Known Pitfalls of the Thyroid Neoplasm Diagnostics in the View of the New (2004) WHO Classification

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Summary

The new (2004) WHO Classification of Tumours of the Thyroid and Parathyroid Gland exhibits both formal and contentual changes compared to the previous one from the year 1988. Comparing both texts we have tried to apply the new norm to some recent diagnostic tasks. The classification of poorly differentiated and undifferentiated neoplasms has been successfully solved by employing the immunohistochemical procedures into the daily routine. Nevertheless, some diagnostic problems persist and can not be solved this way. This is true especially for the borderline neoplasm in the FVPTC category and even more for its oncocytic variant. There appeared shift in the criteria for the diagnosis of oncocytic variant of papillary carcinoma. Newly, the obligatory presence of the nuclei with the characteristics of the conventional papillary neoplasms is required. Thorough elaboration of the TNM system has solved the problem of multifocal lesion staging. Moreover, a web consultation source is recommended. The new Classification includes descriptions of the basic cytodiagnostic features. The post aspiration capsular damage consideration in relation to the diagnosis of the minimally invasive follicular carcinoma is one practical profit thereof.

In terms of formal logic a criticisable feature of the new classification is the introduction of the so called „Synonyms". These listings include in fact partly real synonyms by definition, but together in one table quite often also subunits or variants of the nosologic units described.

In general, the new Classification represents a successful consensus reached. As there are newly also references with varying opinions included, it is presented more like a point of gravity in this field than an undoubted truth. This also makes it a valuable and useful normative text.

Key words: thyroid – thyroid neoplasms – WHO classification of tumours – diagnostic pitfalls – synonyms

Souhrn

Stará úskalí diagnostiky tyreoidálních novotvarů z pohledu nové (2004) WHO klasifikace

Nová WHO klasifikace tyroidálních a paratyroidálních novotvarů z r. 2004 vykazuje řadu formálních i obsahových změn oproti předchozí z r. 1988. Srovnání obou klasifikací jsme doplnili o aplikaci nové normy v některých otázkách aktuální diagnostické praxe. Diagnostiku nediferencovaných, málo diferencovaných a směsně diferencovaných tyreoidálních nádorů vcelku uspokojivě řeší imunohistochemické postupy zavedené do rutinní diagnostiky. Přetrvávají však některé problémy zatřídění nádorů, jež nejsou tímto způsobem řešitelné. Jde zejména o vymezení FVPTC v jeho hraniční podobě, ještě více v případě onkocytární varianty. Posun nastal v klasifikaci onkocytární varianty papilárních karcinomů – je pro ně nově nutnou podmínkou přítomnost jaderných charakteristik papilárního ca. Nejistoty v hodnocení TNM u multifokálních lézí jsou vyřešeny, ve sporných situacích poslouží rovněž odkaz na konzultační stránky.

V klasifikaci jsou zařazeny i základní cytodiagnostické znaky a obrazy. V souvislosti s touto pravidelnou diagnostickou metodou jsou uvažovány následky tenkojehlové aspirace v diagnóze minimálně invazivního folikulárního karcinomu.

Z hlediska formální logiky je kritizovatelnou položkou nové klasifikace „Synonymika" – v odstavci „Synonyms" jsou uváděna jak skutečná synonyma, tak speciální podjednotky – varianty diskutované kategorie. Celkově však nová klasifikace i tím, že zařadila literární odkazy na někdy i variabilní názory a předkládá tedy zjevně spíše názorová těžiště než deklarovaně pevné pravdy, představuje úspěšný a užitečný normativní text.

Klíčová slova: štítná žláza – nádory štítné žlázy – WHO klasifikace nádorů – diagnostická úskalí – synonyma

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Introduction

The last WHO classification of the thyroid tumours used (5) was more often than other volumes of the WHO series referred to as a team consensus reached with considerable difficulties among the twelve participating co-authors – the most respected world thyroid specialists. It represented a reliable normative basis irrespective of the minor objections most pathologists have developed using this handbook in the daily routine. The progress of the new diagnostic techniques esp. genetic methods and the recently ruling "splitting" phenomenon – creation of the new diagnostic entities have resulted into a new classification creation and publishing, this time not as a separate volume but as a part of other endocrine neoplasms classification in one volume (4). The following text reflects our first observation and experience gained using this normative text in the thyroid histodiagnostics.

Material and Method

The subject of this study is represented by the second (5) and third (4) version of the WHO classification of thyroid neoplasms. We focused on both the contentual and the formal differences. The formal changes influence the work while changing the old handbook for a new one. They can either fasten or slow down the work; in any case they require adaptation. Contentually, a considerable increase of information volume could have been expected with certainty. Moreover, we wondered, what kind of consensus has been reached in the long- standing diagnostic problems in this field. We have tried on a selection of cases, how helpful the new classification is in their solution.

