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 3 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 ± 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 131I radioiodine therapy with a mean dose of 130 ± 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, ≥ 109.

ii) The AGES (Age, tumor, Grade, Extent, Size) system (12). This system is obtained by adding together: 0.05 × patient’s age if this is < 40 years, +0.2 × 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.

<table>
<thead>
<tr>
<th>Invasive</th>
<th>Definitive thyroid surgery</th>
<th>Lymph node dissection</th>
<th>131I therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widely invasive (n=27)</td>
<td>Total thyroidectomy (n=27)</td>
<td>No (n=15)</td>
<td>Yes (100 mCi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes (n=12 laterocervical lymph node dissection)</td>
<td>Yes (≥ 100 mCi)</td>
</tr>
<tr>
<td>Minimally invasive (n=39)</td>
<td>Total thyroidectomy (n=31)</td>
<td>No</td>
<td>Yes (n=4; 100 mCi)³</td>
</tr>
<tr>
<td></td>
<td>Hemithyroidectomy (n=6)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dunhill procedure (n=2)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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, ≤3.99; group 2, 4–4.99; group 3, 5–5.99; and group 4, ≥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 ≥51 years and males ≥41 years with tumors ≥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 ≤39 years or 0.08×age if the patient is >40 years, +0.3×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, ≥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 ≥45 years: T1, N0, M0; stage II: age <45 years: any T and N, M1; or if the patient is ≥45 years: T2, N0, M0; stage III: age ≥45 years: T3, N0, M0; or T1–T3, N1a, M0; and stage IV: age ≥45 years: T1–T3, N1b, M0; T4a, N0–N1, M0; T4b, Any N, M0; Any T or N, M1. When T1 ≤2 cm, T2 >2 and ≤4 cm, T3 >4 cm, and T4 tumors with extrathyroidal extension (T4a affecting the subcutaneous 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 multilocaity, extranodular invasion, metastasis, and tumor differentiation. The calculation of tumor staging for this classification system is shown in Table 2.

<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>1</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>1–4</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>III</td>
</tr>
<tr>
<td>Description of the primary tumor</td>
<td>Microsopical multifocal</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Macroscopic multifocal or capsular macroscopic invasion</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Microscopic extranodular invasion</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Macroscopic extranodular invasion</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Cervical adenopathies</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Extracervical lymph node</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: PVE = 1 – exp (–G²/n), where G² is the maximum likelihood ratio that is determined by χ² and Cox’s regression analyses. In all cases, differences were considered significant if P <0.05.

**Results**

**Overall results**

With a mean follow-up period of 99 ± 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 ¹³¹I. 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 \(154 \pm 14\) 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 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 \(\geq 8\), 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...
often the results of papillary carcinoma have been extrapolated to follicular carcinoma (19, 20, 21). Very few studies have examined the risk factors affecting the prognosis of follicular carcinoma (19, 20, 21), and there is great variability between them. This could be a result of fewer patients in most studies, which means that small variations in the variables analyzed can lead to a prognostic factor being significant or not. As a general rule, the following prognostic factors have been reported for this type of carcinoma: age, tumor differentiation, vascular invasion, distant metastasis, nodular affectation, capsular invasion, and tumor extension (13, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37), although, as we have already mentioned, there is a great amount of variability between studies.

In differentiated thyroid carcinoma, many kinds of prognostic systems have been designed with the aim of differentiating low-risk patients who require less aggressive treatment from high-risk ones who need more aggressive treatment to avoid cancer-related morbidity and mortality. These scales have proven their values in papillary carcinoma, although in follicular carcinoma, they have not been sufficiently contrasted (38, 39). In this respect, D’Avanzo et al. (9) analyzed 86 follicular carcinomas comparing the TNM, EORTC, AGES, AMES, and MACIS prognostic systems and suggested that all were significant predictive systems, unlike in our systems where AGES and AMES were not good predictors. In their study (9), the MACIS system was found to be the most precise predictor (which in our study was the third best system after the EORTC and TNM systems), although the TNM, EORTC, AGES, and AMES systems were also found to be useful in that study. However, these findings are not consistent across the studies. For example, Davis et al. (10) from the British Columbia University of Canada analyzed 122 follicular carcinomas and compared the EORTC, AGES, and AMES systems, and concluded that EORTC and AGES were good prognostic systems. However, in our experience, AGES is not a good prognostic system.

If we analyze the different kinds of prognostic systems, we can see that the European Organization for Cancer Diagnosis and Treatment (EORTC) introduced its scale in 1979 based on the multivariate analysis of 507 patients with thyroid cancer after a 40-year follow-up period (11). Kerr et al. (40) applied this system in 441 patients with thyroid cancer and found that it had greater predictive value compared with the pTNM classification system. However, Tennval et al. (41), using the original patients of Byar et al. (11), adding a further 11 years of follow-up and only focusing on differentiated cancers, suggested that the EORTC system places too much emphasis on age, inappropriately mixing non-differentiated tumors with differentiated ones in the analysis, which is the reason why they consider it to be ineffective for clinical practice. In our study, the EORTC has proved to be the most useful system for the prognostic assessment of follicular 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 Hurthle 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.

| Table 4 Analysis of the proportion of variation in survival time explained (PVE). |
|-----------------|-------|----------|----------|
| Method | $G^2$ | PVE | %PVE |
| EORTC | 8.629 | 0.68 | 67.64 |
| TNM | 8.046 | 0.63 | 62.50 |
| MACIS | 7.548 | 0.58 | 57.82 |
| AGES | 7.528 | 0.58 | 57.63 |
| NTCTCS | 6.151 | 0.44 | 43.63 |
| AMES | 3.756 | 0.19 | 19.25 |
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 A Ríos and the co-authors have no conflicts of interest.

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