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mini-review

Overview on surgical management of papillary thyroid microcarcinoma

R. RUGGIERO, R. PIROZZI, G. GUALTIERI, G. TERRACCIANO, S. PARISI, G. NESTA, L. GAZANEO, M. LANZA VOLPE, S. RINALDI, L. DOCIMO

SUMMARY: **Overview on surgical management of papillary thyroid microcarcinoma.**

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Particular interest is now being given to the best treatment of papillary thyroid microcarcinoma (PTMC) due to its significantly increased incidence. PTMC typically shows indolent organic behavior but, in a low percentage of cases, it can express a relative aggressive behavior.

Several risk factors have been shown to negatively influence the rate of regional recurrences and metastases such as tumor diameter, age, sex, multifocality, capsular invasion, extracellular diffusion, lymph node metastases, histological variants, mutated Braf and incidentality. The identification of patients with aggressive PTMCs among the majority with low risk lesions is very important to plan an adequate clinical management, thus the most appropriate surgical treatment. The latter includes thyroid lobectomy and total thyroidectomy with central compartment lymphadenectomy, though several studies did not show statistically significant differences in terms of recurrence and mortality rates between the two techniques. At last, it seems crucial to better define those biological features able to improve selection making process of patients with PTMCs aiming to reserve more radical surgery to those patients carrying more aggressive clinicopathologic features and worse prognosis.

KEY WORDS: Thyroid microcarcinoma - Surgical treatment - Tumor recurrence - Risk factors.

Introduction

Papillary microcarcinoma (PTMC) of the thyroid is defined as papillary thyroid carcinoma (PTC) with a diameter < 1.0 cm according to the World Health Organization (WHO) histologic classification published in 1988 (1, 2).

PTMC typically has an indolent organic behavior with a good prognosis, but it is not always completely harmless. In fact, it is possible to observe patients with PTMC and lymph node or distant metastases having an unfavorable course (Table 1). Indeed, PTMCs include at least two biologically distinct subpopulations such as indolent tumors with minimal or no progression potential, and tumors with propensity for aggressive behaviors and dissemination, so that no large consensus on the appropriate therapy is still available. The aim of this study was to review risk factors predicting patients with aggressive PTMCs among the majority presenting with low risk lesions to better plan an adequate clinical and surgical treatment.

Characteristics and outcome of patients with PTMC

As previously stated by Cady et al. "*Biology is King; patient selection is Queen; technical details of surgical procedures are the Princes and Princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail…technical wizardry cannot overcome biological restraints."* (Cady B.) (3, 4). The treatment of PTMC varies from clinical observation to thyroid lobectomy or total thyroidectomy eventually associated with

Department of Medical, Surgical, Neurologic, Metabolic and Aging Sciences, XI Division of General and Obesity Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

Corresponding author: Roberto Ruggiero, e-mail: roberto.ruggiero@unicampania.it

Table 1 - MORTALITY AND RECURRENCE IN PATIENTS WITH PAPILLARY THYROID MICROCARCINOMA (PTMC).

Studies (Ref.)	Year	Follow-up*	N° of Patients	Mortality	Recurrence rate
KIM (12)	2017	15	8676	NR	1,6
MEHANNA (14)	2014	5,8	3523	0,48%	5,0%
ITO (18)	2006	10	626	0%	5,0%
NOGUCHI (19)	2008	15	2070	0,6%	3,5%
LEE (22)	2013	20	1012	0,9%	5,4%
BUFFET (24)	2012	6,5	1669	0%	4,0%
LIN (26)	2009	NR	7818	0,12%	NR
YU (27)	2011	15	18445	0,5%	NR

Ref= Reference; NR= Not Reported; *expressed in years

lymph node dissection and radioiodotherapy. To date, it does not seem possible to distinguish common PTMCs from those with an aggressive behavior, so that the ability to identify patients with an aggressive disease from the majority of low risk patients is critical to plan a proper clinical management. Unsurprisingly, there is still a considerable debate in literature about the definition of a common, shared strategy in the treatment of PTMC (Table 2). Between 1975 and 2009, the incidence of thyroid cancer in the US increased by 400%, with 87% of cases diagnosed with a tumor diameter less than 2 cm. In 2013, 39% of 60,220 patients presented with lesions less than 1 cm big but with several epidemiological studies reporting an exponential increase of PTMC, mainly due to an "overdiagnosis" and to papillary tumors which represent the less aggressive variety (5).

