KEYWORDS
Follicular – Thyroid – Cancer – Staging

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Follicular thyroid cancer (FTC) is the second most common form of thyroid cancer and accounts for about 10–15% of differentiated thyroid cancers.[1] The incidence of FTC has remained stable worldwide.[2] Nevertheless, in regions where iodine deficiency is endemic, the incidence is around 40%[3] and in Singapore it accounts for a fifth of well differentiated thyroid carcinomas. It is considered a more aggressive disease with poorer prognosis owing to its propensity for vascular invasion and distant metastases at initial presentation.[4,5]

The importance of prognostication as a determinant of treatment has been demonstrated in numerous articles, and scoring systems have been developed by a number of institutions and validated for use with thyroid cancers. These include the TNM (Tumour, Nodes, Metastases),[6] AGES (Age, Grade, Extent, Size),[7] MACIS (Metastases, Age, Completeness of resection, Invasion, Size),[8] AMES (Age, Metastases, Extent, Size)[9] and EORTC (European Organisation for Research and Treatment of Cancer)[10] systems. Other prognostic factors often used are age at time of diagnosis, sex, size of tumour, isthmic invasion, vascular invasion, capsular invasion, recurrence after treatment and use of postoperative radioactive iodine therapy.[11] However, these indices have been developed in heterogeneous groups of thyroid cancer patients or solely for those with papillary thyroid cancer (PTC) and the specific prognostic factors for FTC have not yet been validated.

A limited number of studies have been carried out on the accuracy of prognostic scoring systems in FTC, with results varying widely.[11–13] To date, no study of this nature has been attempted in the local setting. The aim of our study was to establish whether commonly described prognostic factors and scoring systems were significant predictors of overall survival of FTC patients in Singapore.

Methods

This was a retrospective cohort study of patients diagnosed with FTC at a tertiary referral hospital between January 2000 and December 2014. The inclusion criteria comprised histopathological diagnosis of follicular carcinoma, follow-

up duration of at least five years (except patients who died of the disease) and complete surgical treatment. Exclusion criteria were distant metastasis at presentation, concomitant cancers and non-follicular or Hürthle cell thyroid cancers.

Clinical, demographic and epidemiological data were gathered from electronic medical records as well as hard copy case notes. The demographic data included sex and age at diagnosis, operative details (type of operation and date of completion thyroidectomy), histopathological features (size of tumour, local invasion, vascular invasion, capsular invasion and whether the tumour was widely or minimally invasive), postoperative status (use of adjuvant radioactive iodine therapy), and presence and site of recurrence as well as subsequent treatment.

The prognostic scoring systems studied comprised TNM, AGES, MACIS, AMES and EORTC. Table 1 shows the formulas used to calculate the various scores as well as the risk stratification for the different scoring systems.

Statistical analysis

Data were analysed using SPSS® version 21.0 (IBM, New York, US). Univariate analysis was performed using Kaplan–Meier survival curves, significance testing using a logrank test and multivariate analysis using the Cox proportional hazards model. A p-value of <0.05 was considered statistically significant.

Cox proportional hazards analysis was employed to determine the proportion of variation in survival time explained

Table 1 The various prognostic scoring systems and risk stratification used in the study

