Clinical Oncology xxx (2017) 1–5

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Short Report

Recent Developments in the Pathology of Thyroid Cancer

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Received 16 January 2017; accepted 16 January 2017

Abstract

The histopathological features of thyroid cancers can be used to risk stratify patients, allowing prognostication and treatment decisions. A detailed accurate histological assessment by experienced pathologists working within a multidisciplinary context is crucial. Experience is also essential for interpretation of preoperative thyroid cytology specimens, which can be challenging. There is now more international harmonisation of numerical reporting systems for thyroid cytology. Understanding of the molecular basis of thyroid cancer has increased dramatically in recent years. Preoperative molecular pathology testing, when available, can refine cytological diagnosis to rule in or out for surgery, as well as assisting prognostication and enabling targeted treatment for thyroid tumours.

Key words: Cytology; diagnosis; molecular diagnostics; pathology; recent advances; thyroid cancer

Introduction

The most important aspect of thyroid cancer pathology is making a correct and timely diagnosis with provision of sufficient detailed histological information upon which to risk stratify patients for treatment decisions. Some aspects of thyroid pathology are, however, quite subjective and so there is often variation in pathological interpretation even between experienced endocrine pathologists. Recent important developments in thyroid cancer pathology include refinement of some prognostic features for assigning risk, a better understanding of the molecular basis of thyroid cancer and reclassification of one of the lowest risk tumours as non-cancerous tumour. Below is a brief summary of some key developments in the last few years.

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Discussion

Increasing Incidence of Thyroid Cancer

The incidence of thyroid cancer has increased in developed countries, but the mortality has remained unaltered. The rise is primarily due to increased use of thyroid ultrasound [1] and most of the increase is due to lower risk tumour types [2].

Tumour Categorisation and Risk

Traditionally, primary thyroid cancer was classified into either follicular epithelial cell-derived tumours: papillary carcinoma, follicular carcinoma (minimally or widely invasive) and anaplastic carcinoma, with progressively worse prognosis; or C-cell-derived medullary thyroid carcinoma (familial and sporadic), lymphoma and other rarer tumour types. Poorly differentiated thyroid carcinoma (PDC) is now recognised as an intermediate risk cancer between differentiated thyroid carcinoma (follicular and papillary) and anaplastic thyroid carcinoma (ATC).

http://dx.doi.org/10.1016/j.clon.2017.01.006
0936-6555/

Please cite this article in press as: Poller DN, Johnson SJ, Recent Developments in the Pathology of Thyroid Cancer, Clinical Oncology (2017), http://dx.doi.org/10.1016/j.clon.2017.01.006

For thyroid carcinomas, precise tumour typing, as well as accurate TNM staging and assessment of other prognostic features, is crucial in determining the patient's risk group and therefore the appropriate treatment. Histopathology reports need to be accurate and complete with all the relevant diagnostic and prognostic features; this is aided by proforma reporting using datasets or templates of the type issued by the UK Royal College of Pathologists (RCPath) [3] or by the College of American Pathologists (CAP) [4].

Papillary Thyroid Carcinoma Subtypes

There are many subtypes of papillary thyroid carcinoma (PTC) but perhaps the most confusing are papillary microcarcinomas and the 'follicular' variant of PTC (FVPTC).

Papillary microcarcinomas are tumours up to 10 mm in greatest dimension. These may be the diagnostically targeted lesion or, more commonly, found incidentally either on ultrasound or histology. Various additional histological factors enable the assessment of their risk level, and personalised decision making may be required [5].

