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Papillary Thyroid Microcarcinoma – Do Classical Staging Systems Need to Be Changed?

Carles Zafon
Dept. of Endocrinology, Vall d'Hebron University Hospital
Autonomous University of Barcelona, Barcelona
Spain

1. Introduction

It has been broadly demonstrated that there has been a dramatic, worldwide, increase in the incidence of papillary thyroid carcinoma (PTC). Leenhardt *et al.* [2004] showed that there was approximately a 10-fold increase in the ratio of thyroid cancer for the cohort born in 1978 compared to those born in 1928. Davies & Welch [2006] found that the incidence of thyroid cancer in the United States had more than doubled from 1973 to 2002 and that this augmentation was virtually entirely due to an increase in PTC. However, it is uncertain whether this increase is a real phenomenon, or whether it is simply due to an increased rate of detection. Practices for management of thyroid diseases were deeply modified over the past few decades. The wide availability of ultrasonography (US) and fine needle aspiration biopsy (FNAB), as well as the improved accuracy of histopathological examination of surgical samples (that is the thinness of the anatomical slice of the thyroid specimen) are indicated as causes of this so-called spreading of the epidemic [Grodski & Delbridge, 2008]. Furthermore, the characteristics of PTCs, especially its size at diagnosis, have changed over time.

According to the World Health Organization, papillary microcarcinoma (PTMC) of the thyroid is defined as a papillary carcinoma measuring 1 cm or less [Lloyd et al., 2004]. PTMC is not recognized as a specific entity in the Tumor, Node and Metastasis (TNM) classification, and it is included in the T1 category, which has tumors as large as 2 cm.

The aim of the present article is to highlight how PTMC is changing the classical point of view of PTC and how, in the next few years, we must be able to incorporate the new phenotypic characteristics of PTC in the staging systems.

2. PTMC has changed the classical features of PTC

Several authors described a temporal trend toward decreasing tumor size in PTC. Chow *et al.* [2003] found that the percentage of PTMC has increased from 11.9% of all PTCs before the year 1980 to 25.5% in the decade 1990-1999. In an epidemiologic study carried out in a Brazilian region, Cordioli *et al.* [2009] reported that the average size of thyroid tumors

decreased from 1.51 cm in the year 2000 to 1.02 cm in the year 2005. Moreover, in 2000 36.9% of cancers were smaller than 1 cm, whereas in 2005 PTMC accounted for 61.48% of all thyroid carcinomas. In the USA there was a 49% increase in the incidence of PTC, consisting of cancers measuring 1 cm or smaller [Davies & Welch, 2006]. In a large study Hay *et al.* [2008] found that PTMC represented 31% of the total patients with PTC. Additionally, during the decade 1945-1954 PTMC accounted for only 19% of the total patients with PTC, whereas in the decade 1995-2004 the percentage rose to 35%. Leenhardt *et al.* [2004] showed that the proportion of PTMC among cancers, which were operated on, increased form 18.4% in the period 1883 to 1987 to 43.1% in the period 1998 to 2001. Furthermore, in the most recent literature, especially those that analyzed cases from the last decade, PTMC comprises almost half of all papillary cases [D. Lim et al., 2007; Pakdaman et al., 2008].

