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Multicentric Papillary Thyroid Carcinoma: Stratification for Treatment

Salvador J. Diaz-Cano*

Department of Histopathology, King's College Hospital and King's Health Partners, London, United Kingdom

Abstract

Tumor stage is the main prognosticator of differentiated thyroid carcinomas, but it needs further stratification for multicentric neoplasms (most frequently papillary thyroid carcinomas, PTC), which frequently present as foci smaller than 1cm and are considered by default as high-risk tumors. Not all cases of multicentric PTC should be considered of high risk and they should be stratified to avoid unnecessary radioiodine ablation in selected cases. Currently, there are known variables for this stratification: size and number of tumor foci, clonal patterns, and specific markers of aggressive behaviour (infiltrative growth, *BRAF* mutation). In a near future, the identification of a gene expression pattern associated with a higher risk of recurrence would allow us to focus more aggressive treatment appropriately.

Keywords: Thyroid; Papillary carcinoma; Multicentric; Treatment stratification

Abbreviations: miRNA: Micro RNA; PTC: Papillary Thyroid Carcinoma

Short Commentary on Early Multicentric PTC

The treatment of papillary thyroid carcinoma (PTC) has significantly changed recently and it is mainly based on surgery and radioiodine ablation, the latter for high-risk patients only [1-4]. However, this treatment is currently subjected to extensive review especially for low risk carcinomas. Two main factors have contributed to this review: the increased incidence of secondary neoplasms after radioiodine treatment and the efficiency demonstrated by low dose treatment [4,5]. Cancer treatment selection depends on patient stratification according to risk for a given tumor, but it is particularly challenging for patients with low-risk thyroid cancers because of the slow growth of such tumors. Tumor stage is the main prognosticator of differentiated thyroid carcinomas, but it needs further stratification for multicentric neoplasms (most frequently PTC), which frequently present as foci smaller than 1cm and are considered by default as high-risk tumors. Microscopic PTCs (<1.0 cm) are considered a subset of PTCs that behave more benign. They follow an indolent course and carry an excellent prognosis. Distant metastases and mortality rates were reported to be less than 0.5% [6]. However, some authors suggest that there exists a subgroup of microscopic PTCs that can be aggressive, requiring therapeutic management similar to larger tumors [7]. Unfortunately, within this set of patients, prognostic factors have not been well defined. However, in recent years some specific markers for aggressiveness were identified, including sizes larger than 5 mm, multifocality, tumor extension beyond the parenchyma, lymph node involvement, tumor non-incidentally discovered, and the extent of primary surgery [7-10].

Currently, both biologic and pathologic variables provide a reliable basis for risk stratification of early stage thyroid cancer. Intratumor heterogeneity is at the foundation of tumor progression and it correlates with the tumor volume and multicentricity [11]: the potential to metastasize increase directly with primary size (the main element for T staging), and multicentric neoplasms (expressed by (m) in the T classification). These two key elements are the main general prognosticators used to plan any adjuvant radioiodine treatment. Although multicentric PTCs are not stratified further considering that the presence of multicentricity provides a risk for all patients, no statistical difference in cancer mortality has been observed between the ablated and nonablated groups of patients with multicentric PTC [12], most likely reflecting the lack of selection criteria.

Multicentricity is considered an expression of tumor heterogeneity, the main driver of tumor progression by increasing the number of different clones and therefore the probability of sub-clone development with additional acquired capabilities [11]. Multicentric PTC is more frequently detected due to improved diagnostic methods. More than 70% of microscopic PTCs are diagnosed incidentally (in specimens of the thyroid removed for benign thyroid disease) and it is responsible for the 2.4x increase in incidence of differentiated thyroid carcinoma [13]. Multiple foci have been reported in approximately 7-56% of microscopic PTCs [6,14]. A number of clinical studies showed that patients with ≥ two foci had higher recurrence rate and cancer mortality than those with unifocal PTMCs [6,12]. Moreover, multifocality is an independent risk factor for metastases [15]. It was demonstrated that cases with positive lymph nodes had a higher risk of recurrence [13]. Hence, multifocal PTMCs have been considered to have a poor prognosis requiring radioiodine ablation and close surveillance within the first year. Patients with multicentric microscopic PTC need to be treated as highrisk patients, which partially explain the increase in the proportion of patients receiving radioactive iodine [5,16]. The recurrence rate increases significantly in cases with ≥ 5 foci, which frequently undergo ^{131}I ablation [12]. As all foci are governed by the volume growth criteria expressed below, the clinical significance given to each focus must be linked to its size and a demonstrable evidence of different cellular progenitor. Therefore, the stratification of patients with multicentric tumors would require considering both the size of each focus, the number of foci, and a sensible application of clonality tests (such as X-chromosome inactivation and fractional allelic loss assays) [17]. An appropriate use of these markers serves to

