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Poorly Differentiated Thyroid Carcinoma. Are We There Yet?

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Abstract The article reviews the controversial area of poorly differentiated thyroid carcinoma. Consensus criteria that define poorly differentiated thyroid carcinoma have been published in 2007. According to these, poorly differentiated thyroid carcinoma is a distinct histotype and the term "poorly differentiated" should not be used as a synonym for high-grade thyroid cancer. Data in the literature show that tumor necrosis and high mitotic activity, but not growth pattern or histologic subtype, are prognostic markers for thyroid tumors. This underscores the importance of grading to identify thyroid carcinomas that behave aggressively. The issue of grading versus typing thyroid tumors is discussed.

Keywords Thyroid carcinoma · Poorly differentiated carcinoma · Insular carcinoma · Tumor differentiation

The existence and definition of poorly differentiated thyroid carcinoma has involved a long debate in the field of endocrine pathology. A few years ago, in 2004, an entire session of the Endocrine Pathology Society was dedicated to poorly differentiated thyroid carcinoma, [1] and in 2006, an international conference was held in Turin, Italy, to reach a consensus on its diagnostic features [2]. The term poorly differentiated was introduced almost simultaneously in the 1980s by two different groups that used it for different reasons [3, 4]. To understand the issue, it is worth remembering yet again the original formulations. In a landmark paper, Carcangiu and colleagues [3] describe insular carcinoma as a tumor characterized by "solid clusters ("insulae") of tumor cells containing a variable number of small follicles; small size and uniformity of the tumor cells; variable, but consistently present mitotic activity; capsular and blood vessel invasion; and frequent necrotic foci, sometimes leading to the formation of "peritheliomatous" structures. Metastases to regional lymph nodes, lung, and bones are common, and these often lead to the patients' death". They were reporting a tumor entity, distinct to the point of instant pattern recognition, the prototypical example of a poorly differentiated thyroid carcinoma, since it combined loss of glandular differentiation, high-grade features and poor prognosis [1, 3]. They viewed the tumor "situated morphologically and biologically in an intermediate position between the well differentiated (papillary and follicular) and the totally undifferentiated thyroid tumors" [1, 3]. Sakamoto and colleagues were considering the issue from a very different angle. They designated as poorly differentiated those thyroid tumors that had lost histologic evidence of glandular differentiation (follicular or papillary), resulting in "solid trabecular and/or schirrous patterns" [4]. They associated loss of glandular differentiation with reduced survival and proposed the term to grade thyroid carcinoma into well differentiated, poorly differentiated, and anaplastic tumors. In the following years, the objective need to fill the gap between the common but indolent follicular and papillary carcinomas and the rare but lethal anaplastic cancers spurred a flurry of papers that used the term "poorly differentiated" for a wide range of tumors, some similar to the original description of insular carcinoma, others just because they were felt to have a prognosis intermediate between the two extremes [5–12]. This state of affairs generated confusion among pathologists making it

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difficult, if not impossible, to systematically apply a potentially useful diagnostic category to the clinical practice.