Sugitani et al. demonstrated PTMCs of 3-9.9 mm in diameter range between 0.5 and 5.2% of autopsies (6). Takebe found papillary tumors in 3.5% of women over 30 years old involved in a mass screening based on ultrasound and Fnac and with 75% of which being less than 15 mm big (7).

Bilimoria identified 52,173 patients operated for thyroid papillary cancer from the National Cancer Data Base (1985-1998): 43,227 (82.9%) were operated by total thyroidectomy and 8946 (17.1%) by lobectomy (8). Patients treated with lobectomy had

Table 2 - COMPARATIVE RECURRENCE RATES AFTER TOTAL THYROIDECTOMY (TT) *VS* LOBECTOMY (L) IN PATIENS WITH PTMC.

Studies (Ref.)	Year	Follow-up*	N° of Patients	Recurrence rate (TT vs L)
BILIMORIA (8)	2007	5,8	10.247	NS
HAY (9)	2008	20	900	NS
ITO (20)	2006	10	2638	NS
LEE (24)	2013	12	2014	NS
BUFFET (26)	2012	6,5	1669	NS

Ref= Reference; *expressed in years; NS= Not Statistically Significant

survival and recurrence rates comparable to those receiving total thyroidectomy.

Hay et al. reported only 3 out of 900 (0.3%) disease-related deaths after treatment of PTMC (85% of patients receiving total thyroidectomy) with a mean diameter of 7 mm over a 60 years (1945-2004) period (9). The rates of recurrence were 6 and 8% respectively at 20 and 40 years follow-up, and likely linked to multicentricity and lymph node metastases. However, total thyroidectomy did not change the percentage of recurrence compared to lobectomy.

Macedo et al. published a meta-analysis on 2937 patients diagnosed with PTMC comparing lobectomy (803 pts, 27.3%) and total thyroidectomy (2134 pts, 72.7%) aiming to identify any differences in relapse and mortality (10). At a mean follow-up of 10.9 years, a recurrence rate of 4.4% after total thyroidectomy and 8.3% after lobectomies were recorded with a mortality of 0.3% after total thyroidectomy and 1.1% after lobectomies. Authors concluded albeit total thyroidectomy was associated with lower recurrence rate than lobectomy, factors such as multicentricity and lymph node metastases should be considered to plan an appropriate surgical strategy.

Matsuzu et al. studied 1088 patients with papillary thyroid cancer undergoing lobectomy reporting 95.2% disease-free survival rate at 25-year follow-up. In light of such results, they suggested thyroid lobectomy could represent a valid alternative to total thyroidectomy in patients under 45 years with a tumor diameter less than 4 cm and without extracellular diffusion or lymph node metastasis (11).

Nixon et al. analysed 889 patients between 1986 and 2005 (59% total thyroidectomy and 41% lobectomy) with a 99-months follow-up. They found an overall disease free survival of 98% without any statistically significant differences between the two surgical techniques. Independent variables affecting prognosis were age greater than 45 years and male sex (12).

Lupoli et al. reported a 19.2% multifocality rate and a 7.6% relapse rate among 250 patients with PTMC (7.3 mm mean diameter), treated with total thyroidectomy suggesting aggressiveness of PTMCs may be partly explained by multifocality and lymph node metastasis (13).

Kim et al. reported on 8676 patients treated with total thyroidectomy (62.1%) or lobectomy (37.9%) for PTMC (6 mm in mean diameter) finding multifocality in 19.8% of them and a local recurrence rate of 1.7% and 1.6% respectively after total thyroidectomy or lobectomy (58% in controlateral lobe) (14).

Prognostic risk factors

There are several risk factors that can lead to more aggressive PTMCs: diameter, tumor, age, sex, multifocality, capsular invasion, extrathyroidal extension (ETE), lymph node metastases, histological variants, mutated Braf, incidentality of diagnosis. For some of these factors the literature reported very wide ranges for multifocalities (7.1-56.8%), lymph node metastasis (0-64%), ETE (0-13%) and mortality (0 -2.2%) with a less wide range and a generally low frequency (15).