Scoring system	Formula	Risk stratification
TNM	T0 = no tumour detected T1 = intrathyroidal tumour <1cm T2 = intrathyroidal tumour 1–4cm T3 = intrathyroidal tumour >4cm T4 = locally invasive tumour of any size T4a = moderately advanced T4b = very advanced N0 = no regional lymph node involvement N1 = regional lymph node metastasis N1a = metastasis to level VI nodes N1b = metastasis to all other cervical nodes M0 = no distant metastasis M1 = distant metastasis	5-year survival Stage I <45 years: any T, any N, M0 = 100% Stage I ≥45 years: T1, N0, M0 = 100% Stage II <45 years: any T, any N, M1 = 100% Stage II >45 years: T2, N0, M0 = 100% Stage III: T3, N0, M0 or T1–3, N1a, M0 = 71% Stage IVA: T1–3, N1b, M0 or T4a, any N, M0 = 50% Stage IVB: T4b, any N, M0 = 50% Stage IVC: any T, any N, M1 = 50%
AGES	0.05 x age in years (if age is ≥40 years) or +0 (if age is <40 years) +1 if tumour is grade 2 +3 if tumour is grade 3 or 4 +3 if distant metastases +0.2 x tumour size in cm	20-year survival ≤3.99 = 99% 4–4.99 = 80% 5–5.99 = 67% ≥6 = 13%
MACIS	3.1 (if age <40 years) or 0.08 x age in years (if age ≥40 years) +0.3 x tumour size in cm +1 if incompletely resected +1 if locally invasive +3 if distant metastases	20-year survival <6 = 99% 6–6.99 = 89% 7–7.99 = 56% ≥8 = 24%
AMES	Low risk: Men ≤40 years or women ≤50 years with no metastases, or older patients with intrathyroidal lesions, minor capsular invasion, tumour size <5cm and no distant metastases High risk: All patients with distant metastases, extrathyroidal lesions or major capsular invasion, or tumour size ≥5cm in older patients	20-year survival Low risk = 99% High risk = 61%
EORTC	+12 if male, +10 if follicular lesion is poorly differentiated, +10 if ≥T3, +15 if there is one distant metastasis, +15 for each additional metastasis	5-year survival <50 = 95% 50–65 = 80% 66–83 = 51% 84–108 = 33% >108 = 5%

AGES = Age, Grade, Extent, Size; AMES = Age, Metastases, Extent, Sex; EORTC = European Organisation for Research and Treatment of Cancer; TNM = Tumour, Nodes, Metastases; MACIS = Metastases, Age, Completeness of resection, Invasion, Size

Table 2 Baseline characteristics of follicular thyroid cancer patients (n=82)

Characteristic	Number of patients
Mean age in years	47.9 (SD: 18.9, range: 13–89)
Female sex	53 (65%)
Type of surgery	
Hemithyroidectomy with completion	57 (70%)
Total thyroidectomy	25 (30%)
Pathological details	
Mean tumour size in cm	3.79 (SD: 2.01)
Gross invasion	37 (45%)
Vascular invasion	54 (66%)
Capsular invasion	70 (85%)
Completeness of resection	76 (93%)
Postoperative details	
Adjuvant radioactive iodine	52 (63%)
Recurrence	11 (13%)
External beam radiotherapy	3 (4%)
Distant metastasis	20 (24%)
Mean follow-up duration in months	88.2 (SD: 46.5)
Deaths	7 (9%)
TNM	
I	7(9%)
II	7 (9%)
III	66 (80%)
IV	2 (2%)
AGES	
≤3.99	42 (51%)
4–4.99	15 (18%)
5–5.99	6 (7%)
≥6	19 (24%)
MACIS	
<6	40 (49%)
6–6.99	12 (15%)
7–7.99	6 (7%)
≥8	24 (29%)
AMES	
Low risk	17 (21%)
High risk	65 (79%)
EORTC	
<50	24 (30%)
50–65	17 (20%)
66–83	20 (24%)
84–108	20 (24%)
>108	1 (1%)

AGES = Age, Grade, Extent, Size; AMES = Age, Metastases, Extent, Sex; EORTC = European Organisation for Research and Treatment of Cancer; TNM = Tumour, Nodes, Metastases; MACIS = Metastases, Age, Completeness of resection, Invasion, Size; SD = standard deviation

(PVE), which calculates the relative importance of each staging system.[14] PVE can range from 0% to 100%, with higher numbers indicating better cancer specific survival predictability.

