Are prognostic scoring systems of value in patients with follicular thyroid carcinoma?

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Abstract

Purpose: Most prognostic systems for differentiated carcinoma have been designed for papillary carcinoma.

Objective: To analyze the value of the existing prognostic systems for evaluating follicular carcinoma and to determine whether any of them have a better predictive effect.

Methods: A total of 66 follicular carcinomas were analyzed. The following prognostic systems were studied: EORTC, AGES, AMES, MACIS, TNM, and NTCTCS.

Results: The AGES and AMES systems did not demonstrate a good prognostic correlation. In the EORTC system, the rate of disease-free patients was 89% in group 1, 75% in group 2, 69% in group 3, and 0% in group 4. The MACIS system showed 83, 60, 67, and 0% of disease-free patients respectively. The TNM system showed 81, 71, 50, and 0% of disease-free patients respectively. Finally, the NTCTCS system demonstrated 100, 84, 53, and 0% of disease-free patients respectively. Cox’s regression analysis was used to calculate the proportion of variation in survival time explained (PVE). The prognostic classification system with the greatest survival prediction was EORTC at 67.64% of PVE, followed by TNM at 62.5% of PVE, and MACIS at 57.82% of PVE.

Conclusions: MACIS and TNM are good prognostic systems for evaluating follicular thyroid carcinoma, although the one with the most prognostic value was the EORTC system.

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Introduction

Differentiated carcinoma is the most common malignant thyroid tumor. Most studies analyze the different types of this carcinoma by treating them as a whole. However, prognosis of papillary carcinoma is different to that of follicular carcinoma (1, 2). In this way, although follicular carcinoma is less common (10–25% of differentiated carcinoma), it is more aggressive (3, 4, 5, 6).

Prognostic systems for evaluating differentiated carcinoma have generally been designed for large groups of well-differentiated thyroid carcinomas and have been criticized for not differentiating between the different subtypes of differentiated carcinoma, especially papillary and follicular carcinomas (3). Prognostic guides and scales often do not differentiate between papillary and follicular carcinomas but rather join them together (4, 5). As a consequence, and as papillary carcinoma is more prevalent, the prognostic parameters have a better level of predictability for papillary rather than follicular carcinomas (4, 5).

For this reason, specific studies in follicular carcinoma are needed to be able to determine the real value of different kinds of prognostic systems for differentiated thyroid carcinoma, because until now only a few have been carried out analyzing small series of patients and there are discrepancies between the results of one study and the others (7, 8, 9, 10).

The objective of this study was to analyze the value of the main existing prognostic scoring systems for differentiated carcinoma when applied to follicular carcinoma and to determine whether any of these systems has a better prognostic effect than the rest.

Subjects and methods

Patient selection criteria

An analysis was carried out in all the patients diagnosed with follicular thyroid carcinoma who were treated in our Endocrine Surgery Department between 1980 and 2005 (n = 97). The patients’ clinical situation was assessed until December 2010.

All the patients had to meet the following selection criteria:

i) Histological diagnosis of follicular thyroid carcinoma. Follicular variant of papillary thyroid carcinoma and Hürthle cell cancer were excluded.
A pathologist review of all the slides of the patients with diagnosed follicular carcinoma.

ii) Complete follow-up for at least 5 years, except in those patients who died before the 5 years elapsed.

iii) No disseminated disease at diagnosis (distant metastasis).

iv) Surgical resection of follicular carcinoma.

Patients studied

Clinical data A total of 66 patients were selected, having a mean age of $41 \pm 17$ years, and most were female ($85\%; n=56$). The most frequent reason for patients consulting was the appearance of a nodule in the neck ($44\%; n=29$) followed by an increase in the progressive size of a previous nodule ($20\%; n=13$).

On neck exploration, a thyroid nodule was palpated in $94\%$ of cases ($n=62$). Furthermore, adenopathies were palpated in three cases and multinodular goiter in two cases. With regard to symptoms, $5\%$ ($n=3$) had hyperthyroidism, $6\%$ ($n=4$) reported local pain, $6\%$ ($n=4$) had compressive symptoms, and $3\%$ ($n=2$) had dysphonia.

