

PAPILLARY MICROCARCINOMA OF THE THYROID GLAND - DOES SIZE MATTER?

R. Dimov^{1,4}, G. Kostov^{1,4,*}, M. Doykov^{2,4}, B. Hristov³

Medical University of Plovdiv Hospital - ¹Department of Special Surgery, ²Department of Urology and General Medicine, ³Second Department of Internal Diseases, Section "Gastroenterology", ⁴University Hospital Kaspela, Plovdiv, Bulgaria

Abstract

Introduction. Papillary thyroid microcarcinoma has provoked discussion among the endocrinological community due to the extremely diverse therapeutic methods adopted in international guidelines. From the radical approach of total thyroidectomy with prophylactic central lymphatic dissection to "active monitoring" and opinions such as "papillary microcarcinoma is not carcinoma".

Aim. To investigate the factors of invasiveness in papillary microcarcinoma.

Material and methods. We included 184 patients with thyroid microcarcinoma, operated in the Department of General Surgery "Kaspela", Plovdiv, for a period of five years.

Results. Intra-organ metastases or multifocal growth was identified in 38 of the patients. Positive for micro and macro metastases lymph nodes in the central lymphatic basin are found in 54. In 46 of them we identified metastases in the ipsilateral, and in 21 in the contralateral central neck nodes. The analysis of patients with lateral metastases found 7 unilaterally and 3 bilaterally. Skip metastases were registered in 4 of these 10 patients.

Conclusions. The results of our study show that despite the favorable prognosis and non-aggressive behavior of papillary microcarcinoma, factors attesting to the invasive nature of the tumor occur in 44.5% or almost half of patients. This requires careful and individual approach constructing therapeutic strategy for the treatment of patients with papillary microcarcinoma.

Keywords: papillary microcarcinoma, central neck lymph nodes, capsular invasion.

INTRODUCTION

The incidence of papillary carcinoma (PC) has been steadily increasing over the last decade. It is the

most common malignancy of the endocrine system, accounting for 80-85% of all thyroid carcinomas. The increasing rate of the disease is associated with the improvement of diagnostic methods and the skills of endocrinologists allowing the detection during routine ultrasound examinations and the fine needle aspiration biopsy of microcarcinomas (1,2).

Papillary microcarcinoma of the thyroid gland causes many discussions among the endocrinological community, due to the extremely divergent therapeutic approaches adopted in international guidelines. From the radical approach of total thyroidectomy with prophylactic central lymph node dissection to "active surveillance" and opinions such as "papillary microcarcinoma is not carcinoma". This heterogeneity is probably a consequence of the non-aggressive nature of papillary neoplasia, in general, and the excellent survival of these patients (3).

However, the question remains open regarding the presence of factors of invasiveness, such as intra-organ metastases (multifocality), and involvement of the gland capsule, which although more difficult to establish preoperatively, are still possible. In contrast, micro metastasis in the lymph nodes mainly of the central neck compartment are practically undetectable with modern imaging methods. According to a number of authors who are supporters of routine central neck lymph nodes dissection, the presence of central node metastasis should not be underestimated (4-6).

Objective

The aim of the present study was to investigate the factors of invasiveness in papillary microcarcinoma in our patients.

*Correspondence to: Gancho Kostov MD, Medical University of Plovdiv Hospital, Surgery, zhk Hristo Smirnenski, Sofia 64 street, Plovdiv, 4002, Bulgaria, E-mail: caspela@abv.bg

MATERIAL AND METHODS

Initially, as a study group, we included 197 patients with thyroid microcarcinoma who were operated in the "General Surgery Clinic" of University Hospital "Kaspela", Plovdiv, for a period of five (5) years (2017-2021). Thirteen patients dropped out from the study – three with medullary, one with follicular carcinoma, one patient with lobectomy and eight with total thyroidectomy without central lymph node dissection. The remaining n=184 patients underwent surgery, each with a pre-operative fine-needle aspiration biopsy, with results of Bethesda V or VI, respectively. In 174 of them, total thyroidectomy with the bilateral prophylactic central neck lymph nodes dissection adopted in the clinic was performed, and in n=10 total thyroidectomy with central and lateral lymph dissection, due to diagnosed presence of metastatic lesions in the lateral neck compartments, either unilaterally or bilaterally diagnosed preoperatively by FNA from thyroid lesion and from suspicious lateral

neck lymph nodes with thyroglobulin level evaluation from aspirate (Table 1).

