Acta Otorrinolaringol Esp. 2011;**62(1):**14–19

Acta Otorrinolaringológica Española

www.elsevier.es/otorrino

ORIGINAL ARTICLE

Risk groups in differentiated thyroid carcinomas

Jesús Herránz González-Botas,* Carlos Vázquez Barro, José Martínez Vidal

Servicio de Otorrinolaringología, Complejo Hospitalario Universitarios de A Coruña, La Coruña, Spain

Received July 5, 2010; accepted September 3, 2010

KEYWORDS
Thyroid cancer;
Differentiated thyroid cancer;
Papillary carcinoma;
Follicular carcinoma

Abstract
Introduction: Well-differentiated thyroid carcinoma represents 80%of all thyroid malignant tumours, with a survival rate of over 95%at 20 years in 80%of the cases. Although its incidence is increasing, survival remains unchanged. Prognostic factor evaluation allows identifying patients at high or low risk of recurrence, selecting those who will benefit from more aggressive therapy.
Material: We have reviewed the incidence of malignant thyroid neoplasm, selecting them according to three different system definitions (TNM, GAMES, MACIS), as well as by post-surgical complication rate.
Results: Malignant neoplasm represents 28.8% of the thyroid-operated patients, 88% corresponding to well-differentiated carcinomas. 80%are in the low risk group, with similar numbers in all three staging system definitions. Multicentricity was found in 16%, with 50% of the lesions smaller than 2 cm. Permanent recurrent nerve palsy was 1.2%and 2.7%presented permanent postoperative hypocalcaemia.
Conclusions: Risk group percentage is similar to that reported in the literature, with 80%having expected survival over 95%at 20 years. Risk factor evaluation should help to individualise treatment options, avoiding overtreatment and complications in patients that will not benefit from more aggressive therapy.

PALABRAS CLAVE
Cáncer de tiroides;
Carcinomas diferenciados de tiroides;
Carcinoma papilar;
Carcinoma folicular

Grupos de riesgo en carcicomas diferenciados de tiroides

Resumen
Introducción: El 80%de los carcinomas de tiroides corresponden a tumores diferenciados y la supervivencia causa específica a más de 20 años es superior al 90%. A pesar de su incremento en los últimos años, la supervivencia se mantiene estable. La evaluación de los factores pronósticos y de riesgo ha demostrado su utilidad en la selección de los tratamientos más adecuados a cada paciente.

*Corresponding author.
E-mail address: jesus.herranz.gonzalez.botas@sergas.es (J. Herránz González-Botas).

0001-6519/$ - see front matter

Material: Hemos analizado la incidencia de carcinomas de tiroides, agrupándolos según diferentes tipos de criterios (TNM, GAMES, MACIS) comparándolos con los índices referidos en la literatura. Analizamos así mismo el índice de complicaciones.
Resultados: La incidencia de tumores malignos en la población operada de tiroides es del 28,8%, siendo el 88% carcinomas bien diferenciados. El 80% corresponde a grupos de bajo riesgo, equivalentes en los tres sistemas de estratificación. El 16% eran multifocales, y en el 50% la lesión mayor media menos de 2 cm. El índice de parálisis recurrencial definitiva fue del 1,2%, y de 2,7% el de hipoparatiroidismo definitivo.
Conclusiones: La incidencia de grupos de riesgo de nuestra serie es similar a la de la literatura. El 80% de los pacientes tienen una expectativa de vida superior al 95% a 20 años. La evaluación de los criterios de riesgo debería determinar la amplitud de la resección, reduciendo el riesgo de complicaciones en aquellos pacientes que no se beneficien de una cirugía más agresiva.

Introduction

The incidence rate of differentiated thyroid cancer (DTC) has increased significantly in recent years on a global and local level,[1,2] mostly due to an increase in the number of small papillary carcinomas. This increase has not been observed in other histological types of thyroid cancer. The fact that survival rates have remained stable and that there is a portion of the population who suffer papillary carcinomas but never manifest them (they are later found during autopsies) suggest that this increase in the incidence rate reflects an increase in the levels of subclinical detection rather than a real increase in the incidence of this disease.