***Corresponding author:** Salvador J. Diaz-Cano, King's College Hospital, Dept of Histopathology, Denmark Hill, London, Greater London, SE5 9RS, United Kingdom, Tel: +44 20 3299-3041 Fax: +44 20 3299-3670; E-mail: sdiaz-cano@nhs.net

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separate clonal origin from clonal expansion (sub-clones development contributing to heterogeneity and progression). As founding mutations have not been properly established in many tumors, clonality assays carry this caveat. However it is only through fractional allelic loss and mutation burden assessments that the relationships within the sub-clones become established. Tumors showing a common progenitor (monoclonal neoplasms) most likely represent intrathyroidal extension and frequently reveal good prognosis, even when associated with lymph node metastasis, provided that no extrathyroidal extension is identified. Multicentric PTC originates usually from neoplastic transformation and subsequent intrathyroidal spread of a single malignant progenitor clone. Bilateral PTCs frequently show the same pattern of inactivation (80%), suggesting that bilateral, recurrent, and metastatic papillary thyroid carcinomas often arise from a single clone and that intrathyroidal metastasis may play an important role in the development of bilateral tumors [18]. Clonal progression and morphotype differentiation occur through progressive acquisition of genetic alterations subsequent to the initial intra-glandular spread. The combination of both tumor focus size and clonality gives the most biologically meaningful approach to stratify patients.

In the tumor volume stratification, the stages are intimately associated with the size of the primary neoplasm: tumors bigger than 1.0 cm reveal an exponential volume growth with good linear correlation (R^2=0.96463) and slopes over 3 (14.582 for tumors 2-4 cm, 3.646 for neoplasms 1-2 cm); tumors 0.5-1 cm maintains the linear correlation, but showing much lower slope (0.911, R^2=0.96463), while tumors smaller than 0.5 cm reveal a partial loss of the linear correlation (R^2<0.9) and a significantly lower slope (0.202 for tumors 0.2-0.5 cm, 0.021 for tumors 0.02-0.2 cm, and 0.0002 for tumors smaller than 0.02 cm) (Figure 1). These figures represent a slight overestimation of the tumor growth because they are based on the assumption of pure tumor cell proliferation, replication of tumor cells in two descendent cells, and a default spherical tumor volume. The tumor cell burden is going to be smaller than the initially predicted due to the heterotypic neoplasm biology: the presence of interstitial host cells (inflammatory cells, endothelial cells, stromal cells, which can have positive or negative effect on tumor growth) and non-solid tumor cell architecture (follicular of papillary in thyroid neoplasms). These two factors will reduce the number of tumor cells estimated per volume, therefore decreasing the cellular pool on which tumor progression can develop. Based on tumor size alone, its impact on tumor volume would therefore be: clinically relevant for tumor foci 0.5-1.0 cm (1:1), limited for tumor foci 0.2-0.5 cm (1:5), very limited for tumor foci 0.02-0.2 cm (2:100), and almost absent for tumor foci smaller than 0.02 cm (2:10000). These considerations of tumor size must be applied to each focus in case of multicentric neoplasms, including for the risk assessment only those foci clinically relevant according to its size and provided that they do not show other adverse features. This size assessment in the primary tumor also shares the approach with the evaluation of lymph node metastasis, which distinguishes metastasis (>2 mm), micrometastasis (0.2-2 mm) and isolated tumor cells (<0.2 mm, <200 cells).