RESULTS

To fulfill our goal, we divided the patients into two groups: group "A" included those with the total thyroidectomy and prophylactic central neck dissection, and group "B" included patients with total thyroidectomy, central and lateral neck dissection (patients with papillary microcarcinoma). In the analysis of the data from group "A" - we found invasion in the capsule of the gland in n=29 (16.6%) of the patients. Presence of intra-organ metastases (Fig. 1) and/or multifocal growth were identified in n=38 (21.8%). Positive for micro - and macro metastases lymph nodes in the central neck lymph nodes (Fig. 2) were registered in n=54 (31%) cases, in n=33 (61.1%) in the ipsilateral, and in n=21 (38.9%) in the contralateral compartment. It is interesting to note that in this group in n=7 (12.9%) of the patients,

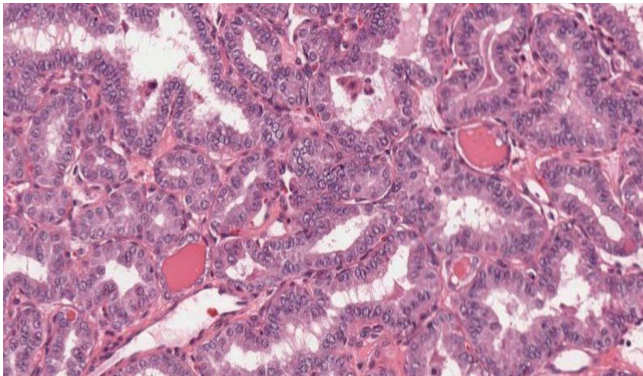


Figure 1. Multifocal metastases.

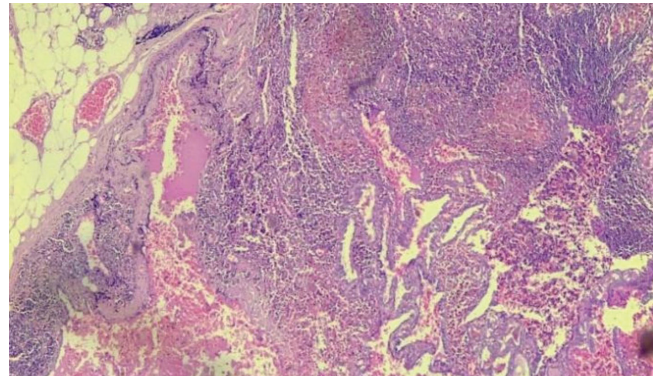


Figure 2. Central node metastases level VI.

Table 1. Patients with papillary micro carcinoma

Patients with thyroid microcarcinoma n=197	
Patients with PC undergone total thyroidectomy with CLND (FNA - Bethesda V or VI) n=184	
Group A - TT + prophylactic CLND bilaterally n=174	Group B - TT + CLND bilaterally + MRLND (uni - or bilateral - FNA of suspected lymph node) n=10

Table 2. Patients with thyroidectomy+central neck dissection, and thyroidectomy+central+lateral neck lymph node dissection

Group A – TT + CLND n=174	Group B – TT + CLND + MRLND n=10
Capsule involvement n=29	Capsule involvement n=6
Multifocal tumor and/or intra-organ metastatic dissemination n=38	Multifocal tumor n=7
Positive lymph nodes in the central neck compartment n=54	Positive lymph nodes in the lateral neck compartment n=10
- Ipsilateral n=33	- Unilateral n=7
- Contralateral n=21	- Bilateral n=3
Positive pre-laryngeal lymph node n=7	Skip metastases n=4

metastases were also found in the pre-laryngeal so-called Delphian lymph node.