Results

Formal Changes

The first change mentioned before lies in including the thyroid neoplasms classification into a common endocrine neoplasms volume and also association of the thyroid and parathyroid neoplasms into one section. Considering the close anatomic relations esp. the possible variable location (incl. the intrathyroid one) of the parathyroid glands and derived lesions, but especially the difficulties appearing sometimes in the intraoperative frozen section diagnostics unsolvable sometimes with the certainty without the immunohistochemical verification, this association seems highly logical. A disputable feature is the pragmatic and perhaps importance reflecting anteposition of the malignant neoplasms prior to their benign versions (and at least sometimes precursors). This order is similar to several newer surgical pathology textbooks, e.g. by Weidner (9). A conservative user (but especially a user possessing a stronger feeling of the cause – sequel sequence) can learn to tolerate, but not to prefer this order. The TNM classification tables with the „p"(pT, pN, and pM) omitted are contextually understandable indeed, and for the thyroid they correspond with the clinical categories TNM. Nevertheless, we would consider the preservation of the „p" marker for the histopathologically verified stage useful for the communication with the clinical specialists. The list of prominent formal changes of the new classification can be ended with the illustrations provided directly within the texts, which by no means makes the work with the handbook easier.

Contentual changes

The first contentual change to be mentioned is a systemic one reflecting the style of the whole new WHO classification series, namely the insertion of genetics coined in the name of the publication itself. This represents a challenge for pathologists, who have to acquire knowledge in this field to apply these characteristics of the neoplasms into the diagnostic algorhythms. Unfor-tunately, the full employment of these undoubtedly enriching methods remains recently limited in some laboratories for both economical and technical reasons. It can be anticipated that the genetic diagnostics will become a regular part of the morphological diagnostics like immunohistochemistry did in the past. Despite some overestimated views we do not expect the genetic diagnostic to substitute the morphology, analogously to the immunohistochemical diagnostic tools. The reason rests in the continual cautious approach to the interpretation of the results acquired with these methods mentioned. An expected contentual change of the new classification is represented by the increase of the nosologic entities to a double compared to the former classification (from 13 to 26). Many of the new entities have been described in the meantime and their enlistment was expected – e.g. carcinoma with the thymus like differen-

tiation (CASTLE). The insertion of the ICD-O codes not only into the introductory overview classification tables but also their repetition in the beginning of any section eases the process of coding. The same is valid for the TNM classification listing with the formal objection mentioned above.

In the TNM classification, compared to the older texts (1) microcarcinomas (diam. less or equal 10 mm) do not match the borders of TNM categories. The stage pT1 encompasses the tumours up to 20mm in diameter. The reference to the official UICC web pages (3) proved to be very useful together with the rule to classify in doubtful cases the lower of the categories considered. A papillary microcarcinoma diam. 6mm localized in the isthmus and growing inside but not expansively outside the capsule was classified pT1 using this rule and reference (Fig.1).

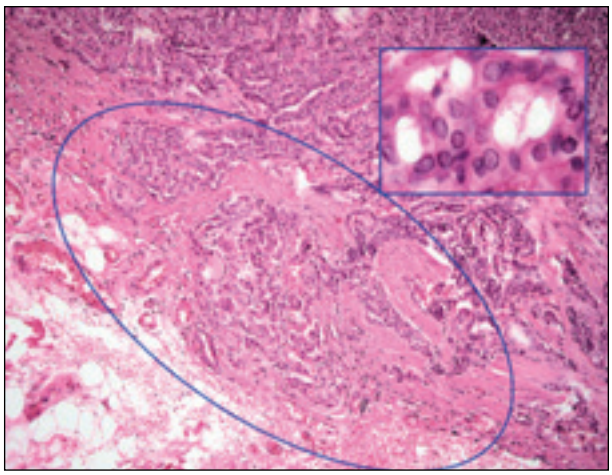

Fig. 1. Papillary microcarcinoma (diam. 6 mm) in the isthmus. Capsular invasion. Inset – diagnostic nuclei. The Tumour classifield pT1, invasive growth beyond the capsule was not found even with serial section H&E. Original magnification 60x

