Endocrinol Nutr. 2011;**58(4):**157–162

ENDOCRINOLOGÍA Y NUTRICIÓN

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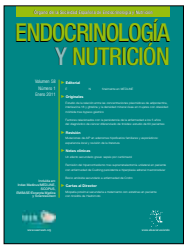

SPECIAL ARTICLE

Differentiated thyroid carcinoma: survival and prognostic factors

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Received 30 November 2010; accepted 25 January 2011

KEYWORDS
Differentiated thyroid carcinoma;
Survival;
Risk factors

Abstract
Background and aims: Differentiated thyroid carcinoma (DTC) is the most common endocrine tumor. DTC has a good prognosis and survival rates are higher than 85%. The aim of our study was to assess our current survival rate and to analyze prognostic factors.
Patients and methods: A retrospective study was conducted of 308 patients with DTC (93.5% with papillary tumors, 78.8% females). Mean age at diagnosis was 45.4 ± 15.8 years, and mean follow-up time was 8.9 ± 6.8 years. The whole group was treated and followed up using the same protocol at our hospital. The following data were collected: age at diagnosis, sex, histology, TNM stage, treatments, and date and cause of death. Survival probability was calculated using Kaplan-Meier analyses. Prognostic factors were analyzed using a univariate log rank test and a multivariate Cox regression analysis model.
Results: Twenty-six patients died during follow-up, 15 of them (4.9%) from DTC. Thyroid carcinoma-related survival was 92.7% for the whole group. Variables independently associated with a significantly increased risk of death from DTC in multivariate analyses included distant metastases, follicular histology, age at diagnosis older than 60 years, and extrathyroid involvement.
Discussion: The survival rate in our series was similar to that reported in the literature. However, assessment of the prognostic factors related to an increased risk of death within our patient group is necessary in order to establish active therapeutic approaches for high risk patients.

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PALABRAS CLAVE
Carcinoma diferenciado de tiroides;
Supervivencia;
Factores de riesgo

Carcinoma diferenciado de tiroides: supervivencia y factores relacionados

Resumen
Antecedentes y objetivo: El cáncer diferenciado de tiroides (CDT) es el tumor endocrino más frecuente, con buen pronóstico y supervivencias superiores al 85%. El objetivo de nuestro trabajo es conocer la supervivencia actual de nuestra serie de CDT y analizar los factores relacionados.
Pacientes y métodos: Realizamos un estudio retrospectivo de una cohorte de pacientes con CDT (n: 308), 93,5% eran papilares, el 78,2% eran mujeres con una edad media al diagnóstico de 45,4 ± 15,8 años y un tiempo de seguimiento de 8,9 ± 6,8 años. Han sido tratados y seguidos de forma homogénea en nuestro centro hospitalario. Para cada paciente se ha recogido edad al diagnóstico, sexo, histología, estadio TNM, tratamientos empleados y fecha y causa de la muerte. La probabilidad de supervivencia fue calculada por el método de Kaplan Meier. Para analizar los factores relacionados con la supervivencia se realizó un análisis univariante (Log Rank test) y multivariante (Riesgos proporcionales de Cox).
Resultados: Se produjeron 26 casos de muerte, de ellos 15 pacientes (4,9%) murieron como consecuencia del CDT. La probabilidad de supervivencia acumulada del grupo total fue del 92,7%. En el análisis multivariante las variables asociadas de forma independiente con mortalidad por CDT fueron: metástasis a distancia, tipo histológico folicular, edad al diagnóstico más de 60 años y afectación extratiroidea.
Discusión: La probabilidad de supervivencia de nuestra serie es equiparable a la de la literatura. El conocimiento de los factores relacionados con peor supervivencia en el medio que trabajamos es importante para establecer estrategias más activas de tratamiento en pacientes de alto riesgo.

Introduction

Differentiated thyroid carcinoma (DTC) derived from follicular epithelium is the most common endocrine tumor, and its incidence has tended to increase in recent years[1,2]. DTC usually has a favorable course, with survival rates of approximately 85%-90%[3-5]. However, all series include a proportion of cases with more aggressive behavior, with local recurrence or distant metastases, suggesting the existence of variants with a poorer prognosis and course.

