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**POORLY DIFFERENTIATED CARCINOMA: FROM MORPHOLOGY TO
MOLECULAR DATA AND BACK.**

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Definition and classification criteria - The term "poorly differentiated (PD) carcinoma" has been proposed twenty years ago to define a thyroglobulin-producing non-follicular, non-papillary thyroid carcinoma, having an intermediate behavior between well differentiated and anaplastic carcinomas (1-10). In the 2004 WHO classification of Endocrine Tumors (11), PD carcinomas have been introduced as a separate entity, and their recognition has been proposed on both architectural and high-grade cellular features. In fact, PD carcinomas have been defined according to both their non-follicular/non-papillary growth pattern, being trabecular/insular/solid (TIS) areas usually predominant, and their unequivocal high grade histology, with atypias, high mitotic count and necrosis. By definition, high grade variants (i.e. tall cell or columnar) of papillary carcinomas have been excluded from the PD tumor group. However, in the diagnostic practice the above mentioned criteria are still controversial and heterogeneously applied, some overlap therefore existing between other tumor categories: these include the solid variant of papillary carcinoma and well-differentiated follicular carcinomas with predominant solid/trabecular growth patterns.

A diagnostic algorithm for the diagnosis of PD carcinomas has recently been proposed, as the result of a consensus conference held in Turin, involving 12 pathologists from Japan, US, and Europe (12). An agreement was reached concerning the diagnostic criteria which were proposed as follows:

(1) presence of a solid/trabecular/insular (STI) pattern of growth in an otherwise malignant thyroid lesion. It is important to note that these different growth patterns are usually admixed in the same tumor, and to an extent not clearly settled for the diagnosis of PD carcinoma ("the majority of the tumor" is mentioned as a requirement in the WHO book) (12).

(2) absence of the conventional nuclear features of papillary carcinoma. One of the most common sources of disagreement in the diagnosis of PD carcinoma is represented by the solid variant of papillary carcinoma which is characterized by a solid/trabecular growth pattern, in the presence of the diagnostic nuclear features of papillary carcinoma. Since it has been demonstrated to bear a significantly better prognosis than PD carcinoma in the adult population (13), this tumor type should be kept separate.

(3) presence of at least one of the following features: convoluted nuclei; mitotic activity >3x10 HPF; tumor necrosis. Convoluted nuclei are defined as small round hyperchromatic nuclei with convolutions of the nuclear membrane, which are smaller and darker, with irregular ("convoluted" or "raisin-like") contours as compared to the typical nuclei of papillary carcinoma, but with only occasional grooves and loss of ground-glass appearance and pseudoinclusions. These changes are believed to reflect de-differentiation of the papillary carcinoma, with loss of many of its characteristic nuclear features, but preservation of the irregularity of nuclear contours. Concerning high grade features such as high mitotic activity and necrosis, they represent strong negative prognostic indicators in thyroid carcinoma (14,15). Therefore, the presence of at least one of those high-grade parameters was incorporated at a certain step of the proposed diagnostic algorithm. However, necrosis and mitotic activity (although present in most of the cases that were grouped as PD carcinomas) were not considered

patognomonic criteria by themselves, because they may also be recognised in otherwise well-differentiated carcinomas.

Molecular data - Since the original insular carcinoma description by Carcangiu and coworkers (3), both follicular and papillary derivations have been considered for PD carcinoma (6,8,16). To define PD carcinoma histogenesis, several molecular alterations have been investigated. TP53 mutations were described in a subset of PD carcinomas by different authors (17,18), and proposed as a molecular marker of thyroid tumor dedifferentiation and progression, despite the limited case series analysed. *Ras* point mutations were found in variable proportions of PD carcinomas and associated to prognosis, being N-*ras* mutations exclusively present in some reports (4,19) whereas K-*ras* more prevalent in others (20). Conversely, data concerning β -catenin mutations in PD carcinomas are controversial, having been detected in none (21) or in up to 32% (22) of the cases analyzed. Recent molecular evidence have shown that a link of PD carcinoma and papillary carcinoma exists, since activating BRAF mutations have been detected in a series of PD carcinomas having residual papillary carcinoma foci (23), but not in PD carcinoma cases lacking such morphological link to papillary carcinoma (24). RET/PTC1 rearrangements were also found in a small fraction of PD carcinomas having the nuclear features and/or (residual) foci of papillary carcinoma (25).

As a matter of fact, all the above mentioned molecular studies are difficult to compare due to the heterogeneous inclusion criteria. In this perspective, a collaborative study was designed with dr Y. Nikiforov (University of Pittsburg) based on a series of 63 PD carcinomas, re-classified according to the recently proposed diagnostic algorithm. *ras* point mutations were found as the exclusive molecular alteration in a subset of 23% of cases, being N-*ras* 61 codon mutation by far the most common. One single case arising from a tall cell variant of papillary carcinoma harbored a BRAF mutation. No RET/PTC or PAX8/PPAR γ rearrangements were found (*Volante, Nikiforov et al, manuscript in preparation*). Taken together, these findings and previous literature data support the hypothesis that PD carcinomas may de-differentiate from both well differentiated conventional follicular and papillary carcinomas, following a distinct molecular pathway involving *ras* molecular alterations that are alternative to the involvement of BRAF or RET/PTC for papillary carcinomas and PAX8/PPAR γ for follicular carcinomas.

Back to morphology - Molecular data are limited by the heterogeneous case series analyzed, but apparently identify *ras* alterations as the most common molecular signature in strictly re-classified PD carcinomas, depicting a peculiar molecular pathway in this tumor type as compared to well differentiated follicular and papillary carcinomas. Unfortunately, PD carcinoma of the thyroid has been heterogeneously defined and interpreted in the world. Nevertheless, large tumor series selected on the basis of structural and/or other morphological criteria showed that PD carcinomas have a distinct biological behavior, justifying the classification of these tumors into a separate group (also encompassing solid/trabecular oncocytic carcinomas). The call back to morphology is therefore meant to homogeneously classify thyroid carcinomas with poorly differentiated features, applying strict and reproducible diagnostic criteria. The recent Japanese study (26) aimed to investigate the prevalence and clinical significance of “three types of poorly differentiated carcinoma” as defined by Sakamoto (1), the WHO classification (11) and the Turin proposal (12), as well as of the tall cell variant of papillary carcinoma in a large series of thyroid cancers with papillary features, confirmed that different tumor groups are identified by the different inclusion criteria and showed that significant differences among the groups were also present in terms of survival, being cases identified according to the Turin proposal those associated to the worst survival rates.

Key words – Thyroid, poorly differentiated carcinoma, diagnostic algorithm, ras oncogene, solid insular growth.

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