A rational enrichment of the new version is represented by *basic* cytopathology images included in the more frequent neoplastic nosologic entities. FNAC cytodiagnostics has become a regular procedure in the thyroid lesions and in many cases it can provide a final diagnosis. Moreover, cytopathology falls into the authority of experienced histopathologists to carry all its potency. That is why we consider this inclusion so useful. Histopathologists performing the FNAB diagnostics of the thyroid lesions are thus led to the cytopathology evaluation as close as possible to the corresponding histopathological nosologic units. On the other hand, the appreciation of the cytodiagnostic features and the knowledge of the post-aspiration changes can refine the histopathology diagnostics. An overview of the post - aspiration changes has been published recently by Ryška et al. (7). We have used our experience in post - aspiration changes evaluating a doubtful transcapsular invasion in a consultation biopsy of follicular neoplasia. In the absence of FNAC history and with no siderophages present in the capsule together with only a minimal residual reparative inflammation led us to the postaspiration etiology consideration. A subsequent search proved a FNAC performed, supporting thus our hypothesis (Fig. 2).

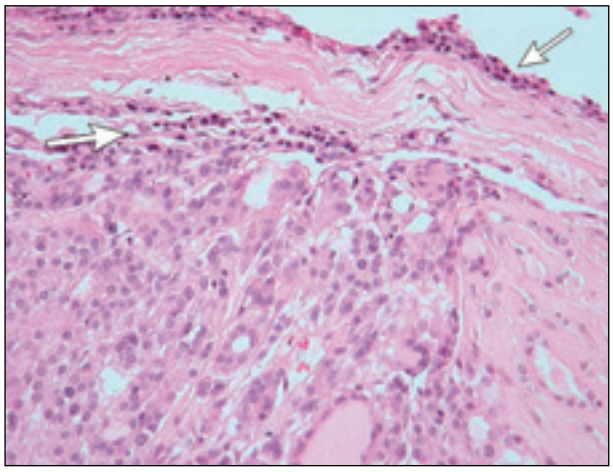

Fig. 2. Follicular neoplasia. Penetration of the capsule. Arrows indicate discrete lymphoplasmocellular infiltrates. Absence of haemosiderophages. The FNAB history proven subsequently. The tumour reported as adenoma. H&E. Original magnification 250x. (Consultation material, courtesy of Dr. K. Pelikán, Jindřichův Hradec)

We were curious about the new "state of art" in the new classification considering the old problem in evaluating the neoplasms possessing the nuclei of papillary carcinoma type. We will probably have to reconcile for ever with the illogical term "follicular variant of papillary thyroid carcinoma (FVPTC)" like with mycosis fungoides in haematology. Nevertheless, the very substance of this problems remains unresolved, especially a precise (arbitrary of course) definition of the necessary quantity and quality of such nuclear features to classify a neoplasms as FVPTC. The classification refers to the publication by Williams (10) supporting this way the diagnostic category formulated as "well differentiated neoplasms with uncertain malignant potential". In the past we have sometimes overdiagnosed slightly such doubtful cases for the sake of patient's safety. Recently, we can refer to this newly defined entity following

the contemporary trend of tactful patient informing. Analogously to the papillary urothelial neoplasias of low malignant potential (PUNLMP) these tumours exhibit mostly non-aggressive behaviour. The problem remains to be solved – possibly employing the genetically defined thyroid precanceroses. On the morphology level itself, we investigated in the past FVPTC with only a focal incidence of the diagnostic nuclei in which the application of this borderline diagnostic category would be substantiated. Both in the tumour and in the regional lymph node metastasis the nuclei had only discrete diagnostic features (Fig. 3).

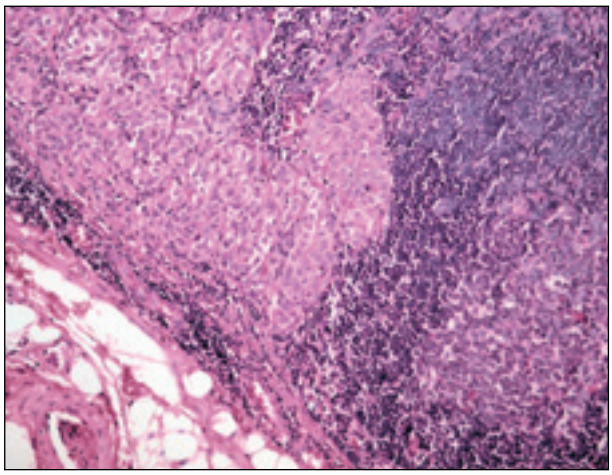

Fig. 3. Micrometastasis of papillary carcinoma (FVPTC) in the lymph node. The nuclear diagnostic features present discreetly. H&E. Original magnification 200x

To a certain surprise the diagnostic criteria for the oncocytic variant of the papillary carcinoma have changed. In the 1988 WHO classification (5) Oxyphilic cell variant p.11, (WHO Fig.42) "Their nuclei generally resemble the nuclei seen in other oxyphillic tumours and do not show the nuclear changes commonly associated with papillary carcinoma". In the new classification 2004 Oncocytic variant p. 61, WHO Fig.2.015c on the contrary, "the diagnosis of the oncocytic variant is based on the nuclear features of these lesions which are identical to those seen in papillary carcinomas of conventional type". This change is based on the publication of Berho et al. (2). From this point of view one of our papillary tumours with oncocytic features diagnosed in the past as carcinoma and lacking entirely the diagnostic nuclei (but having a lymph node metastasis of the same morphology) would falsely fall into the adenoma category.