Results

There were 29 male and 43 female patients with a mean age of 47.9 years (standard deviation: 18.9 years, range: 13–86 years). Total thyroidectomy was performed in 25 cases (30%) as the first operation and lobectomy followed by completion thyroidectomy in 57 (70%). The mean follow-up duration was 88 months and 7 patients (8.5%) died during the study period. Adjuvant radioiodine ablation was administered in 52 cases (63%) and external beam radiotherapy in 3 (4%). Disease progression was seen in six individuals (7%). The baseline characteristics of the study population are summarised in Table 2.

The results of the Kaplan–Meier analysis are shown in Table 3. On univariate analysis, gross invasion, extrathyroidal extension, capsular invasion and completeness of resection correlated with poor survival. Following surgical excision, factors that correlated with poor prognosis included adjuvant radioiodine ablation, external beam radiotherapy, metastasis and recurrence. Of the various scoring systems, AGES and MACIS correlated with a poorer overall survival. The overall survival rates at five and ten years for the whole cohort were 91% and 90% respectively. The Kaplan–Meier survival curves for the different risk groups of the various scoring systems are illustrated in Figure 1.

Table 3 Univariate analysis of prognostic factors for overall survival

Prognostic factor	χ^2	p-value
Age	45.310	0.159
Sex	0.044	0.663
Pathological details		
Tumour size	3.710	0.354
Gross invasion	1.147	**0.024**
Extrathyroidal extension	0.310	**0.048**
Vascular invasion	0.064	0.617
Capsular invasion	0.617	**0.027**
Completeness of resection	0.970	**0.009**
Postoperative details		
Adjuvant radioactive iodine	1.066	**0.036**
Metastasis	4.404	**0.009**
Recurrence	0.348	**0.024**
External beam radiotherapy	0.476	**0.009**
Scoring systems		
TNM	1.855	0.315
AGES	11.638	**0.001**
MACIS	13.693	**0.009**
AMES	0.360	0.161
EORTC	3.587	0.121

AGES = Age, Grade, Extent, Size; AMES = Age, Metastases, Extent, Sex; EORTC = European Organisation for Research and Treatment of Cancer; TNM = Tumour, Nodes, Metastases; MACIS = Metastases, Age, Completeness of resection, Invasion, Size