The analysis of patients from group "B" showed the presence of lateral metastatic lesions (Figs 3,4) in n=10, and in n=7 (70%) they were found unilaterally and in n=3 (30%) bilaterally. We registered skip metastases in n=4 (40%), and the same were present only in the lateral group of lymph nodes (LN), without such in the central basin. We found capsular invasion in 6 (60%) and multifocality in 7(70%) patients (Table 2).

The capsular involvement in patients with papillary micro carcinoma undergone TT with CLND and MRLND (group B) is significantly higher (p=0.0038, p<0.05) compared to patients undergone TT with CLND (group A) (Table 3).

Multifocal dissemination of the papillary micro carcinoma is significantly higher (p= 0.0023, p<0.05) in patients with lateral lymph node metastases (group B) compared to patients with no lateral neck metastases (group A) (Table 4).

DISCUSSION

According to a number of studies, overall mortality, one of the main indicators in the classification of oncological diseases, in thyroid carcinoma is negligibly low (<2% at 5 years) (7). The risk of death in differentiated thyroid carcinoma (DTC) is usually estimated using the American Joint Committee on Cancer and Union Internationale Contre le Cancer (AJCC/UICC). Respectively the majority (90-95%) of patients are classified as stage I or II, thus they have a low risk of death from this malignancy (<1%). The risk of recurrence in DTC is estimated to be significantly higher than risk of death. The American Thyroid Association (ATA) risk stratification system classifies the probability of persistent and/or recurrent disease in the case as low (<5%), based on specific characteristics of tumors of this type identified and documented at the time of diagnostic process (8). On this basis, papillary micro carcinomas (≤10mm in diameter), unifocal, intra-thyroidal located and in the absence of aggressive



Figure 3. Modified radical neck dissection.

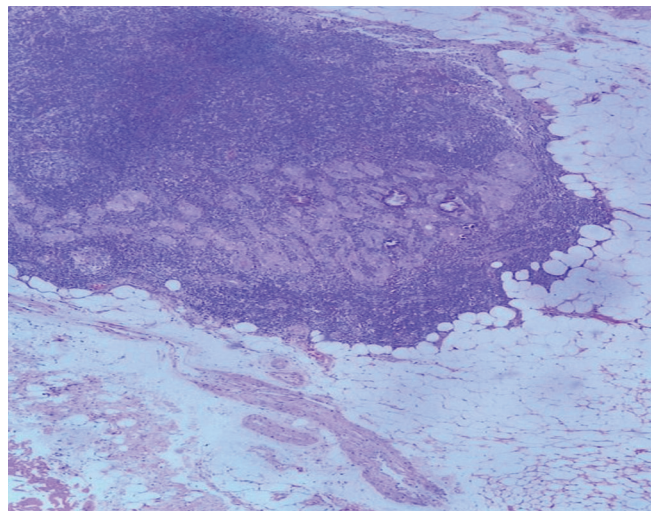


Figure 4. Metastases in lateral lymph nodes.

Table 3. Capsular involvement

	Results		Marginal Row Totals
	Capsular involvement	No capsular involvement	
Group A	29	145	174
Group B	6	4	10
Marginal Column Totals	35	149	184 (Grand Total)

Table 4. Multifocality

	Results		Marginal Row Totals
	Multifocal	Not multifocal	
Group A	38	136	174
Group B	7	3	10
Marginal Column Totals	45	139	184 (Grand Total)

histological features, are considered to have a low risk of recurrence (<1%) (9).

According to the same recommendations supported by other scientific teams, the probability of recurrence associated with the presence of metastatic lymph nodes is also considered. The number of metastases (<5 or ≥ 5), their size (≤ 2 mm, >2 mm or ≥ 3 cm), the number of affected lymph nodes with extracapsular invasion (≥ 3 or <3) and possibly their location (central or lateral compartment) should be taken into account when assessing the risk of recurrence (10). Minimal extra thyroidal spread is assumed to have a nonsignificant effect on the chance of disease relapse, in cases where other risk factors are absent (11).