3. Staging systems

There exist different scoring systems currently used to stratify patients with differentiated thyroid carcinoma (DTC). With the identification of certain clinicopathological parameters, associated with indolent or aggressive tumor behavior, patients may be separated in to risk groups based on these parameters, such as age, gender, size of tumor, and cancer extension. Consequently, treatment and follow-up decisions should be based on the analysis of these risk groups. Although they are broadly accepted, prognostic significance of the scoring systems is limited for several reasons [Sherman, 1999]. For example, all the systems are based on retrospective studies and the vast majority of them were published more than 20 years ago using historical cases. Thus, the age, grade, extent, size (AGES) scoring system was verified in a cohort of subjects with papillary thyroid carcinoma treated in the Mayo Clinic from 1946 through 1970 [Hay et al., 1987]. The age, distant metastases, extent, and size (AMES) staging proposal was developed in a controlled study of 821 patients with differentiated thyroid carcinoma (including both PTC and follicular thyroid carcinoma, FTC) between 1941 and 1980 [Cady et al., 1988]. The Clinical Class staging system, proposed by deGroot, was based on 269 patients with PTC treated during the interval of 1968-1980 [DeGroot et al., 1990]. The Ohio State University (OSU) study first enrolled 1355 patients (including PTC and FTC), treated between 1950 and 1993 [Mazzaferri & Jhiang, 1994].

It is interesting to note that treatment of PTC has significantly changed from those early years. Radioiodine ablation was introduced some years later. In the aforementioned cohort study of the Mayo Clinic only 3% of patients underwent postoperative ablation [Hay et al, 1987]. Moreover, the utilization of thyroglobulin levels as a tumor marker was introduced in 1975 [Van Herle & Uller, 1975]. Tubiana et al.[1985] showed that patients treated after 1960 had a better outcome than patients treated earlier, though they did not differ in age, histological characteristics, sex ratio or incidence of palpable lymph nodes. In addition, it has been said that most of the scoring systems do not take in to consideration the clinical status of the patient or the treatment procedure [Duntas & Grab-Duntas, 2006]. Moreover, it was proposed that different staging systems should be evaluated and validated independently for PTC and FTC [Lang et al., 2007a]. Finally, PTMCs are excluded from some studies [Schindler et al., 1991].

Some authors compared the utility of several staging systems in their series of patients, with the aim to find out the one that is the most predictive [Kingma et al., 1991; Lang et al., 2007b; Passler et al., 2003; Voutilainen et al, 2003]. Results do not confirm that any of them are

better than the other. However, the TNM staging system, employed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is currently the most widely used.

3.1 PTMC in the staging systems

PTMCs 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% [Hay et al., 2008; Roti et al., 2008]. However, some authors suggest that there exists a subgroup of PTMCs that can be aggressive, requiring therapeutic management similar to larger tumors [Page et al., 2009]. 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, capsular invasion, tumor extension beyond the parenchyma, lymph node involvement, tumor non-incidentally discovered, and the extent of primary surgery [Küçük et al., 2007; S. Le et al., 2008; Mercante et al., 2009; Paget et al., 2009; Pelizzo et al., 2006; Roti et al, 2006]. Probably, three of the most accepted factors are multifocality, lymph node metastasis, and the mode of diagnosis.

Multiple foci were reported in approximately 7-56% of PTMCs [Dietlein et al., 2005; Hay et al., 2008; J. Lee et al., 2006; Roti et al., 2008]. A number of clinical studies showed that patients with ≥ two foci had a higher recurrence rate and cancer mortality than those with unifocal PTMCs [Baudin et al., 1998; Hay et al., 2008; J. Lin et al., 2009]. Moreover, multifocality is an independent risk factor for metastases [Gülben et al., 2008]. Hence, multifocal PTMCs have been considered to have a poor prognosis.

PTMCs also showed a high incidence of regional lymph node metastasis, occurring in 12--64% of patients [Besic et al., 2008; Choi et al, 2008; Chung et al., 2009; J. Lee et al., 2006; S. Lee et al., 2008; Y. Lim et al., 2009; Roh et al., 2008]. It was demonstrated that cases with positive lymph nodes had a higher risk of recurrence [Chow et al., 2003]. Kim et al. [2008] found that lateral cervical node metastasis was the most powerful independent predictor of clinical recurrence.