Surgical data Surgery was indicated in $88\%$ of cases ($n=54$) due to suspected malignancy, in $11\%$ ($n=7$) due to the goiter being very large, and in one case due to hyperthyroidism (Table 1). Total thyroidectomy was performed in $40$ cases ($61\%$), hemithyroidectomy in $24$ cases ($36\%$), and the Dunhill procedure in the remaining two cases (total hemithyroidectomy on one side of the tumor plus subtotal contralateral hemithyroidectomy). Lymph node dissection was carried out in $12$ patients ($18\%$) and $18$ patients were reoperated on in order to complete thyroidectomy. In the two cases in which the Dunhill procedure was used and in the six hemithyroidectomies, the thyroidectomy was not completed because the tumor was minimally invasive. During the postoperative period, there were four hypoparathyroidisms (one permanent) and four recurrent laryngeal nerve injuries (one permanent).

Thirty-one patients ($47\%$) underwent $^{131}$I radioiodine therapy with a mean dose of $130 \pm 40$ mCi (Table 1).

Histological data A histological analysis confirmed the presence of follicular carcinoma and, in $13$ cases ($20\%$), it was associated with multinodular goiter. The tumor was multicentric in four cases ($6\%$), there were positive adenopathies in two cases ($3\%$), and vascular invasion was found in $35$ cases ($53\%$). The tumor was minimally invasive (limited capsular and/or vascular invasion) in $39$ cases ($59\%$) and widely invasive in the remaining $27$ cases ($41\%$).

Definition of recurrence

The following were considered as cases of tumor recurrence:

i) Lesions located using physical exploration or imaging techniques, regardless of thyroglobulin levels, in which the cytological findings were suggestive of malignancy.

ii) Patients who had had total thyroidectomy, with thyroglobulin levels $>2$ ng/ml, with or without detection of the lesion on physical exploration or during explorations complementary to the imaging.

Prognostic systems studied

The following prognostic systems have been assessed:

i) The European Organization for Research and Treatment of Cancer (EORTC) system (11). This staging system is based on adding a series of values to the patient’s age (in years): $+12$ if the patient is male, $+10$ if the tumor is a poorly differentiated medullary or follicular carcinoma, $+45$ if it is an anaplastic carcinoma, $+10$ if there is tumor invasion in the thyroid capsule, $+15$ if there is one distant metastasis, and $+15$ if there are multiple metastases. Patients are divided into different prognostic groups depending on their scores: group 1, $<50$; group 2, $50–65$; group 3, $66–83$; group 4, $84–108$; and group 5, $\geq109$.

ii) The AGES (Age, tumor, Grade, Extent, Size) system (12). This system is obtained by adding together: $0.05 \times$ patient’s age if this is $<40$ years, $+0.2 \times$ the size of the primary tumor diameter in centimeters, $+1$ if it is an histological grade 2

| Table 1 | Treatment of patients with follicular carcinoma. |
|----------------|---------------------------------|---------------------------------|-----------------|
| Invasive        | Definitive thyroid surgery       | Lymph node dissection           | $^{131}$I therapy |
| Widely invasive | Total thyroidectomy ($n=27$)     | No ($n=15$)                     | Yes ($100$ mCi)  |
|                 |                                 | Yes ($n=12$ laterocervical lymph | Yes ($\geq100$ mCi) |
|                 |                                 | node dissection)                |                  |
| Minimally invasive | Total thyroidectomy ($n=39$)     | No                             | Yes ($n=4$; $100$ mCi)³ |
|                 |                                 |                                 | No ($n=27$)      |
|                 | Hemithyroidectomy ($n=6$)        | No                             | No               |
|                 | Dunhill procedure ($n=2$)        | No                             | No               |

³Tumor $>4$ cm.
tumor. +3 if it is a grade 3 or 4 tumor, +1 if there is extrathyroidal invasion, and +3 if there is distant metastasis. Risk groups are established using the following scores: group 1. \( \leq 3.99 \); group 2. 4–4.99; group 3. 5–5.99; and group 4. \( \geq 6 \).

### iii) The AMES (Age, distant Metastases, Extent, Size) staging system (13).

This is divided into two groups: low risk (i) females <51 years and males <41 years without any distant metastasis and (ii) elderly patients with tumors <5 cm with no extrathyroidal extension of the papillary carcinoma or minor capsular involvement in follicular cancer) and high risk (i) patients with distant metastasis and (ii) females \( \geq 51 \) years and males \( \geq 41 \) years with tumors \( \geq 5 \) cm or extrathyroidal extension if it is papillary carcinoma and major capsular invasion if it is follicular carcinoma).