Representing about 90% of thyroid tumours, DTCs can be classified into risk groups based on criteria related to the tumour (size, local infiltration, metastasis) and the patient (age, gender). In most cases, the risk of death by DTC is lower than 1% at 20 years.[3]

The most adequate treatment for low-risk differentiated carcinomas is a common debate topic. There is no degree 1 or 2 scientific evidence that clarifies positions, due to the absence of randomized prospective studies. Guides are consequently based on retrospective studies and expert panels.[4]

One of the topics in this debate is the rate of complications due to the treatment of a disease with a mortality index that is, in most cases, lower than 1% at 20 years.

The objective of this study was to assess the incidence rate of DTC in the population of patients who underwent surgery for thyroid diseases, to classify them according to risk groups and to analyse the rate of complications caused.

Material and method

A total of 103 patients underwent surgery for previously untreated malignant thyroid tumours between January 2005 and June 2010. Of these, 91 were DTC and constituted the sample used for this study. We reviewed the data referring to age, gender, distant metastasis, extrathyroid extension, presence of lymph node metastases, previous history of radiation, histology, multifocality, size and type of surgery and total thyroidectomy (TT) or hemithyroidectomy (HT) status.

We grouped the results of these data with the prognostic criteria of the TNM,[5] GAMES[6] (histology, age, metastases, extrathyroid extension and size) and MACIS (distant metastasis, age, complete resection, invasion and size)[7] staging guides; the MACIS was specific for capillary carcinomas (Table 1, Table 2, Table 3).

The incidence of postoperative recurrent paralysis was calculated based on the number of recurrences dissected, with definitive paralysis defined as that which persisted for

Table 1 Correlation between assessment and mortality in GAMES

Criterion	Risk			
	Low	Intermediate		High
Age	<45	<45	>45	>45
Distant metastasis	M0	M+	M0	M+
Size	T1-T2	T3-T4	T1-T2	T3-T4
	<4 cm	>4 cm	<4 cm	>4 cm
Histology and grade		Follicular or high grade	Papillary	Follicular or high grade
Survival at 5 years, %	100	96	96	72
Survival at 20 years, %	99	85	85	57

Table 2 MACIS rating system

Criterion	Evaluation
Metastasis	
Absent	0
Present	1
Patient age	
<40	3.1
>40	0.08 x age
Resection	
Complete	0
Incomplete	1
Invasion	
Absent	0
Present	1

Table 3 Correlation between estimation and mortality (at 20 years) in MACIS

Evaluation	Stage	Mortality %	Patients (%)
<6	1	1	58 (71.5)
6-6.99	2	11	46 (19.5)
7-7.99	3	44	6 (7.2)
>8	4	76	2 (2.4)

more than 12 months after the surgery that caused it. A total of 74 TT and 17 HT were carried out, with a combined total number of 165 deemed recurrent towards risk. Two patients presented recurrent paralysis at the moment of diagnosis, by infiltration of the recurrent nerve. This paralysis was not counted as a complication. In both cases, the nerve had to be included in the resection due to its massive involvement. The evaluation of the superior laryngeal nerve paralysis, responsible for dysphonia with preserved cord mobility, was not included in the study.

The incidence rate of postoperative hypoparathyroidism was calculated based on the number of patients who underwent a total thyroidectomy, whether this was performed as a single intervention or as the consequence of two hemithyroidectomies. We considered definitive hypoparathyroidism as that which persisted for more than 12 months after the intervention causing it.

Results

A total of 103 malignant tumours were diagnosed (22.8% of the 451 patients who underwent surgery for their thyroid disease during that time), without there being any significant differences in incidence rate during the 5 years of the study. Of these, 88.3% (91/103) corresponded to differentiated carcinomas, with 82 being papillary carcinomas and 9, follicular carcinomas. The rest were 5 anaplastic carcinomas, 5 lymphomas and 2 medullary carcinomas. Women accounted for 79.1% (72/91) of all patients; mean age was 48.5 for women and 47.8 for men. Up to 36% of papillary carcinomas presented a maximum diameter ≤1cm. The TNM distribution can be seen in Table 4. All of the patients (40/40) younger than 45 years were Stage 1. Among those older than 45 years, 47% (24/51) were Stage I, 37.2% were Stage II, 9.8% were Stage III and 6% were Stage IV (Table 4).