More than 70% of PTMCs are diagnosed incidentally (in specimens of the thyroid removed for benign thyroid disease) [Chow et al., 2003; Roti et al., 2008]. It has been suggested that clinical and biological behaviors may differ between incidental and non-incidental PTMCs [Barbaro et al., 2005; Chow et al., 2003; J. Lin et al., 2008]. Overt tumors are associated with a higher incidence of multicentricity, extrathyroidal involvement, lymphovascular invasion, higher stage, risk of relapse, and death [Besic et al., 2009; Chow et al., 2003; J. Lin et al., 2008; Lo et al., 2006; Noguchi et al., 2008; Pisanu et al., 2009].

4. Immunohistological markers

The knowledge of the molecular basis of cancer has changed dramatically, and what is more important, the accuracy of the diagnosis has changed as well [Chan, 2000]. The diagnosis of cancer in pathology is mainly based on the morphology of tissues and cells. Immunohistochemistry allows us to detect molecules in these tissues, including cell components, cell products, tumor markers or molecules, which help to predict the tumor

behavior. The immunological reaction that takes place with this technique has remarkable sensitivity and specificity and it is applicable to routinely processed tissues, including fixed tissues. A great advantage of immunohistochemistry is the fact that we can simultaneously visualize the morphology of the cells and the immunostaining, so that we can locate the antigen we are detecting, in a particular subcellular localization or in a specific subtype of cells. Another advantage of the technique is that it is applicable to several types of material including tissue sections and cytological specimens [Chess & Hajdu, 1986].

In PTC, immunohistochemistry could be a useful tool to help not only in identifying the subset of patients at high risk, but also in those cases with no clear histological diagnosis [Rezk & Khan, 2005]. Several novel markers were tested, but, unfortunately, none of them were proved to be useful enough in clinical diagnosis [Asa, 2005]. At present, it is thought that their utility depends on the use of a panel of markers that include various combinations of them [Zafon et al., 2010]. For example, simultaneous immunohistochemical expression of HBME-1 and galectin-3 differentiates papillary carcinomas from hyperfunctioning lesions of the thyroid [Rossi et al, 2006].

Also in PTMC several possible immunohistological markers were proposed to assess the biological aggressiveness of the cancer [Boucek et al., 2009; Cvejic et al., 2008; Khoo et al., 2002; D. Lim et al., 2007] (table). Some authors compared molecular expression in PTMCs and PTCs of larger size. For example, Cvejic et al [2009] reported differences in the expression of the apoptotic molecule Bax and in the ratio Bcl-2/Bax between PTMC and larger tumors. Batistatou ***et al*** [2008] found a negative correlation between E-cadherin and dysadherin expression and the tumor size. Other authors attempted to define molecular characteristics of aggressiveness. For instance, D. Lim et al. [2007] showed that the absence of EGFR expression was correlated with extrathyroid extension and lymph node metastases. Lantsov et al. [2005] found a significant association between Cyclin D1 expression and both tumor size and lymph node metastases. Khoo et al. [2002] obtained similar results. Finally, Ito et al. [2005] reported that expression of proliferating markers such as Ki-67, Cyclin D1 and the retinoblastoma gene product (pRb) increased in PTMCs with clinically apparent metastases.

Molecule	Size	Aggressiveness	Reference
E-Cadherin	**--**		Batistatou *et al* [2008]
Dysadherin	**--**		Batistatou *et al* [2008]
Bcl-2/Bax ratio	**+**		Cvejic *et al* [2009]
MUC4	**+**		Nam *et al*. [2011]
Cyclin- D1	**+**	**+**	Lantsov *et al*. [2005]
		+	Khoo *et al*. [2002]
		+	Ito *et al*. [2005]
Ki-67		**+**	Ito *et al*. [2005]
pRb		**+**	Ito *et al*. [2005]
S100A4		**+**	Min *et al*. [2008]
EGFR		**--**	D. Lim *et al*. [2007]
Galectin-3		**0**	Cvejic *et al* [2005]

Table 1. Correlation (+ positive, - negative, 0 no correlation) between molecular markers and papillary thyroid microcarcinoma features.