In order to establish the final prognosis of DTC and to be able to prescribe more aggressive treatment, different risk factors such as age at diagnosis, sex, size and extent of primary tumor, nodal or distant metastases, histological subtype, or initial treatment used should be taken into account[6-8]. In recent years, deeper understanding of the molecular changes leading to DTC has allowed for the establishing of other genetic markers associated with a poorer prognosis and a lower survival rate[9].

The objective of our study was to assess the probability of survival in our cohort with differentiated thyroid carcinoma and to analyze the factors related to survival.

Patients and methods

A retrospective study was conducted of a cohort of 308 patients with DTC, treated and followed up using the same protocol at our hospital from 1976 to 2009. Data from patients with DTC have been routinely recorded in a computer database since 1996. Patients who were not operated at our hospital and those for whom data for adequate initial categorization were not available were excluded from the study.

The following data were collected for each patient:

1. *Demographic characteristics:* age at diagnosis, sex, family history of thyroid disease and/or DTC, and personal history of external head and neck radiotherapy.
2. *Tumor characteristics at diagnosis:* main histological type and histological subtype (if any) according to the WHO classification[10]; mean tumor size, the presence of multiple foci, bilateral thyroid involvement, the presence of thyroiditis in the surgical specimen, the existence of nodal metastases, extrathyroid invasion, and distant metastases.
3. *Characteristics related to the treatment used:* initial surgery (total thyroidectomy, total thyroidectomy in two stages, hemithyroidectomy, etc.), lymphadenectomy and its extent, the number of doses and total dose of radioactive iodine (^{131}I).

   All patients were staged based on the above data using the staging system of the AJCC (American Joint Committee on Cancer), based on the TNM classification system (6th edition)[11] and age.
4. *Date of the final follow-up (in both patients on follow-up and lost to follow-up) and date and cause of death.* Cause of death was taken from hospital records, death reports provided by relatives, and autopsy reports. Causes of death were categorized as death related to thyroid carcinoma and from other causes, if thyroid carcinoma was not the main cause of death.

Statistical analysis

Results are given as mean ± standard deviation for quantitative variables, and as proportions for qualitative variables (with 95% confidence intervals). Survival

Table 1 Demographic characteristics, risk factors, and form of presentation of the Toledo cohort of differentiated thyroid carcinoma at diagnosis

	% (95% CI)
Sex	
Female	78.2 (73.4-83.0)
Male	21.8 (17.0-26.6)
Family history of thyroid disease	21.3 (16.1-26.5)
Family history of differentiated thyroid carcinoma	3.5 (1.1- 5.9)
Neck irradiation	1.2 (0.5-1.9)
Other tumors	5.5 (2.9-8.1)
Form of presentation	
Single nodule	40 (37.3-45.4)
Multinodular goiter	44 (38.6- 49.4)
Autoimmune thyroid disease[a]	5.5 (3.1-7.9)
Adenopathies	6.8 (4.0-9.6)
Distant metastasis	0.3 (0-0.6)
Initial thyroid function	
Normal function	75.8 (71.0-80.6)
Hypothyroidism	5.3 (2.9-7.7)
Hyperthyroidism	7.5 (4.5-10.5)
Unknown	11.4 (7.7-14.9)
Age groups	
< 45 years	26.9 (21.8-32.0)
≥ 45 years	73.1 (71.2-81.0)
< 60 years	63.6 (58.1-69.1)
≥ 60 years	36.4 (30.9-41.9)

95% CI: 95% confidence interval.
[a]Includes patients with Graves disease and Hashimoto thyroiditis.

probability was calculated using the Kaplan-Meier method. Univariate (log rank test) and multivariate (Cox proportional hazards) analyses were performed to analyze the factors related to survival. A value of $p < 0.05$ was considered statistically significant. Statistical study was performed using the SPSS V15.0 package.

Results

Table 1 shows the demographic characteristics of the study population and variables related to initial diagnosis. Mean age at diagnosis was 45.4 ± 15.8 years, and there was a clear female predominance in the group (3.5:1). Mean follow-up time was 8.9 ± 6.8 years (range, 1-33 years).