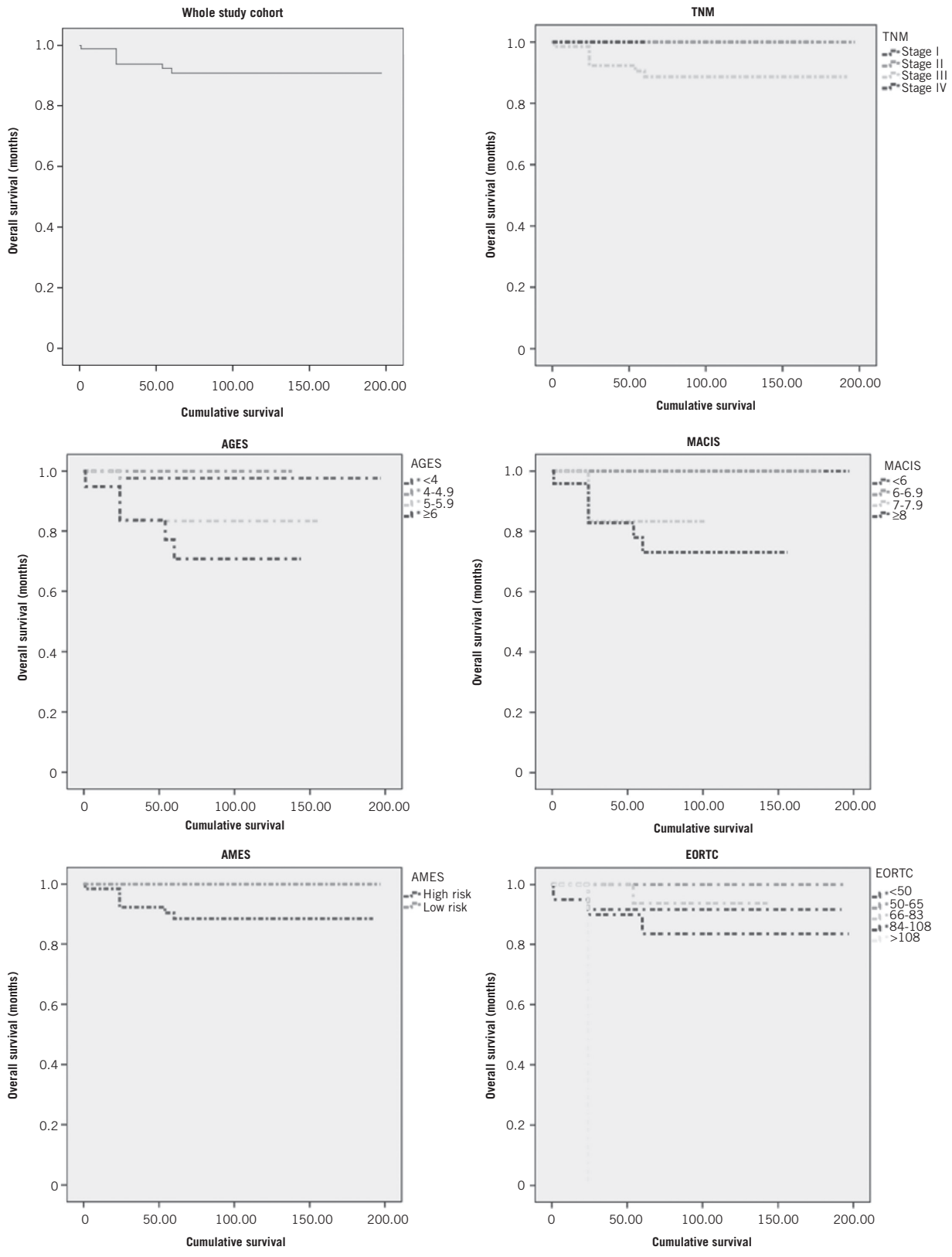

Figure 1 Kaplan–Meier survival curves

Table 4 Multivariate analysis of prognostic factors for overall survival

Prognostic factor	χ^2	*p*-value
Type of surgery	3.357	**0.030**
Pathological details		
Gross invasion	4.681	**0.030**
Extrathyroidal extension	0.310	**0.048**
Capsular invasion	0.617	**0.027**
Completeness of resection	0.970	**0.009**
Postoperative details		
Adjuvant radioactive iodine	1.066	**0.044**
Metastasis	4.404	**0.009**
Recurrence	0.348	**0.038**
External beam radiotherapy	0.476	**0.001**
Scoring systems		
TNM	1.021	0.635
AGES	11.090	**0.008**
MACIS	14.766	**0.003**
AMES	2.002	0.170
EORTC	2.455	0.113

AGES = Age, Grade, Extent, Size; AMES = Age, Metastases, Extent, Sex; EORTC = European Organisation for Research and Treatment of Cancer; TNM = Tumour, Nodes, Metastases; MACIS = Metastases, Age, Completeness of resection, Invasion, Size

Table 5 Comparison of the various prognostic scoring systems

Scoring system	Number of patients	Deaths	Logrank statistic	G^2/n	PVE	Rank
TNM	82	7 (8.5%)	1.021	0.012	1.19	5
I	33	0 (0%)				
II	12	0 (0%)				
III	28	5 (17.8%)				
IV	9	2 (22.2%)				
AGES	82	7 (8.5%)	11.090	1.499	77.66	2
≤3.99	42	1 (2.4%)				
4–4.99	15	0 (0%)				
5–5.99	6	1 (16.6%)				
≥6	19	5 (26.3%)				
MACIS	82	7 (8.5%)	14.776	2.658	92.99	1
<6	40	0 (0%)				
6–6.99	12	0 (0%)				
7–7.99	6	1 (16.6%)				
≥8	24	6 (25.0%)				
AMES	82	7 (8.5%)	2.002	0.048	4.76	4
Low risk	17	0 (0%)				
High risk	65	7 (10.8%)				
EORTC	82	7 (8.5%)	2.455	0.073	7.03	3
<50	27	2 (8.3%)				
50–65	17	0 (0%)				
66–83	20	1 (5.0%)				
84–108	20	3 (15.0%)				
>108	1	1 (100%)				