5. The age factor

Some studies failed to identify independent prognostic factors, arguing that to distinguish PTC on the basis of size alone may be clinically irrelevant [Arora et al., 2009; Sugino et al., 1998]. Moreover classical scoring systems seem to be less accurate when the PTC is of a smaller size. Additionally, the role of age, as the paradigm of prognostic factors, remains to be established.

Most reports in the literature show that older patients with PTC have a worse prognosis. In DTC age is the most important factor and this parameter is included in the TNM staging system as well as in the vast majority of the other scores. Older age is especially significant in patients with advanced tumors [Pelizzo et al., 2005]. However, once again, though articles recognize the age factor, most of them are retrospective studies that include cases without current standardized therapeutic protocols. Moreover, few reports specifically analyze the behavior of thyroid cancer in the elderly. Vini et al. [2003] studied the biological behavior in 111 patients with DTC, who were older than 70. The authors found that older age was an important risk factor for overall survival. It is noteworthy that only 52% of patients had PTC, total thyroidectomy was performed in only 41% of cases and postoperative radioiodine was administered in the 72%. Furthermore, investigators showed that the probability of survival changed significantly according to the decade in which the patient was treated. Thus, median survival improved from 4.7 years before 1970, to more than 10 years after 1990 [Vini et al., 2003]. J. Lin et al. [2000] analyzed thyroid cancer in patients age 60 or older. Less than half of all the cases were papillary. They concluded that one important difference with respect to younger subjects was the delay in the diagnosis.

The increased aggressiveness of PTC in elderly patients may be attributed to a variety of factors. It is assumed that older subjects have tumors with a higher percentage of histological types with less favorable prognosis [Hundahl et al., 1998]. Also, effectiveness of radioiodine therapy decreases in the elderly. Schlumberger et al. [1996] found that metastases of DTC uptake iodine in 90% of patients less than 40 years of age and in 56% of patients over 40. Mihailovic et al. [2009] found that age is related with the radiodione avidity of distant metastases. Moreover, aged patients show a higher rate of large tumors. Biliotti et al. [2006] found that in subjects, who were older than 70, with thyroid tumors > 2 cm in diameter, the survival rates were markedly lower than rates among patients with a tumor diameter of < 2 cm. Other factors have been proposed such as the sexual hormone status and the impaired immune response, which accompanies older individuals [Haymart, 2009a]. Accordingly, it appears that thyroid cancer in the elderly and in younger patients could have a different behavior [Biliotti et al, 2006].

5.1 Age in PTMC

Some reports also demonstrate the importance of age in PTMCs [J. Lin et al, 2005]. H. Lin & Bhattacharyya [2009] examined the Surveillance, Epidemiology and End Results (SEER) registry, a database from the National Cancer Institute of the USA. The authors analyzed 7,818 cases of PTMC, which presented without local or distant metastasis. They found that only an increased age at diagnosis predicted decreased disease-specific survival. In a recent report, Elisei et al. [2010] showed that though patients diagnosed during the last

two decades have smaller tumors, older age still represents the most important prognostic factor for survival.