Ninety-two percent of patients underwent surgery consisting of deliberate total thyroidectomy, while hemithyroidectomy was only performed in 4.6% of patients (the remaining 3.4% includes patients not operated on and those undergoing non-complete surgery, such as subtotal thyroidectomy). Lymphadenectomy was performed in 47.6% of patients using different procedures during the years of follow-up. After surgery, ^{131}I ablation therapy was administered to 90.8% of patients at a mean dose of 146 ± 132 mCi.

Table 2 shows the histological characteristics and TNM classification of the patient series.

Twenty-six deaths occurred in the overall group, of which 15 (4.9%) were directly related to DTC, while the remaining 11 deaths were due to other causes.

Survival probability was 92.7% for the overall group. In our series, the AJCC classification was able to establish different survival probabilities for each stage (Fig. 1). All stage I patients (n: 205) survived for longer than 20 years. In stage II patients (n: 26), survival probability was 94.1%. In stage III patients (n: 28), survival significantly decreased to 78.1%. Finally, among stage IV patients, probability of survival decreased to 71.6% in stage IVa (n: 30) and to 46.6% in stage IVc (n: 12) ($p < 0.001$).

In the univariate analysis, sex, the presence of adenopathies, bilateral thyroid involvement, multifocality, or the presence of thyroiditis were not associated with a lower probability of survival. In the multivariate analysis (Table 3), variables associated with a lower survival rate included age over 60 years, follicular histological type, the

Table 2 Histological characteristics and TNM classification of patients with differentiated thyroid carcinoma

	% (95% CI)
Histological type	
Papillary	93.5 (90.7-96.3)
Microcarcinoma	23.1 (18.3-27.9)
Follicular variant	13.6 (9.7-17.5)
Follicular	6.5 (3.7-9.3)
Hürthle cell variant	1.9 (0.3-3.5)
Multifocal	38.6 (33.1-44.1)
Thyroiditis	32.4 (27.1-37.7)
Bilateral thyroid involvement	12.7 (8.9-16.5)
Extrathyroid extension	18.9 (14.4-23.4)
TNM-T stage	
T1	44.5 (38.8-50.2)
T2	24.8 (19.9-29.7)
T3	17.6 (13.3-21.9)
T4	7.2 (4.3-10.1)
T unknown	5.5 (2.9-8.1)
TNM-N stage	
N1	33.8 (28.4-39.2)
TNM-M stage	
M1	6.7 (3.9-9.5)
T 1-3 NX M0	81.2 (76.7-85.7)
T4 M1	7.8 (4.7-10.9)

95% CI: 95% confidence interval.

Table 3 Variables independently associated with a lower probability of survival in differentiated thyroid carcinoma

	OR	95% CI	p
Age at diagnosis > 60 years	12	1,5-95,1	<0,05
Follicular histological type	4,3	1,4-13,2	<0,05
Extrathyroid involvement	16,6	4,7-57,9	<0,001
Distant metastasis	7,0	2,1-23,7	<0,01

95% CI: 95% confidence interval; OR: odds ratio.

presence of extrathyroid involvement, and the existence of distant metastases.

Based on these results, the patients were divided into two large groups: 1) patients with a low mortality risk (81.2%), including those with T1 to T3 tumors and no metastases (M0), and 2) patients with a high mortality risk (7.8%), including all patients with T4 tumors and/or those with metastases at diagnosis (M1).

Survival probability was 97.2% in the low mortality risk group (T1-3, NX, M0), as compared to 36.1% in the high risk group (T4, NX, MX Ó TX, NX, M1) ($p < 0.001$) (Fig. 2).