PTC is diagnosed primarily by its nuclear features and may show either a papillary (classical) or follicular architecture, or a mixture of both. FVPTCs show an almost exclusively follicular architecture and are classified into subtypes, including infiltrative (non-encapsulated), with molecular genetics and behaviour similar to classical PTC, and encapsulated (eFVPTC), where the molecular genetics and behaviour are more akin to follicular neoplasms [6]. The distinction of eFVPTC from follicular thyroid carcinoma (FTC) therefore hinges on whether the nuclei show PTC-type nuclear features or not, which is notoriously subjective, even among experienced endocrine pathologists [7]. The diagnosis of FTC has also evolved with time. In a very recent study, a group of American pathologists reviewed a series of 66 thyroid tumours originally diagnosed in 1965–2007 as FTC. Forty-seven (71%) cases were reclassified: 24 (36%) to PTC, 18 (27%) to follicular adenoma and five (8%) to PDC. Nine of 23 (39%) cases from 2000–2007 were reclassified as benign (follicular adenoma) [8].

Poorer prognostic variants of PTC include tall cell, columnar cell and diffuse sclerosing types, and any foci of such change need documentation [3,9].

Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

An international consensus group of pathologists led by Professor Yuri Nikiforov, University of Pittsburgh, reviewed 109 cases of non-invasive eFVPTC followed up for 10–26 years (median 13 years). Using consensus pathological criteria, this study showed that these tumours have a very good prognosis with less than 1% risk of death or recurrent disease on long-term follow-up, implying that this tumour should be regarded as of very low malignant potential. In 2016, these lesions were re-designated 'NIFTP' - non-invasive follicular thyroid neoplasm with papillary-like nuclear features [10]. The diagnosis of NIFTP requires the application of strict pathological criteria, including examination of the entire tumour capsule, confirmation of the nuclei according to the NIFTP nuclear scoring system, absence of psammoma bodies and no capsular or vascular invasion. If these criteria are not met it is not possible to make a diagnosis of NIFTP and the default diagnosis remains eFVPTC. NIFTPs are follicular-derived tumours, they are *RAS*-driven lesions and they do not show evidence of *BRAF* V600E mutations [10]. The UK RCPath has produced an addendum to the 2014 Dataset For Thyroid Cancer Histopathology Reports detailing the diagnosis of NIFTP [11]. This could have a major impact, because in some centres up to 20% of newly diagnosed thyroid cancers are non-invasive eFVPTC [12].

Minimally Invasive Follicular Thyroid Carcinoma

These are single encapsulated nodules of tumour with a follicular architecture but the cells lack the nuclear features of PTC. Carcinoma is diagnosed when there is invasive growth, either through the tumour capsule (capsular invasion) [13] or within the blood vessels of the tumour capsule or adjacent thyroid tissue (vascular or angioinvasion) [13,14], both of which can be subjective histologically [7]. Vascular invasion carries a higher risk than capsular invasion, so there should be thorough examination of the tumour capsule histologically and the type of invasion present should always be clearly stated. Precise criteria for vascular invasion in the literature are also conflicting [4,14]. Minimally invasive FTC with capsular invasion only and no other adverse risk factors has a very low risk of recurrence or metastasis and may not require a complete thyroidectomy [15–17]. Frequent vascular invasion is an adverse prognostic feature and should be commented upon, with the 2016 CAP Protocol requiring distinction between focal (less than four vessels) versus extensive (four or more vessels), whereas the 2014 UK RCPath dataset does not [4].

Poorly Differentiated Thyroid Carcinoma

These uncommon tumours have an intermediate prognosis between PTC/FTC and ATC. A previous term was 'insular carcinoma', but not all PDC have an insular architecture. Diagnosis is aided by the Turin consensus criteria [18,19]. Diagnosis requires a follicular cell-derived tumour with a solid/insular/trabecular growth pattern, lacking the nuclear features of PTC, and with necrosis and/or a mitotic count of three or more per 10 high-power fields. The entire tumour should be designated as PDC if more than 50% of the tumour shows this appearance, but even a minority component of PDC in an otherwise well-differentiated tumour should also be mentioned in the pathology report because this may worsen the patient's prognosis [20].

Other Newly Described Pathological Entities

These are extremely rare and are well reviewed by Eloy [21]. They include meningioma-like tumour of the thyroid, glomeruloid variant of FTC, angiomatoid PTC, hobnail/micropapillary variant of PTC, small cell primary non-

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