What We Know about Poorly Differentiated Thyroid Carcinoma

The World Health Organization (WHO) Classification of Tumors in 2004 defined poorly differentiated thyroid carcinomas as "follicular-cell neoplasms that show limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviorally an intermediate position between differentiated (follicular and papillary carcinomas) and undifferentiated (anaplastic) carcinoma", stressing the importance of both differentiation loss, evidenced by non-glandular solid, trabecular or insular growth patterns, and high-grade features (necrosis and mitoses) [13]. The international conference of 2006 in Turin reached a consensus on a simple algorithm to standardize the diagnosis of poorly differentiated thyroid carcinoma, not a small feat given the premises [2]. The consensus identified poorly differentiated thyroid carcinoma as a tumor with "(1) a solid/trabecular/insular pattern of growth, (2) absence of conventional nuclear features of papillary carcinoma, and (3) presence of at least one of the following features: convoluted nuclei, mitotic activity ($\geq 3 \times 10$ HPF), necrosis". Essentially, it represented a generalization of the original concept of insular carcinoma, and validated the existence of a poorly differentiated carcinoma with clinical behavior in an "intermediate position between the well differentiated (papillary and follicular) and the totally undifferentiated thyroid tumors" [3]. The consensus definition is consistent with the WHO criteria mentioned above, since it takes into account both loss of differentiation as well as high-grade features. It is also consistent with the current models of tumor progression (papillary and follicular carcinoma→poorly differentiated carcinoma→anaplastic carcinoma): the co-existence in the same tumor of poorly differentiated carcinoma with areas that have the appearance of conventional follicular or papillary carcinoma (a common occurrence) does not preclude the diagnosis. According to the WHO for a diagnosis of poorly differentiated carcinoma, the majority of the tumor must (obviously) exhibit poorly differentiated features. Although the consensus conference did not state a precise percentage, 75% is a reasonable quote [14]. It is, however, a good practice to report the presence of poorly differentiated carcinoma—even if it does not represent the majority of the tumor—in an otherwise conventional follicular or papillary tumor, since the high-grade component may drive the prognosis. This practice is even more important if anaplastic carcinoma is present and any significant undifferentiated component in a poorly differentiated carcinoma should definitely be noted and reported. Also reasonable is to apply the diagnosis of poorly differentiated carcinoma to tumors that meet the criteria discussed above, but are composed of particular cell types such as oncocytic or clear cells [9, 13, 14].

Probably, the greatest contribution of the WHO Classification of Tumors and of the consensus conference in Turin [2, 13] has been defining what *does not* constitute a poorly differentiated carcinoma: solid variant papillary carcinoma, because of its clinicopathologic features, including functional differentiation with response to radioactive iodine treatment and better prognosis, and follicular carcinoma with solid or trabecular growth patterns, because it does not have high-grade features. Obviously, any tumor that shares with poorly differentiated carcinoma a substantial lack of glandular differentiation but is not derived from follicular cells should be excluded. In fact, poorly differentiated carcinoma—unlike anaplastic carcinoma—retains clear evidence of its origin from follicular cells. It is therefore immunoreactive for both TTF1 and thyroglobulin, although positivity for the former may be weaker than in conventional follicular and papillary carcinomas, and positivity for the latter is often focal sometimes displaying a peculiar dot-like paranuclear pattern [2, 13]. The retention of TTF1 and thyroglobulin immunoreactivity can be used to rule out anaplastic carcinoma predominantly composed of epithelioid elements. The role of immunoistochemistry is, however, mainly limited to the exclusion of tumors not derived from follicular cells, primarily medullary carcinoma, but also parathyroid carcinoma that can directly infiltrate the thyroid or metastatic tumors. The increased proliferation rate of poorly differentiated carcinoma can be demonstrated by immunohistochemistry using Ki67 [15], and p53 often accumulates in the nucleus of neoplastic cells [16], but at the moment, there are no immunohistochemical markers that define the tumor. The diagnosis relies thus mainly on the careful analysis of hematoxyin and eosin sections.

A uniform set of criteria to diagnose poorly differentiated thyroid carcinoma is producing reliable data on its true prevalence (~5–10% in the mountain region around Turin, <2% in the USA and <1% in Japan) [14]. It will also clarify the molecular alterations of the tumor and allow the selection of the most appropriate therapy for the patients.

Histologic Typing and Histologic Grading: Is There a Problem?

In its current definition, poorly differentiated carcinoma represents an entity or histotype. As such, it can be reproducibly diagnosed, based on a specific set of histological features, and has distinctive clinical and prognostic

characteristics. However, is poorly differentiated carcinoma the only tumor with a prognosis intermediate between that of the usual follicular and papillary carcinomas and anaplastic thyroid cancer? If there are other such tumors, how do we flag them so that the patient can receive appropriate treatment?