Discussion

This study reviewed survival rates and causes of death in a large cohort of patients with DTC (more than 300) who were similarly treated and followed up by the same multidisciplinary team for a long mean follow-up time (more than 8 years). Overall survival probability in our series was

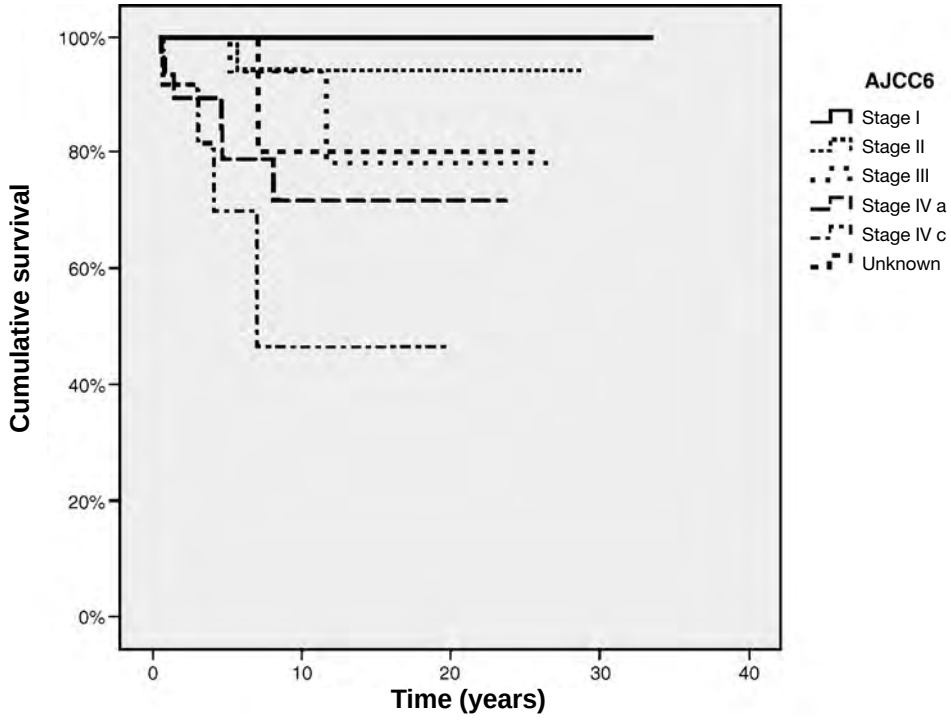

Figure 1 Survival probability depending on AJCC stage (6th edition) at diagnosis. ($p < 0.001$).