Grouping patients according to the GAMES risk groups (6), in differentiated carcinoma cases, 32% (29/91) were low risk, 61% (56/91) were intermediate risk and 6.5% (6/91) were considered high risk.

According to the MACIS criteria,[7] only for capillary carcinomas, 71.5% (58/82) were Stage I, 19.5% (16/82) were Stage II, 7.2% (6/82) were Stage III and 2.4% (2/82) were Stage IV (Table 3).

Lesions were found in both lobes in 16.2% (12/74) of the patients who underwent a total thyroidectomy as their initial treatment (n=49), or in whom the thyroidectomy was completed due to a papillary carcinoma larger than 1 centimetre being found in the definitive histological study, not previously detected in the intraoperative histological study (n=25). The remaining 17 patients underwent HT.

Of all the nodules found on the side opposite to the larger tumour, 33% (4/12) were unique and smaller than 1 cm. Another 50% (6/12) presented multiple microscopic foci, and a diffuse sclerosing variant of papillary carcinoma was found in two cases. Two (17%) of the patients presented massive bilateral involvement, both with unilateral recurrent paralysis and soft tissue involvement at the time of diagnosis.

Up to 50% of the lesions (45/91) had a maximum diameter smaller or equal to 2 cm, and 33% (30/91) were smaller or equal to 1cm. In the remaining 16 patients (17%), the nodules were larger than 2 cm.

Table 4 TNM[a] distribution

	Younger than 45 years (n=40)			Older than 44 years (n=51)		
T/N	N0	N1a	N1b	N0	N1a	N1b
T1	19	1	1	24	1	1
T2	11	2	1	19	0	0
T3	5	0	0	3	1	0
T4a	0	0	0	0	1	1

[a]AJCC, 5th edition. 2010.

The incidence rate of postoperative recurrent paralysis was 4.2%(7/165 dissected nerves), with an incidence rate of definitive paralysis of 1.2% (2/165) and of transitory paralysis of 3%(5/165). Paralysis was unilateral in all cases. In the two cases of definitive paralysis, the intervention performed was hemithyroidectomy with isthmectomy.

The incidence rate of transient hypoparathyroidism was 12.1%(9/74 patients who underwent total thyroidectomy), with an incidence rate of definitive hypoparathyroidism of 2.7%(2/74). Resection of the larynx and several tracheal rings was necessary in one patient, given the presence of a tumour with invasion of the prelaryngeal muscles, thyroid cartilage, involvement of the tracheal lumen and cord paralysis.

No local recurrences were observed, and no deaths were caused by this disease.

Discussion

The incidence rate of thyroid cancer has been increasing over the past years,[1,2] with no change in mortality rates. This leads some to believe that most of the tumours diagnosed have a limited impact. In fact, 50% of these lesions have a diameter under 2cm, and 80%of tumours have an excellent diagnosis, with a cause-specific survival rate over 95% at 20 years.[3,8] Our data matches the incidence rates described in the medical literature with more extensive series, with a majority of the patients in low-risk groups, regardless of the clustering method chosen (TNM, GAMES or MACIS).

Treatment for differentiated thyroid cancer seeks to resect the lesion completely as well as its possible regional metastases, preserving functional structures, properly staging the lesion, allowing the use of radioactive iodine (for both long-term patient control and minimisation of the risk of recurrence and distant metastasis) and the use of thyroglobulin as a control element.[9] Some suggest total thyroidectomy and the subsequent use of radioactive iodine as a routine treatment. This concept makes postoperative control of patients easier through the use of radioactive iodine and thyroglobulin. The recommendation expressed in the 2009 American Thyroid Association review suggests a thyroidectomy in cases where the tumour has a diameter over 1cm, but it does not recommend systematic ^{131}I treatment, except if there are risk factors such as lymph node metastases or a histology related to a higher rate of recurrence or a poorer prognosis.[10]

The recommendation for total thyroidectomy when the tumour is larger than 1cm is not based on prospective studies but, as in the majority of cases, on retrospective studies and expert consensus. A publication on 52,173 patients with papillary thyroid cancer, obtained from the North American *National Cancer Data Base*, reached the conclusion that total thyroidectomy reduced recurrence rates and improved survival rates in patients with lesions larger than 1cm.[11] These conclusions were questioned, based on the lack of information on known risk factors that a general database involves versus data obtained from a single institution.[12] None of the previously published studies, which analysed different risk groups according to specific criteria (AGES, AMES, APES, DAMES, GAMES, MACIS), made any reference to the extent of surgery as a determining factor, with these results being obtained during monitoring periods lasting over 20 years.