The molecular genetic profile of the tumor may play an important role in risk stratification (Haugen *et al.* 2016). BRAFV600E mutation alone is not an independent factor for recurrence in papillary carcinoma, but the presence of other clinic pathological features, such as extracapsular spread and multifocality, can already identify an increased risk of recurrence compared to wild-type tumors BRAF. The presence of a TERT promoter mutation is also associated with a poor prognosis in both PC and FC, and tumors of this type are considered high-risk for recurrence (12).

In the 1990s, the progression of small papillary neoplasms was not clear, but it was assumed that most did not grow or, if they did, they progressed slowly over long time intervals. Based on this hypothesis, Miyauchi *et al.* proposed and introduced for the first time the term "active surveillance" in patients with papillary neoplasia <10mm and absence of invasive signs. They recommend an ultrasound every 6 months in the first year and once annually after that. Surgical treatment in these patients is initiated when the tumor grows ≥ 3 mm or when metastases occur in the lymph nodes (13). By 2014, this research team had followed up n=1235 patients and only in 8% of microcarcinomas recorded growth of the primary neoplasia >3 mm, and 3.8% present metastatic lesions in the neck compartments. They also noted that in the young (<40 years), growth of the primary tumor was more often recorded (14,15).

To assess whether an individual with papillary microcarcinoma is amenable to "active surveillance" various criteria must be considered. The Memorial Sloan Kettering Cancer Center (MSKCC) together with the Kuma Hospital group are developing a clinical framework to assess the suitability of each individual patient for "active surveillance". The rationale for developing this risk-stratified framework rests on the

2015 ATA guidelines that support "active surveillance" as an alternative to immediate fine-needle biopsy or surgical treatment of lesions suspicious for papillary microcarcinomas. According to this recommendation, an "ideal" candidate would be an elderly patient (>60 years), with low-risk, well-margined PC confined to the thyroid parenchyma away from the gland capsule. A "suitable" candidate would be a patient under 60, with tumor multifocality, with a potentially aggressive molecular phenotype, in close proximity to the thyroid capsule but not in risk areas, or with other imaging findings that may make follow-up more problematic (eg, thyroiditis, concomitant benign nodules). An "unsuitable" candidate has tumors at risk subcapsular sites (eg, in close proximity to the trachea or recurrent laryngeal nerve), evidence of loco-regional or distant spread, or evidence of disease progression on serial studies (16).

Ideal patients demonstrate a <2% risk of progression, "suitable" have disease progression at 10%, and active surveillance may be offered by an experienced team, as delayed surgery will still be effective, with good clinical outcomes. Finally, patients in the "unsuitable" category should not be offered active surveillance, given the possibility that mild disease progression may lead to significant morbidity and because a high rate of disease progression is expected (17).

There is also opposite opinion based on the difficulties for risk evaluation, occurrence of an even rare progression of the disease, problematic follow-up by a trained team able to register the early signs of progression, as well as the exact determination of the "risk profile" and the classification of the patients. And right here is the controversy, most of these risk factors excluding sex, age, size of the primary tumor cannot be determined preoperatively. And the determination of the histological variant and the complete staging of the process, according to the available invasion in the capsule, multifocality and metastatic lesions in the lymph nodes from the central compartment are possible only after finale histological report. In addition, for correct staging and necessity of adjuvant therapy, the nodal status plays a major role. Molecular genetic markers are perhaps the future, but at this stage they are not accessible in daily practice, especially in developing countries. Moreover, recurrences, although rare, have been described in the literature and they are mainly observed in the central neck compartment, being mainly due to the presence of metastatic lesions in the lymph nodes located there.