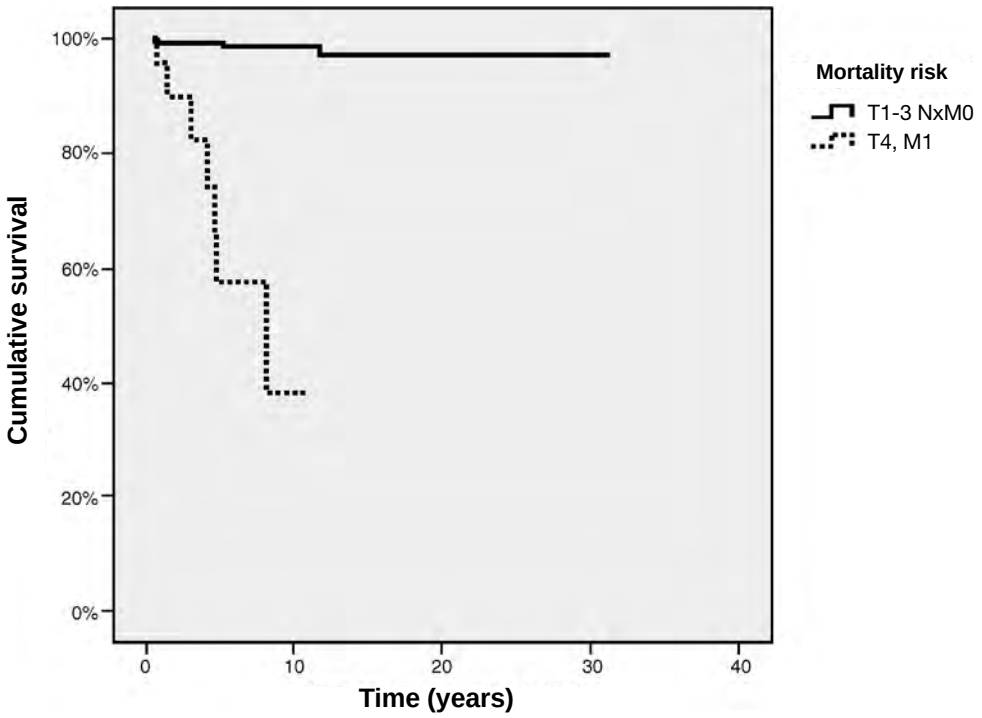

Figure 2 Probability of survival for patients with low-risk (T1-T3 M0) and high-risk (T4 M1) differentiated thyroid carcinoma ($p < 0.001$).

higher than 90%, which agrees with reports in both the European and the American literature[4].

Prior survival analyses performed on this same series in 1997[12] and 2003[13] showed survival rates of 87.7% (in 70 patients with a follow-up time of 5.1 ± 3.9 years) and 89.5% (in 151 patients with DTC and a follow-up time of 61 ± 4.8 years) respectively. Current results would thus suggest a 5% improvement in the probability of survival of patients with DTC over the past 12 years. Such improved survival probability could be related to an earlier diagnosis of DTC (imaging techniques, use of fine needle aspiration), a more aggressive treatment (deliberately total surgical approach, prophylactic lymphadenectomy, widespread use of ^{131}I at ablation doses), and the development of new diagnostic procedures facilitating both diagnosis and treatment of recurrence[14].

The rapid changes undergone in DTC diagnosis, treatment, and follow-up have led to the recent updating of international guidelines[15], and our own expert panels have encouraged us to be aware of the current scientific evidence[16,17] when standardizing our management of DTC.

Factors found to have an independent influence on survival in our series (advanced age at diagnosis, follicular histological type, extrathyroid involvement, and distant metastases) agree with those reported by most studies in the literature, with some qualifications. In our group, the follicular histological type was an independent factor associated with lower survival. In other series reported in the literature[18,19], histology also determines a poorer chance of survival. We do not know the proportion of patients with the macroinvasive histological variant in our series of follicular carcinomas, and the high mortality of our patients may possibly be accounted for by a higher percentage of macroinvasive follicular carcinomas. Similarly, male sex is associated in some series with poorer results[20,21], which did not occur in our patients.

Two clearly differentiated patient groups were obtained based on the results of tumor size and the presence of gross extrathyroid involvement (T4) and distant metastases. Survival in the low mortality risk group was higher than 97%. This is, therefore, a group of patients with a very good prognosis for whom a too aggressive treatment approach may bring more risks than benefits. By contrast, greater attention regarding both the treatment and the early detection of recurrence should be directed to the high risk group, which shows a survival rate lower than 40%, and for which new experimental therapies may possibly be required[22].

The Toledo healthcare area, where our study was conducted, has a middle to low mortality rate from DTC as compared to the country overall. Regions with a higher risk of mortality include the Canary Islands and the northern part of the Iberian peninsula (Galicia and western Asturias)[23]. Overall mortality from DTC in our series, approximately 5%, is not different from that reported in the historical series of papillary carcinomas from the Mayo Clinic[24] or by other European groups[4]. Our mortality rates are however slightly higher than those found in two healthcare areas in the south of Madrid (geographically very near to Toledo), which were 3.9% in the Leganés area[25] and 3.2% in the Móstoles area[26]. A recently performed pooled analysis of data from two hospitals in Catalonia ,which reviewed their DTC series,

reported a mortality of only 1.8%[27]. The difference in mortality rates found between our group and the other national series analyzed may be explained by the long follow-up time of our patients and by the active search for deaths from DTC among them.

In conclusion, our results suggest that the survival rate of our patients with DTC is high and has improved in the last 12 years. Factors with an independent influence on mortality are not different, with some exception, from those found in other series. Greater understanding of the risk factors for mortality in our setting is a determinant factor in allowing for treatment individualization, for optimization of therapeutic approach, and for the improvement of final results in our patients with DTC.

Conflict of interest

The authors state that they have no conflict of interest.

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