In the biological behaviour of the follicular neoplasms assessment the new classification preserves the morphological diagnostic criteria – invasion through the capsule and into the vessels – irrespective of the years lasting effort to find markers facilitating the benign versus malignant decision, preferably already on the cytology level to solve the problem of the so called microfollicular proliferative lesion. Up to now all the markers tested, like DPPIV, TPO, Galectin proved certain predictive potency merely statistically. For an individual diagnostic decision they fail. Beside many foreign authors Kholová et al. tested these markers (6). The spectrum of the diagnostic tools and markers to solve this problem is certainly not exhausted. Yet the contemporary official diagnostic criteria for the malignancy confirmation require unequivocal evidence of invasion (capsule, vessels). Only the immunohistochemistry for endothelia identification is recommended. This by no mean new aid proved to be useful in our daily practice.

A certain shortage of the new publication compared to the previous one resides in deletion of the special section devoted to the pseudotumorous – tumour – like lesions. Some hyperplastic processes and activated glands can form due to the neuroendocrine regulation disturbances, as well as complicated inflammatory changes combined with regressive and regeneratory changes, very complicated morphology, where already the first decision step, i.e. neoplasm versus non neoplastic lesion can be really difficult. To illustrate this topic, a special article is needed for the extensive and heterogeneous nature of this problem.

A controversial feature is the heading „Synonyms" that introduces the sections of the new classification. The idea itself is by no means useful, if it were not for the fact that the term Synonyms is used definitely incorrectly. Regarding the English being the original language of this text written by a team of international co-authors, we have checked the meaning of the word „Synonym" in two English written sources, both from the era of the first and the contemporary classification (8,3). In the Webster's dictionary (8) the following definition stays:

Synonym
[fr.lat. synonymum, gr. synōnymon]
One of two or more words or expressions of the same language that have the same or nearly the same meaning in some or all senses.
In the lexical database of English (3) the definition is even stricter:
Synonym
Equivalent word - *two words that can be interchanged in a context.*

Let's check the „synonyms" like:

/1/ Follicular carcinoma
Follicular adenocarcinoma
Oncocytic carcinoma
Hürthle cell carcinoma

/2/ Mixed medullary and follicular cell carcinoma
Mixed follicular and C cell carcinoma
Mixed medullary and papillary carcinoma
Composite carcinoma
Biphasic carcinoma
Simultaneous carcinoma
Compound medullary and follicular carcinoma
Concurrent medullary and follicular carcinoma
Stem cell carcinoma
Differentiated carcinoma –intermediate type

/3/ Hyalinizing trabecular tumour
Hyalinizing trabecular adenoma
Paraganglioma-like adenoma
Hyaline cell tumour with massive accumulation of cytoplasmic microfilaments
Hyalinizing trabecular adenoma-like lesion

Papillary carcinoma; hyalinizing trabecular variant

A user having the meaning of the concept Synonym petrified in his memory finds out that beside the historically erroneous term (Hürthle cell adenoma) and real synonyms subunits/variants are listed on the same level – see example /2/. In the example /3/ cited surprisingly enough carcinoma shares the same synonym group with adenoma (see the first and last rows of the list) which can lead to a certain frustration. The problem could be solved easily – just to take into account the cited actual web database of the English language (3). This way the term Synonyms could be substituted with the heading Related terms. The database cited offers for this term four different definitions, anyone of which matches better the usage in the context given compared to the incorrect in terms of formal logic term Synonyms.

An advantage beyond dispute is represented in the new classification by the rich literature overview and index. Their presence is a tangible evidence of the fact that the authors themselves intended to facilitate the confrontation with the meaning variations.

Conclusion

The necessity of international consensus in diseases and especially neoplasms classification is beyond doubt. The former much briefer classification of thyroid neoplasms has been memorized and mastered quickly in the daily routine. The new classification provides a highly inspiring and rich in content source of information. More time and effort will be required to master it (while a new classification will be already emerging…). In spite of some critical remarks mentioned, it represents a successful and useful normative text.

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