### iv) The MACIS (Metastases, Age, Completeness of resection, Invasion, Size) staging system (14).

This is obtained by adding 3.1 if the patient is \( \leq 39 \) years or 0.08 \( \times \) age if the patient is \( >40 \) years, +0.3 \( \times \) tumor size in centimeters, +1 if it is not completely resectable, +1 if it is locally invasive, and +3 if it has distant metastasis. Patients are divided into four groups: group 1. <6; group 2. 6–6.99; group 3. 7–7.99; and group 4. \( \geq 8 \).

### v) The TNM staging system (12).

This system was carried out in the following way: stage I: age <45 years with any T and N, M0; or if the patient is \( \geq 45 \) years: T1, N0, M0; stage II: age <45 years: any T and N, M1; or if the patient is \( \geq 45 \) years: T2, N0, M0; stage III: age \( \geq 45 \) years: T3, N0, M0; or T1–T3, N1a, M0; and stage IV: age \( \geq 45 \) years: T1–T3, N1b, M0; T4a, N0–N1, M0; T4b, Any N, M0; Any T or N, M1. When T1 \( \leq 2 \) cm, T2 \( >2 \) and \( \leq 4 \) cm, T3 \( >4 \) cm, and T4 tumors with extrathyroidal extension (T4a affecting the subcortaneous area, larynx, trachea, esophagus, or the recurrent nerve; T4b affecting the prevertebral fascia, mediastinal vessels, or the carotid artery), N0, no adenopathies: N1, positive regional adenopathies (N1a, VI pretracheal and paratracheal level including the pre-laryngeal and delphian node; N1b, nodes in another unilateral, bilateral, or contralateral cervical or upper mediastinal region). M0, no distant metastasis; M1, distant metastasis.

### vi) The National Thyroid Cancer Treatment Cooperative Study Prognostic system (NTCTCS) (15).

This is based on age at diagnosis, tumor histology, size, intrathyroidal multilocality, extranodular invasion, metastasis, and tumor differentiation. The calculation of tumor staging for this classification system is shown in Table 2.

### Table 2 Calculation of tumor staging according to the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) system.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age &lt; 45 years</th>
<th>Age &gt; 45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>1–4</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Description of the primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopical multilocal</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Macroscopical multilocal or capsular</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>capsular macroscopic invasion</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Microscopic extranodular invasion</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Macroscopic extranodular invasion</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical adenopathies</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Extracervical lymph node</td>
<td>III</td>
<td>IV</td>
</tr>
</tbody>
</table>

### Statistical analysis

Descriptive statistical analysis was carried out on the characteristics of the carcinoma. For the bivariate analysis, survival curve analysis was carried out, applying the Breslow test. To the survival period the initial day of this period was the next day to the definitive diagnosis.

Cox’s proportional hazards analysis was used to determine the relative importance of each staging system by calculating the proportion of variation in survival time explained (PVE). PVE (%) ranges from 0 to 100 with large numbers suggesting better predictability for cancer-specific survivals. To determine PVE, a mathematical formula was used: \( \text{PVE} = 1 - \exp \left( -G^2/n \right) \), where \( G^2 \) is the maximum likelihood ratio that is determined by \( \chi^2 \) and Cox’s regression analyses. In all cases, differences were considered significant at \( P < 0.05 \).

### Results

#### Overall results

With a mean follow-up period of \( 99 \pm 38 \) months, there have been 25 cases of tumor recurrence (38%). In all cases, the initial suspicion of recurrence owed to the gradual increase in the thyroglobulin levels in the periodical tests. The recurrences were treated according to the localization and size of the recurrence. In most cases (20 lesions), the recurrences were cervical according to the iodine screening test but were negative according to imaging tests and were initially treated using radioactive \( ^{131} \)I. In the other five cases, surgery...
was carried out on the recurrent lesion in thyroid bed \((n=2)\) or cervical lateral adenopathies \((n=3)\). Two surgical interventions were needed in three patients during the evolution time. Two patients (3\%) have died due to the evolution of the disease, and currently, another two patients (3\%) have distant metastasis.

The mean disease-free interval was 154 ± 14 months. The rate of disease-free patients was 71\% at 5 years and 58\% at 10, 15, and 20 years. No cases of tumor recurrence were detected after 9 years of post-surgical evolution time.

**Assessment of the prognostic classification systems**

The EORTC prognostic classification system demonstrated a good correlation with disease recurrence to such an extent that at 5 years the rate of disease-free patients in group 1 was 89\%; in group 2; 75\%; in group 3, 69\%; and in group 4, 0\%. At 10 years, these percentages were 79, 60, 46, and 0\% respectively \((P=0.000; \text{Table 3})\). However, neither the AGES nor the AMES system demonstrated a good prognostic correlation, as shown in the Table 3.