However, despite the fact that older age is a universally identified poor prognostic factor in PTC, other investigators failed to find that age affects the outcome of patients with PTMC. In the aforementioned report of Chow et al. [2003], the authors found that, in PTMC, age was not a significant factor in predicting disease recurrence or survival. Gülben et al. [2008] found that mean age was higher in patients with lymph node metastases but the difference was not significant. In the large study reported by Pakdaman et al. [2008] investigators showed that the prevalence of PTMC was higher in patients 45 years and older, than in patients under 45. However, age was not related with multifocality, bilaterality and extrathyroid extension, risk factors shown to increase recurrences. Of particular interest is the recent article of Besic et al. [2009], which reported that in PTMC, lymph node metastases were more common in patients over 45 years of age. The same authors also showed that there was no correlation between the duration of the disease-free interval and the age of patients [2008]. Moreover, in an adjusted model, Noguchi et al. [2008] found that age was not a risk factor for recurrence in PTMC. Mercante et al. [2009], in their large study of 445 cases demonstrated that age was not a significant risk factor for neck recurrence or distant metastasis. Another study reported that patients with lymph node metastasis were younger than those without lymph node metastases [Chung et al., 2009]. Y. Lim et al. [2009] also found that in patients under 45 there was a higher incidence of ipsilateral central lymph node metastases. Previously, Baudin et al. [1998] described that patients with non-incidental PTMC were significantly younger. Non-incidental diagnosis was proposed as a criterion for a poor outcome. Another study reported that patients with PTMC were significantly older that patients with larger tumors. Moreover, in the PTMC group lymph node metastasis at diagnosis was correlated with a younger age [Tzvetov et al., 2009]. Jacquot-Laperrière et al. [2007] found that age did not become a prognostic factor for the risk of metastatic spread.

In the meta-analysis carried out by Roti et al. [2008] a younger age (< 45 years) was significantly associated with cancer recurrence. Haymart et al. [2009b] found that patients who received radioiodine ablation were younger that those not receiving this treatment. Recently, we reported that PTMCs in older patients were associated with less multifocality, bilaterality, fewer lymphadenectomies and a decreased rate of non-incidental tumors than in younger patients [Zafon et al, 2011].

In summary, several data suggest that age is not a significant factor in predicting disease recurrence or survival for PTMC. On the contrary, some reports suggest that younger age could be a worse prognostic factor. It is conceivable that in older patients there exist two different forms of PTMC. One form is the "clinical PTMC" which behaves as PTC. The second form is a "silent PTMC," a tumor incidentally discovered that will never be apparent and that may be in concordance with the occult carcinoma detected in thyroid glands from autopsies. In this regard, it is interesting to note that gender distribution of PTMC found in autopsies shows differences as compared to clinical papillary tumors [Kovács et al, 2005]. It is well established that the incidence of PTC in women is significantly higher than that in men (with a female to male ratio greater than 2 to 1) [Yao et al, 2011]. However, several authors have not found any significant gender-related differences in PTMC found at autopsies [Lang et al, 1988; Neuhold et al, 2001; Kovács et al, 2005].

6. Conclusions

The rising incidence of PTMC demands the identification of specific prognostic factors for cancers measuring 1.0 cm or less, to differentiate those truly aggressive neoplasms from the clinically insignificant tumors. For that, it is mandatory to reevaluate the classic prognostic scores with the aim to define their usefulness in the management of PTMC. To date, the clinical significance of many of these variables is yet to be established. As a consequence, there is no agreement about the optimal treatment of smaller tumors [Küçük et al, 2007]. Whereas some authors argue for an aggressive approach, others suggest that no further treatment is needed after lobectomy or thyroidectomy. Moreover, some even propose observation, without surgical treatment [Ito et al, 2003]. In the next few years, we will need to improve the role of the staging systems in accordance with the new phenotypic characteristics of PTC. Finally, age, as a prognostic factor, must be cautiously interpreted in PTCs less than 1 cm.

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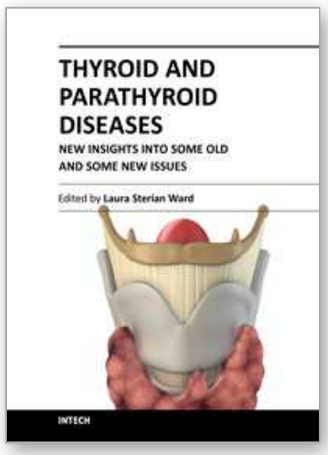

Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues

Edited by Dr. Laura Ward

ISBN 978-953-51-0221-2
Hard cover, 318 pages
Publisher InTech
Published online 07, March, 2012
Published in print edition March, 2012

This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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