The most important argument for the recommendation of total thyroidectomy in a patient with papillary thyroid carcinoma is the risk of multifocality. In our series, the risk of multifocality was 16.2%. In 33% of these, the additional nodule was unique and presented a size under 1cm. During the surgical procedure, after the removal of the hemithyroid and isthmus, the surgeon palpated the contralateral hemithyroid to detect nodules, completing the thyroidectomy in case palpable nodules were found. The procedure followed for the anatomopathological study of the thyroid in our centre consisted of serialising the thyroid tissue in 0-5 cm sections, including all suspicious macroscopic lesions. A more extensive study might have detected a greater number of multifocality cases, given that most of them are usually smaller than 1cm in diameter. Despite the fact that risk of multifocality oscillated between 30% and 40%, the consequences of a contralateral microscopic tumour nodule were not contrasted, with the risk of appearance of a metachronic papillary carcinoma on the opposite side being 5%10% A recent study of 217 patients with differentiated thyroid carcinoma, with a monitoring period of 27 years, did not find any relation between the extent of the resection and survival rates.[13] Our series does not have a sufficient number of cases or length of follow-up period to compare between patients undergoing total thyroidectomy or hemithyroidectomy, or to evaluate recurrences with regard to the presence of multiple foci.

Authors who recommend total thyroidectomy indicate that the procedure has a low mortality rate when performed by experienced surgeons, it allows the resection of undiagnosed contralateral tumoral foci and it makes it possible to use radioactive iodine and thyroglobulin to detect and treat recurrences.[11] On the other hand, there is data showing that 80%of patients with differentiated thyroid carcinomas can be cured by hemithyroidectomy+isthmectomy.[12,14] This avoids the need for a lifelong replacement therapy, in addition to avoiding the risk of hypoparathyroidism and bilateral recurrent paralysis. Furthermore, these patients do not need radioactive iodine or lifelong control with thyroglobulin.[12,14]

The medical literature contains series defending more or less aggressive positions, but, as is also the case with other pathologies, treatment individualisation should adapt the extent of resection to the needs and priorities of each patient. Some patients are perfectly capable of withstanding the periodic control of their thyroid neoplasm by ultrasound, with or without punctures. Others regard this situation as a permanent risk of recurrence, despite the risk level being objectively low; they consequently prefer a total thyroidectomy, even though they will have to suffer definitive hypothyroidism and an additional risk of hypoparathyroidism and recurrent paralysis without improving their survival rate.

Patients in high-risk groups (large tumours, aggressive histology, extrathyroid infiltration) are candidates for total thyroidectomy and subsequent radioactive iodine treatment. Patients who are not in this risk group, but who would benefit from radioactive iodine treatment (older than 45 years, presence of distant metastases,

contralateral lymph nodes) would also benefit from total thyroidectomy. Patients in low-risk groups are candidates for more conservative treatment because the cause-specific mortality rate of their disease is around 5% at 20 years.

There can be no doubt about the fact that complication rates in thyroid surgery performed by experts are low. In our case, the rate was 1.2% for permanent recurrent paralysis and 2.7% for permanent hypoparathyroidism. In our opinion, the issue is not whether complication rates are low, but whether these complications could be avoided, saving patients from an intervention that does not offer them any benefits. This is why young patients, with lesions smaller than 4cm, without metastasis, with no history of radiotherapy, with DTC, can be offered a hemithyroidectomy without the need for further risks.[11,12,14] Undoubtedly, subsequent control will be more laborious. The experience of the surgeon also influences this decision, along with the corresponding complication rate. It should also be taken into account that thyroid surgery also involves recurrence surgery, both local and regional, which, in turn, is associated with a significantly greater complication rate. Thyroid surgery is a very attractive area of cervical surgery for otolaryngologists, because the neck is their usual region of work, and laryngeal complications are their responsibility. Acquiring experience in this type of surgery is a matter of cases and criteria. This last factor should take precedence when evaluating the type of treatment. If a physician is very experienced, the patient will be at a low risk of complications. If, on the other hand, the experience of the surgeon represents a higher risk of complications, a less extensive treatment, in low-risk patients, offers the same oncological benefit with a lower risk of complications.