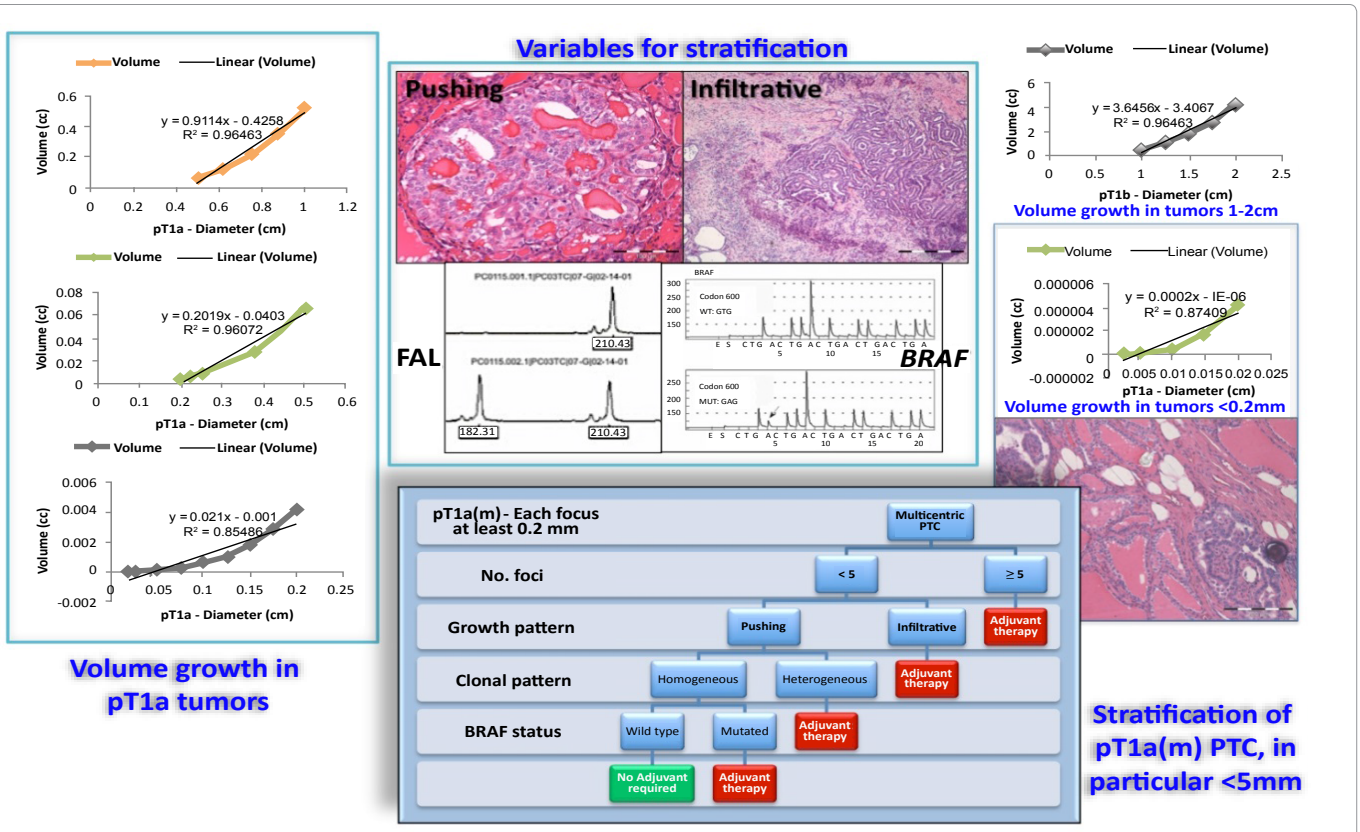

Figure 1: Tumor focus size approach from the upper range clearly separates four scenarios for pT1a tumors: (a) tumors 0.5-1.0 cm reveal almost 1:1 increase of tumor volume per diameter unit, (b) tumors 0.2-0.5 cm show about one fifth growth of tumor volume per diameter unit, (c) tumors 0.02-0.2 cm increase around 2 hundredth of tumor volume per diameter unit, and (d) tumors smaller than 0.02 cm expand about 2 ten-thousandth the tumor volume per diameter unit. This volume growth has to be coupled with number of foci, histological growth pattern (pushing vs. infiltrative), clonality pattern (homogeneous vs. heterogeneous) and simple genotyping (BRAF status) to determine the need of adjuvant therapy in multicentric PTC less than 1cm (pT1a(m)), but with particular emphasis for tumor smaller than 5 mm that are being more frequently detected due to more exhaustive histological examination. FAL = Fractional allelic loss.

Apart from generic variables (size and clonality), there are a number of specific known criteria of high clinical risk for metastasis. These factors are normally referred to as markers of aggressive behaviour and they must be considered for patient stratification. Established markers of aggressive PTC behaviour include both morphological and genetic variables that need to be evaluated in each PTC focus: histologic growth patterns (such as sclerosing, infiltrative or tall cell variants) and *BRAF* mutations.

Only rarely tumors less than 0.5 cm have associated metastases. However, despite the presence of lymph node metastases, the incidence of death from lesions of this size range is extremely rare, frequently associated with other risk factors, such as the presence of aneuploid cell populations in the tumor, sclerosing infiltrative architecture and peripheral location within the gland where it can invades perithyroidal soft tissues and lymphatics [19]. Cyclin D1 staining of PTC is very useful for identifying the intrathyroidal spreading or multifocality of the tumors [20]. In monoclonal *BRAF* V600E-positive multicentric PTCs, *BRAF* V600E is not always present in all tumor foci, indicating that other tumor-genetic factors in the primary progenitor clone can also trigger PTC neoplastic transformation [2]. Micro-RNA (miRNA) profiles can distinguish tumors containing the *BRAF* mutation from the other tumor types, and to differentiate between the more aggressive histological patterns linked to various processes involved in tumor growth and proliferation. Hierarchical clustering analysis of miRNA expression suggests that both discrete areas do not evolve from clonal expansion of tumor cells and independent mutational events can occur simultaneously within a tumor to enhance cancer progression in geographical micro-environments within a tumor [21].

Multicentric PTC should also be stratified and not all cases considered of high risk and, therefore, requiring radioiodine ablation. Currently, there are known variables for this stratification: size and number of tumor foci, clonal patterns, and specific markers of aggressive behaviour (infiltrative growth, *BRAF* mutation). In a near future, the identification of a gene expression pattern associated with a higher risk of recurrence would allow us to focus more aggressive treatment appropriately.

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