Incidental tumors

Sugitani identified 3 different PTMC presentation modes: "pathological" PTMCs diagnosed at histological examination after surgery for benign lesions, "clinical incidental" PTMCs detected during instrumental exams (ultrasound plus Fnac) and "clinical symptomatic" PTMCs which manifest with symptoms such as cord paralysis, lymph node or distance metastasis (occult PTMC) (6). A fourth type of PTMC that could fall into the first two groups is the microcarcinomas detected at the autopsy. In a meta-analysis of 3523 PTMCs (2669 non-incidentally and 854 incidentally detected) Mehanna found at a mean follow-up of 70-months a recurrence rate of 0% in the incidentally and 7.9% in the non-incidentally detected PTMCs; a mortality of 0% and 0.1% was recorded respectively in the incidentally and non incidentally detected PTMCs (16).

On the basis of these works it is therefore that incidental PTMC has different clinical characteristics and a much lower recurrence rate than nonincidental PTMC, suggesting that management protocols (thyroidectomy *vs* lobectomy) should be re-considered.

Age

Yu et al. analysed the SEER Cancer Database data, a premier source for cancer statistics in the

US, identifying age over 45 as a risk factor for recurrence (17). On the contrary, others found age under 45 as a risk factor for recurrence (18, 19). An observational study on PTMC carried out by Ito et al. found patients under 40s having more possibilities of tumor growth than patients over 60 years old (20).

It seems that age (<45 years) is an independent predictor of subclinical central lymph node metastasis (LNM) but large volume LNM was more frequently found in young (<40 years) and male patients.

Diameter

In a study about 2070 patients with PTMC Noguchi et al. reported those with a tumor diameter greater than 6 mm had a 14% recurrence rate at 35 years follow-up compared to a 3% rate for those than 6 mm (21). Lai highlighted PTMC smaller than 5 mm have less aggressive features, whereas Wu suggested total thyroidectomy for PTMC bigger than 5 mm (22, 23). Conversely, others have not found PTMC diameter in association with an increased recurrence (24-26).

In conclusion, it seems that larger tumor size (>0,5 cm) is associated with high prevalence of central lymph node metastasis in patients with clinically lymph node-negative PTMC.

Extrathyroid spread (ETE)

Several studies have identified extracapsular spread (ETE) as a potential risk factor for local recurrence. Chen linked ETE, male sex, age under 45 and multifocality to the risk of disease progression (27). In a meta-analysis of 19 studies on 8345 PTMC (16 study with prophylactic central compartment's linfectomy) Lin reported a correlation between ETE, male sex, age under 45, a diameter smaller than 6 mm and multifocality as risk factors for central compartment's node metastases (28). Yu et al. also identified ETE, male sex, age under 45, a diameter less than 7 mm all as predictive factors for central compartment's lymph node metastases (17). Cai suggested a "scoring system" based on the presence of nodule at the lower thyroid pole, tumor's diameter greater than 5 mm, Ete with an infiltration greater than 25% of the capsule predictive of central compartment's lymph node metastases (29).

Braf 600

The BRAF (V600E) mutation in PTMC has been reported to range between 30 and 62.5%.

In a meta-analysis of 63 studies on 20764 enrolled patients, Chunping reported this mutation was related to ETE, lymph node metastases and recurrence without distance metastases (30). Lu et al. confirmed Braf (V600E) mutation was related to ETE, lymph node metastases, thyroiditis and a worse prognosis (31). For PTMC with a diameter greater than 5 mm, Sin suggested central compartment's prophylactic linfectomy if Braf V600 E resulted positive (32). In a meta-analysis of 2274 PTMC, Chen reported a correlation between this mutation and recurrence (33). Besides, the association between Braf V600 E and a Tert mutation (Pik3 Ca, Tp 53, Akt1) was related to an increased risk of recurrence (34).

For PTMC with Braf V600E gene mutation surgical treatment is suggested and in high cell subtype total thyroidectomy is preferred in order to reduce the potential risk of recurrence.