AGES = Age, Grade, Extent, Size; AMES = Age, Metastases, Extent, Sex; EORTC = European Organisation for Research and Treatment of Cancer; TNM = Tumour, Nodes, Metastases; MACIS = Metastases, Age, Completeness of resection, Invasion, Size; PVE = proportion of variation in survival time explained

The results of the Cox proportional hazards analysis are shown in Table 4. Of the scoring systems, only AGES and MACIS were good predictors of survival. On comparison of the systems using PVE, MACIS was the most accurate scoring system, followed by AGES, EORTC, AMES and TNM (Table 5).

Discussion

FTC is the second most common differentiated thyroid cancer; it has a more aggressive biological behaviour than PTC.[15] Despite this, the majority of studies on prognostication have included a combination of PTC and FTC cases. As such, their results reflect the prognostic factors associated with PTC rather than FTC.[16] There are only a handful of studies that have looked purely at prognostic scoring in FTC, with varied results.[11,13] In the local setting, prognostic scoring has not been well characterised.

The ten-year overall survival rate among our patients was 90%. Factors that have been described as predictors of survival are age,[17] tumour size,[18] vascular invasion,[13,17] tumour invasiveness[19] and distant metastasis.[17,20,21] In our cohort, aside from these factors, completeness of resection, recurrence and external beam radiotherapy were also prognostic for survival.

A study in Egypt arrived at a similar overall survival rate of 89% for patients with FTC[22] and this is comparable with studies in other regions. Our study spanned a total of 14 years, the mean follow-up duration being 88 months. This corresponds with the lengthy follow-up period in numerous studies on FTC conducted in Italy (104 months),[23] Brazil (113 months)[15] and Slovenia (117 months).[24] Our sample size and demographics also correlated well with studies on FTC in populations worldwide, such as in California and Italy.[13,23]

Various prognostic systems have been designed to identify high risk patients who require more aggressive treatment to reduce morbidity and mortality.[25] These include the TNM,[6] AGES,[7] MACIS,[8] AMES[9] and EORTC[10] scoring systems. In our study, MACIS was the most accurate prognostic system once PVE had been determined, followed by AGES, EORTC, AMES and TNM.

The MACIS system was developed to predict survival in papillary thyroid cancer following evaluation in 1,779 patients over a 50-year period.[8] MACIS has been shown to have the best predictice value in papillary thyroid cancer;[8,26,27] the results are similar in FTC.[12,13] While TNM is the most widely accepted staging system,[11,12] it was found to be the least useful in terms of predictive survival in our cohort.

The predictive value of the various prognostic scoring systems seems to vary in different populations.[12,15,19] This inconcistency may be due to treatment bias from the different institutions, either in the surgical approach or in the use of adjuvant radioactive iodine therapy and external beam radiotherapy.[28] Each of the scoring systems was developed by different institutions using a specific database of their patient population. This could also explain why a single scoring system may not be applicable across the board.[28]

Study limitations

It is acknowledged that our study is limited owing to its retrospective nature. Furthermore, the relatively small sample size could limit the strength of any conclusions that can be drawn from the results.

Conclusions

Of the scoring systems studied, MACIS appears to be the most accurate prognostic system currently available for FTC. However, in order to best guide patient management, the scoring systems require further development to accommodate variations in clinical practice and improve the prognostic accuracy.

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