On the other hand, for the overall staging and planning of adjuvant therapy, the histological subtype and nodal status are essential. And here we come across another controversy regarding the performance of central nodes dissections, especially in the initial stages and in microcarcinomas. Although a consensus has been published regarding the CLND for therapeutic purposes, there is currently considerable controversy among endocrine surgeons as to which patients should be object of prophylactic ones, particularly for papillary carcinoma, and this is rarely discussed in microcarcinomas. The 2009 ATA consensus recommended therapeutic dissection for all patients with clinically positive nodes and with stage T3 and T4 primary tumors without evidence of metastases in the central and lateral neck compartments (18,19).

These recommendations remained unchanged in the 2015 update, with the important addition that prophylactic dissection may be used if the resulting information about nodal status will improve subsequent therapy (20). The 2015 guidelines did not consider however, it is recommended to carry out such a procedure for T1 and T2 tumors, in which category papillary microcarcinoma also falls. Roh *et al.* in his prospective study including 184 patients with unilateral PC and clinically negative LN on physical examination and ultrasound follow-up with total thyroidectomy and prophylactic CLND, observed metastases in the ipsilateral nodes in 42.9% and in 9.8% of cases in the contralateral nodes, similar to ours (31% and 11.4%). Their multivariate analysis also confirmed that tumor size >1 cm, extrathyroidal spread and age <45 years were factors increasing the risk of ipsilateral metastases. The presence of such, increases the possibility of their appearance in the contralateral compartments as well (21).

The European Association of Endocrine Surgeons (ESES) recommend that prophylactic dissection should be considered in high-risk groups: T3-T4 tumors, age <15 years or >45 years, male sex, poor histological variant, bilateral or multifocal disease or proven metastases in the lateral lymph nodes. ESES emphasizes the importance of prophylactic dissections being performed by surgeons in specialized centers with significant experience in thyroid surgery (22).

In contrast to the recommendations listed above, the Japanese Society of Thyroid Surgeons/Japanese Association of Endocrine Surgeons recommends the routine application of prophylactic CLND, based on the significantly increased risk of complications, in cases of re-operation for lymph node recurrence and the

already mentioned high frequency of detection of micro metastases in the central compartments ipsilaterally or/ and contralaterally (23).

The importance of central lymph node dissection in microcarcinomas was reviewed by Kim *et al.*, in their study they found that the ratio of removed to metastatic neck lymph nodes > 0.3 and the size of the largest removed >3cm were poor prognostic markers associated with high risk of relapse and increased mortality. These results were also confirmed by other authors who investigated and found a frequency of associated mortality in these cases (20.9%) compared to patients of the same stage without the presence of these aggravating factors (3.2%) (14).

In an attempt to improve postoperative results, reduce the risk of recurrence and complications, predictive systems are being proposed to identify high-risk patients who are candidates for prophylactic dissection. These characteristics of the primary tumor may help predict patients at high risk for clinically negative cervical lymph node metastases. However, many of these criteria are unknown preoperatively. Factors that can be assessed prior to intervention and are associated with future aggressive disease include: age, male sex, large primary tumor size or bilateral disease, capsule invasion. Pathologic features predictive of aggressive PC variants include tumor subtypes such as large cell, columnar cell, Hurthle cell carcinomas, as well as the rare diffuse sclerosing, islet cell, and Hobnail variants, the presence of vascular, extra thyroidal invasion, and low tumor differentiation (15).

As already commented, these high-risk markers is possible to be detected postoperatively, which practically makes these systems useless.

In conclusion, capsular involvement and multifocality in our patients are commonly associated with advanced diseases and presence of lateral neck lymph node metastases. Our results reveal that, despite the favorable prognosis and less aggressiveness of papillary microcarcinoma, some of the indicators of invasive nature of the tumor are practically undetectable in the pre-operative period. Thus, we believe papillary micro carcinomas requires re-evaluation of the volume of surgery due to high percentage of micro-metastatic spread in central and even lateral neck compartments.

Conflict of interest

The authors declare that they have no conflict of interest.

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