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Review article

Treatment of Thyroid Follicular Carcinoma☆

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ABSTRACT

Differentiated thyroid carcinoma includes 2 different tumour types, papillary (PC) and follicular carcinoma (FC), and although similar, their prognosis is different. FC is uncommon, and this has led to it often being analysed together with PC, and therefore the true reality of this tumour is difficult to know. As a result, the diagnostic and therapeutic management and the prognostic factors in differentiated carcinoma are more predictive of PC than FC. In this review we analyse the current state of many of the therapeutic aspects of this pathology. The best surgical technique and the usefulness of associated lymphadenectomy is also analysed. Regarding post-surgical ablation with ^{131}I, the indications, doses and usefulness are discussed. For the remaining therapies we analyse the few indications for radiotherapy and chemotherapy, and of new drugs such as tyrosine kinase inhibitors.

Tratamiento del carcinoma folicular de tiroides

Palabras clave:
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RESUMEN

El carcinoma diferenciado de tiroides incluye 2 tipos tumorales diferentes: el carcinoma papilar (CP) y el folicular (CF) y, aunque similares, su pronóstico es diferente. La infrecuencia del CF ha hecho que habitualmente se analice conjuntamente con el CP, lo cual dificulta conocer su verdadera realidad. En esta revisión se analiza la situación de los diferentes aspectos terapéuticos de esta dolencia. Se revisa cuál es la mejor técnica quirúrgica y la utilidad de realizar vaciamiento ganglionar asociado. Respecto a la ablación posquirúrgica con ^{131}I se evalúan las indicaciones, las dosis y su utilidad. En el resto de terapias se analizan las pocas indicaciones que tiene la radioterapia y la quimioterapia, y la aparición de nuevos fármacos como los inhibidores de la tirosin-cinasa.

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Introduction

Differentiated carcinoma is the most common thyroid tumour, and in the majority of cases it is associated with a favourable prognosis.[1] The denomination of differentiated carcinoma covers two tumour types with very different pathogenesis, biology and clinical behaviour. The current tendency is to consider them as different entities. These two tumours are papillary carcinoma (PC) and follicular carcinoma (FC), which although similar have different prognoses. Thus FC is more vascularised and usually presents a higher rate of vascular invasion and clinical aggressiveness.[1]

The incidence of FC is strongly related with iodine deficit, and it is decreasing due to iodine supplementation.[1,2] Although there are major variations between populations, its incidence is estimated to stand at 1–2 cases for every 100 000 women/year, and around 0.4–0.5 cases for every 100 000 men/year. This rareness has led to its usually being analysed together with PC, hindering knowledge of the true nature of the former.[1] Thus the majority of studies analysing the usefulness of certain diagnostic tests, the therapeutic efficacy of different treatments and which prognostic factors are the most significant for differentiated carcinoma, as the series include more PC than FC, their results are more predictive and useful for PC than they are for FC.[3] Few studies contain a sufficient number of FC cases to allow it to be studied independently, and the results of these studies are not consistent.[3–5]

The treatment of FC currently depends on tumour extension. Thus patients with greater extension or a higher risk of recurrence are treated more aggressively and monitored more closely. However, in localised low risk tumours a more conservative treatment is equally effective.[1] Additionally, the different subtypes of FC have to be taken into account, as they directly influence patient prognosis (Table 1).

Many controversies surround the diagnosis, treatment and evolution of FC. This revision aims to analyse the current state of the different therapeutic options for FC and determine which is the best medical and surgical treatment for this group of patients, based on the scientific evidence.

To this end two bibliographical searches were performed. On the one hand scientific publications indexed in the different databases (Pubmed, Embase and Conchrane Library) and, on the other, the guides and consensus documents of different Spanish, European and American scientific societies on the treatment of FC.

Table 1 – Histological Types of Thyroid Follicular Carcinoma.

Variants	Incidence %
Classic follicular carcinoma	83–90
Minimally invasive, not angioinvasive	
Minimally invasive, angioinvasive	
Widely invasive	
Hürthle cell carcinoma	2–6
Insular or poor differentiated carcinoma	10
Clear cell variant carcinoma	<1

Controversies in the Surgical Treatment of Follicular Carcinoma

The Utility of Molecular Cytological Markers in Preoperative Diagnosis and Surgical Planning

Fine needle aspiration (FNA) is currently the gold standard for differential diagnosis between a benign nodule and thyroid cancer, and its sensitivity largely depends on the cytologist's experience.[1,6] Nevertheless, the main problem with this technique is its lack of sensitivity in the evaluation of follicular neoplasia, as it is unable to distinguish between benign lesions (follicular adenoma) and malignant entities (thyroid follicular carcinoma and the follicular variant of papillary carcinoma),[1,7] given that it is no longer possible to diagnose vascular or capsular invasion.[1,8] To improve the diagnostic sensitivity of FNA in follicular neoplasia, immunohistochemical and molecular diagnosis techniques are being analysed. Several molecules have therefore been said to be involved in the carcinogenic process, and they have been proposed as thyroid malignity markers to increase the diagnostic precision of FNA. They include telomerase, thyroperoxidase, keratan-sulphate, the group of high mobility proteins I (Y) (HMGI[Y]), the cell surface mesothelial antigen HBME-1, thyroperoxides, cytokeratin 19 and galectin-3 (GAL3).[9,10] Several gene expressions are also being analysed, and the expression of more than 100 genes has been detected.[11] It should be pointed out that the fusion of oncogene PAX8/peroxidase proliferator–gamma receptor (PPARγ) has been identified in approximately 25%–50% of FC, with a translocation between regions 3p25 and 2q13.

Although advances are occurring very quickly, the results on the utility of the different proposed malignancy markers often disagree.[12–15] Some studies have shown that, in comparison with using markers in isolation, a sequential combination of two markers is more useful. The combination of GAL3 and HBME-1, or GAL3 and cytokeratin 19 in the case of oncocytic lesions therefore improve the diagnostic sensitivity of FNA.[12,14] Cytological markers are not currently in widespread use.

Lastly, although analysis of the BRAF (V600E) mutation has been shown to be of use in selecting nodules with indeterminate cytology (AUS/FLUS), it is highly specific for PC and not FC, so that it is not useful for the diagnosis of CF.[16–19] However, the RAS mutation may be important in the identification of the follicular variant of PC and even FC, although more studies are required to confirm these preliminary results.[20,21]

Which is the Best Initial Surgery for Follicular Carcinoma?

The main problem which tends to arise when considering surgery for FC is that the operation is usually indicated by the diagnosis of follicular neoplasia, but without knowing that it is a carcinoma. This means that the definitive diagnosis of FC usually takes place after the patient has been operated on. Due to this, we have a patient diagnosed with FC who has usually already been subjected to a hemithyroidectomy. There is now consensus and it is accepted that hemithyroidectomy is the correct surgery in only 2 cases: (1) microcarcinoma (tumour<1 cm) that is unifocal with no vascular invasion or