The answer to the first question is clearly no. Poorly differentiated carcinoma is not the only thyroid tumor that can behave aggressively without reaching the lethality of anaplastic cancer. Follicular tumors with extensive angioinvasion do worse than the usual follicular carcinoma in spite of their well differentiated follicular features. Similarly, columnar or tall cell papillary carcinoma that clearly are not poorly differentiated as judged by their degree of papillary (i.e., glandular) proliferation have a worse clinical behavior than the usual papillary carcinoma [17]. More than 40% of aggressive thyroid cancers that do not respond to radioactive iodine treatment are indeed papillary carcinomas [18]. Recently, review of over a thousand thyroid carcinomas diagnosed in a single Italian institution during a period of 25 years identified 44 fatal tumors, after the exclusion of anaplastic and medullary cancers: 29 were papillary carcinomas, 5 were follicular carcinoma (3 widely invasive, 2 oncocytic), 1 was a mucoepidermoid carcinoma, and only 9 tumors were poorly differentiated carcinomas according to the current definition [19]. Even in the original description of insular carcinoma, of which the current definition of poorly differentiated carcinoma represents an extension, Carcangiu and colleagues described it as *one* of the tumors with these intermediate clinicopathologic features [1, 3]. There was no implication that the tumor was the only form of aggressive non-anaplastic thyroid cancer.

The answer to the second question is more complex. We all wish we had the answer since the definition of the prognostic characteristics of a tumor is essential to optimize cancer treatment. The group of pathologists at Memorial Sloan Kettering Cancer Center has produced over the last several years a number of important papers aimed at defining the histologic features that correlate best with the outcome of patients with thyroid carcinoma. In particular, they have convincingly shown that elevated mitotic activity (≥5 mitoses per 10 high power fields) and (even more so) tumor necrosis are associated with aggressive behavior among non-anaplastic thyroid cancers [18, 20]. The presence of a solid, trabecular, or insular growth pattern, the first requirement for a diagnosis of poorly differentiated thyroid carcinoma (and a common occurrence among aggressive tumors) was not per se statistically associated with poor outcome [18, 20]. We all know that tumor prognostication is based on host factors, such as age and sex and tumor factors such as tumor burden (stage), histotype, and grade. Grade is usually a combination of differentiation that measures how much the tumor has departed from the normal reference tissue (also called *architectural grade* since it is usually based on growth pattern) and of morphologic features such has cellularity, atypia, mitoses, and necrosis (*cytologic grade*). Incidentally, since the concept of tumor grading was introduced by Broders in 1921 [21], grade has been used to gauge the intrinsic biologic aggressiveness of neoplastic cells, not how much they invade. Therefore, it should not be confused with histologic microstaging that measures microscopically how much a tumor has invaded adjacent structures (blood vessels, the capsule of an organ, the tumor capsule itself, etc.). The combination of features selected for grading varies with different tumors, so architectural grading is very important for prostate cancer, while cytologic grading is essential for gliomas. There is a general parallel between architectural grade (differentiation) and cytologic grade: a poorly differentiated tumor usually features high cellularity, marked atypia, etc., vice versa a low-grade tumor usually has few mitoses and no necrosis. However, it is important to recognize that this may not always be the case: squamous cell carcinoma can produce vast amounts of keratin and numerous horn pearls (a sign of differentiation) and yet have markedly atypical cells and numerous mitoses; small cell neuorendocrine carcinoma is highly differentiated, since it express numerous markers of neuroendocrine differentiation, but is also of high cytologic grade. On the contrary, basal cell carcinoma of the skin is poorly differentiated by definition, since it reproduces the undifferentiated layer of the epidermis, but may lack high-grade cytologic features.

In the thyroid, it is difficult to use architectural grading as a prognostic marker because of the common occurrence of complex patterns and of tumors that combine different types of growth [22, 23]. It has also been correctly noted that since there are no papillae in the normal thyroid, papillary carcinoma cannot be called well differentiated in spite of its evident glandular growth [22, 23], while tumors with solid architecture and little evidence of glandular differentiation may still be able to uptake iodide and are therefore (at least) functionally differentiated. Even cytologic grading is problematic. Cellularity and atypia are of little use in endocrine tumors in general and particularly in the thyroid (cfr. nuclear atypia and even pleomorphism in oncocytic adenomas). That leaves us with mitotic activity and necrosis. It is very reassuring that these are precisely the features that have been shown to be of the highest prognostic significance to predict thyroid cancer outcome [2, 20]. To quote the words of Dr. Rivera and colleagues "in addition to architectural grading, it is necessary to take into account 'proliferative' grading features (i.e., necrosis and mitosis)" to reliably predict aggressive behavior and lack of response to radioactive iodide treatment [18].