The MACIS classification system proved to have a good prognostic correlation. In this way, the rate of disease-free patients at 5 years was 83, 60, 67, and 0\% according to the following groups: <6, 6–6.99, 7–7.99, or ≥ 8, and the rates at 10 years were 70, 38, 67, and 0\% respectively \((P=0.000)\).

The TNM classification system also had a good prognostic correlation with disease-free survival according to staging at 5 years of 81\% at stage I, 71\% at stage II, 50\% at stage III, and 0\% at stage IV, and at 10 years, the rates were 69, 54, 50, and 0\% respectively \((P=0.009)\).

Finally, the NTCTCS classification system demonstrated a significant prognostic correlation with 5-year rates of 100, 84, 53, and 0\% respectively and 10-year rates of 80, 71, 41, and 0\% \((P=0.017)\).

**Cox’s regression model and the PVE**

Using Cox’s regression analysis and the PVE calculation, the prognostic classification system with the greatest survival prediction was EORTC at 67.64\% of PVE, followed by TNM at 62.5\% of PVE, and MACIS at 57.82\% of PVE. The rest, as shown in Table 4, had a lower PVE.

**Discussion**

Follicular thyroid carcinoma is a relatively uncommon subtype of differentiated carcinoma \((16, 17, 18)\). Its lack of frequency has made it more difficult to study and evaluate compared to other subtypes of thyroid carcinoma.
The AGES system was created by the Mayo Clinic after carrying out a regression analysis of thyroid carcinomas, but only the papillary kind. In studies focusing more on follicular carcinoma, it has not been found to be the most useful; in fact, in our study, it was not found to be a good prognostic system in the bivariate analysis; although Emerik et al. (19) have reported that the AGES risk group stratification is a good predictor of recurrent disease and death in patients with follicular carcinoma.

In 1988, Cady and Rosai proposed a system that was similar to the AGES system but with modifications called the AMES system. This has been demonstrated as being among the most valid risk predictors for papillary cancer (42, 43). As the AMES criteria were developed with a combined group of papillary and follicular carcinomas, including Hürthle cell carcinoma, its value for just follicular carcinomas has been questioned (10). In our study, it has not been a good prognostic system, although Sander et al. (13) have demonstrated that in follicular carcinoma, taking away patients with just capsular invasion, AMES is a good predictor.

In 1993, and also focusing on papillary carcinoma, Hay et al. (14) created a new system called MACIS, also in the Mayo Clinic. For us, it has been a good prognostic scale for follicular carcinoma. For authors such as D’Avanzo et al. (9), the MACIS is the most predictive prognostic system.

However, it should not be forgotten that the pTNM classification system is the most widely used one internationally (44). In our series, it is a good prognostic system, although it was outperformed by the EORTC system. Gemsenjäger et al. (45), in a study on 84 papillary and 82 follicular carcinomas, also found it to be valuable as a prognostic system. Although it is not the most predictive system, it has the advantage of being internationally recognized making the comparison between series easier. More importantly, for several authors, it is actually the best prognostic system (7, 46). In this regard, Lo et al. (7), in an analysis of 156 follicular carcinomas using the AMES, TNM, Degroot, and MACIS systems, concluded that TNM was the best prognostic scale for follicular thyroid carcinoma. However, it must be said that all the predictive systems analyzed were useful.
As a final point, after a multicenter prospective study (14 centers) of more than 1600 thyroid carcinomas, the NTCTCS prognostic system was created (15). This system has not become as widely used as was initially intended, and in our series, it was a good prognostic system, although it did not outperform the EORTC, TNM, or MACIS systems. Moreover, some authors (47) have indicated that even for papillary carcinoma, this prognostic system has limitations, among them is the fact that stages I and II have practically no prognostic differences.

Based on these data, we can conclude that the MACIS and TNM systems are good prognostic scales for assessing follicular thyroid carcinoma, but the one with most prognostic value is the EORTC system. However, larger series are needed, possibly multicenter studies conducted by more powerful groups, to be able to reach more definitive conclusions given that the data obtained are very heterogeneous between individual centers. Perhaps a new scoring system, taking into account additional prognostic factors for follicular carcinoma, will need to be designed if we want to obtain greater prognostic precision.

Declaration of interest
The author ARíos and the co-authors have no conflicts of interest.

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