Lymph node metastases

In 18,445 PTMC, Yu et al. identified lymph node metastases as a risk factor for recurrence; besides, patients with tumor larger than 7 mm with a TSH lower than 2.5 mIU/l were found at higher risk for central compartment's lymph node metastases (17). In line with this, Buffet et al. confirmed the same finding in 1669 PTMC (26). In a research carried out on 900 patients with a 60 years follow-up, the presence of lymph node metastases was a risk factor for recurrence (9). On the other hand, Ito et al. did not found lymph node metastases negatively influenced disease-free survival in patients diagnosed with PTMC (20). In a study about 281 PTMC, Cho found that tumors larger than 6 mm and capsular invasion were risk factors for central compartment's lymph node metastases (35). Liu highlighted male sex, age younger than 45, tumor's diameter beyond 5 mm, lympho-vascular invasion among risk factors for central compartment metastases (36). In a meta-analysis on 31017 PTMC, Lin recognized Ete as a risk factor for lymph node metastases (37). In another meta-analysis of 19 studies on an overall number of 8345 PTMC, Ou pinpointed male sex, age younger than 45, tumor's diameter beyond 5 mm,

multifocality, and ETE, all as risk factors for lymph node metastases. However, prophylactic lymphadenectomy of the central compartment was not linked to a reduced rate of recurrence (38).

Surgical treatment

During the "Controversy session at the 58th Annual Cancer Symposium of the Society of Surgical Oncology" in Atlanta (U.S.) focused on the most appropriate treatment of differentiated thyroid cancer, Udelsman supported total thyroidectomy. Arguments in favour of his theory were: 1) substantial frequency of bilateral tumors even for PTMC (30-85%), 2) reduction of recurrences, 3) reduction of mortality in patients at high risk, 4) reduction of re-operations, 5) possibility of an immediate radioiodine therapy if necessary, 6) easier follow-up by thyroglobulin assay (39). On the other hand, Shaha supported lobectomy for the treatment of this tumors reporting comparable recurrence and mortality rates to total thyroidectomy along with lower morbidity and no needing for thyroid hormone replacement therapy (THR). As previously stated by Cady "an operation that is not worth doing is not worth", but it's clear that this remains a hotly debated topic and, above all, needs a multidisciplinary approach to avoid overtreatment and legal conflicts (4). Other previous studies didn't found any substantial differences in survival between TT and LT (28, 33, 39). Concerning the role of prophylactic lymphadenectomy of the central compartment in warranting any advantages in terms of recurrence and mortality rates of patients with PTMC it has been previously questioned (40). The 2009 and 2015 ATA guidelines defined central compartment lymphadenectomy not useful in non-invasive and clinically node negative (N-) PTMC (41, 42). Wada et al. showed no significant differences in recurrence rates (0.43 *vs* 0.65%) by comparing patients undergone (235 pts) or not (155 pts) central compartment lymphadenectomy at 60 months follow-up (43). Thyroidectomy after lobectomy recurrence rate is not significantly different in patients who had already undergone thyroidectomy after lobectomy for an incidentally discovered tumour (44). In a long-term follow-up study, Lee et al. reported thyroidectomy after lobectomy should not be recommended unless a relapsed disease in the controlateral lobe had been evidently proven (45).

Howewer, appropriate selection of patients, based on risk stratification is the key to differentiate therapy options and gain better results (46-50).

It is needed to ensure that patients make well-informed about preference based decisions. At last, it seems crucial to better define those biological features able to improve selection making process of patients with PTMCs aiming to reserve radical interventions to those patients carrying more aggressive clinic-pathologic features (non incidental, age, diameter, Ete, Braf E600V, multifocality, lymph node metastasis) and more likely to have worse prognosis. Postoperative us imaging studies are important for patients who undergo lobectomy because most recurrences are in the contralateral lobe. In the follow-up it is important collaboration of endocrinologist and radiologist for detecting recurrent disease with serum thyroglobulin dosage and imaging [ultrasound, radioactive iodine (RAI)], computed tomography (CT), single photon emission computed tomography (SPECT).

Conclusions

In conclusion, the identification of patients with aggressive PTMCs among the majority presenting with low risk lesions is very important to plan an adequate clinical management, thus the most appropriate surgical treatment. The latter may include thyroid lobectomy and total thyroidectomy with central compartment lymphadenectomy, though several studies did not show superiority of one treatment over the other in terms of recurrence and mortality rates. At last, it seems crucial to better define those biological features (non incidental, age, diameter, Ete, Braf E600V, multifocality, lymph node metastasis) able to improve selection making process of patients with PTMCs aiming to reserve radical surgery to those patients carrying more aggressive clinic-pathologic features and more likely to have worse prognosis.

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