Poorly differentiated thyroid carcinoma is in its current definition a distinct type of tumor and as such has been included as one of the reportable histotypes by the College of American Pathologists (CAP) Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland Based on the 7th AJCC/UICC TNM edition (October 2009) (grading has been included in the protocol but is not considered a requirement because of ambiguities in its definition). Like the original entity of insular carcinoma, the current definition of poorly differentiated carcinoma combines loss of glandular differentiation with high-grade features, specifically mitotic activity and necrosis. The very name ("poorly differentiated" is grade terminology) and the fact that its definition depends on the presence of high-grade characteristics has certainly engendered confusion in the past and may still do so today [24]. It is important to underscore that poorly differentiated carcinoma is not a synonym for high-grade thyroid cancer. As a matter of fact, many tumors that are aggressive and have lost the ability to retain iodine are not poorly differentiated carcinomas according to the consensus criteria discussed above [18, 19], and carcinomas that are poorly differentiated according to the same criteria may even be relatively indolent if surrounded by a well-defined capsule [25]. Paradoxically, poorly differentiated carcinomas that lack necrosis or significant mitotic activity may not even be high-grade tumors, at least as far as cytologic grade is concerned. Although high mitotic activity and necrosis have always been considered important to predict prognosis one may wonder why their relevance has only recently been validated [2, 18, 20]. One reason is certainly the difficulty in assembling and studying large number of cases with accurate follow-up, another may have been the preeminence of tumor typing versus grading in thyroid pathology.

In fact, tumor typing and grade provide different, complementary information [22, 26]. While grading is an extremely (cost)effective tool to predict prognosis, typing defines tumors with distinct clinicopathologic profiles and biologically relevant features that have in many cases passed the test of gene expression profiling [27]. While high-grade tumors accumulate numerous alterations that may mask distinctive molecular features, tumor histotypes can be more easily linked to specific genetic changes, a fact that greatly facilitates molecular targeted tumor therapy [28]. The correlation between histotype and genotype among thyroid tumors is very good, and has allowed the identification of putative progression pathways that are useful models to understand the biology of the different tumor types and may also be clinically relevant [29]. In poorly differentiated thyroid carcinoma, as currently defined, Ras mutations are common and also represent a negative prognostic marker, while BRaf mutations, RET/PTC, and PAX8/PPARγ rearrangement are rare [30]. Since Ras mutations are also highly prevalent among follicular thyroid neoplasms and in the follicular variant papillary carcinoma, it is reasonable to suggest that poorly differentiated carcinoma evolves primarily from them rather than from papillary carcinoma with papillary growth pattern or tall cell features that typically have mutated BRaf [31]. On the other hand, BRaf mutations represent the most common mutation among radioactive iodine refractory thyroid cancers, indicating that many of these aggressive tumors are (or originate as) papillary carcinoma [32].

Prognostic schemes based on grading have been successfully applied to predict outcome for specific types of thyroid tumors, including papillary carcinoma [22]. In principle, it may be possible to apply a single grading system to all thyroid cancers. One of the more sophisticated and effective prognostic score systems is that introduced by the French Federation of Cancer Centers (FNCLCC) Sarcoma Group to grade soft tissue sarcomas [33]. According to this system, specific histotypes are assigned a "tumor differentiation score" from 1 to 3 (e.g., Ewing sarcoma has a score of 3) and so are mitoses and tumor necrosis. Something similar, that includes both histotypes (or subtypes) as well as cytologic grading elements like mitotic activity and necrosis, should work for thyroid carcinomas, although other features, like the presence of a tumor capsule may also be very important.

Conclusion

Poorly differentiated thyroid carcinoma is a histologic type of thyroid cancer with distinctive clinicopathologic characteristics, not a synonym for high-grade thyroid cancer. The existence of a consensus about its diagnostic features will facilitate the definition of its molecular alterations and of the best treatment modality for the patient. Prognostic score systems that take into account both histotype and grading should be implemented. Increased mitotic activity and (even more) tumor necrosis should prominently figure in them. Meanwhile, it is a good idea to record their presence in the pathology report and to mention that they have been linked with poor outcome in several studies.

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