For an endocrinologist, the monitoring period for a patient with DTC is simpler after a total thyroidectomy, both due to the possibility of using radioactive iodine and to the availability of thyroglobulin as a detector of recurrences. The question is whether this availability for monitoring provides any benefit for the patient with respect to the certain risk of hypothyroidism, and potential risk of hypoparathyroidism and recurrent paralysis. All unnecessary risks must be avoided. There is no defined stance in the literature, and the philosophy of each centre will depend on the team responsible for treating these patients. In our experience, the possibility of postoperative complications is evaluated differently from the perspective of those responsible for medical treatment and from the perspective of those responsible for surgical treatment, and responsible for any complications.

The individualisation of treatment according to risk criteria and availability of monitoring and control, along with adequate and objective information for the patient, are the most important criteria in the treatment of a pathology with such a low mortality rate as that of differentiated thyroid cancer. The factors for alarm that determine the need for more aggressive surgery are clear (age, extrathyroid extension, metastases, aggressive histological variants).

There are patients with low-risk criteria who, after being treated by hemithyroidectomy, reject the option of periodic control for fear of recurrence in the contralateral lobe, or those who feel anxiety over the non-availability of thyroglobulin to detect metastases. These motives must be correctly explained and assessed objectively, so that the patient will know which risks and benefits come with one procedure or the other. The patient must be part of the therapeutic decision, and this decision must provide medical and personal benefits to the patient.

Conclusions

There have been no randomized prospective studies that shed light on which the best treatment for low-risk DTC is and controversy consequently persists. However, due to the good DTC prognosis, the use of less aggressive surgical procedures must be taken into account in cases where tumour extension and size, along with patient characteristics, allow it. Postoperative complications, which are rare among expert surgeons, can be reduced in cases where the long-term survival rate is higher than 90%. Is hemithyroidectomy enough or is total thyroidectomy necessary? Does the patient always benefit from it? There is no contrasted data available to allow for a decision that ends the controversy, but it is important to question whether low-risk thyroid cancer, with low local, regional and distant recurrence rates, may not benefit from total thyroidectomy.

Conflict of interest

The authors declare no conflict of interest.

References

1. Davies L, Welck G. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006;2164-7.
2. Rego Iraeta A, Pérez Méndez L, Mantiñan B, García Mayor V. La incidencia del cáncer de tiroides está aumentando en el noroeste de Epaña. Thyroid. 2009;19:333-40.
3. Randolph GW, Thompson GB, Branovan DI, Tuttle RM. Treatment of thyroid cancer: 2007 – a basic review. Int J Radiat Oncol Biol Phys. 2007;69:S92-7.
4. Iyer NG, Shaha AR. Management of thyroid nodules and surgery for differentiated thyroid cancer. Clin Oncol. 2010. Doi:10.1016/j.clon.2010.03.09.
5. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FK, Trotti A, editors, AJCC Cancer Staging Manual. 5th Printing. Springer. 2010.
6. Shaha AR, Loree TR, Shah JP. Intermediate-risk Group for differentiated carcinoma of thyroid. Surgery. 1994;116:10367-1040.
7. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohjort of 1779 patients surgically treated at one institution Turing 1940 through 1989. Surgery. 1993;114:1050-78.
8. Shaha AR. Implications of prognostic factors and risk groups in the Management of differentiated thyroid cancer. Laryngoscope. 2009;114:393-402.

9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mendel SJ, et al. Revised American Thyroid Association Managemente guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167-214.
10. Wartofsky L. Highlights of the American Thyroid Association guidelines for patients with thyroid nodules or differentiated thyroid carcinoma: The 2009 revision. Thyroid. 2009;19: 1139-43.
11. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamont MS, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg. 2007;246:375-84.
12. Letter to the Editor. Shah J Annals Surg. 2008;247:1082-3.
13. Vorburger SA, Übersax L, Schmid SW, Balli M, Candinas D, Seiler CA. Ann Surg. 2007;246:375-84.
14. Shaha AR. Treatment of thyroid cancer base on risk groups. J Surg Oncol. 2006;94:683-91.