

Micropapillary Thyroid Carcinoma: Not So Harmless as it Seems. A 5-Year Follow-Up Cohort Retrospective Study

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ABSTRACT

Introduction: Differentiated thyroid cancer is becoming increasingly prevalent mostly due to the increasing incidence of micropapillary carcinoma. For low-risk tumors, hemithyroidectomy does not reduce survival and may be associated with higher local recurrence. This study aimed to compare Micropapillary versus Papillary thyroid carcinomas regarding overall survival and disease-free survival. **Methods:** A retrospective, unicentric, cohort study was carried between 2012 and 2016. Consecutive cases with (micro)papillary thyroid carcinoma were enrolled and divided in microcarcinoma group and control group. Exclusion criteria were loss to follow-up, previous thyroid surgery and non-operative treatment. A comparison of several clinical and pathological parameters, recurrence rate and cumulative survival was performed between groups. **Results:** Patients with micropapillary carcinomas were younger and frequently asymptomatic. 6.5% of these carcinomas presented a benign cytology (Bethesda II) in this study. 18.9% of these patients were submitted to hemithyroidectomy but 71.4% were thereafter totalized. Micropapillary carcinomas presented higher rate of multifocality but similar lymph node invasion rate, lymph node dissection rate and adjuvant iodine therapy. Patients with micropapillary carcinomas presented less advanced staging but similar recurrence rate and time to recurrence; moreover, higher stage was only related with (older) age of presentation. **Conclusions:** In this study micropapillary carcinomas presented better staging but similar recurrence rate comparing with papillary carcinomas. Moreover, most of these patients were submitted to totalization. These results question if hemithyroidectomy is still a good option for micropapillary carcinomas and if this staging system is adequate. Larger studies with longer follow-up are needed to confirm or refute these results.

Keywords: thyroid neoplasms, thyroidectomy, surgical oncology

INTRODUCTION

Although plateauing, incidence rates of thyroid cancer (TC) have increased in Europe in the last thirty years, while mortality showed negative trends.[1] The rising incidence rates are mainly due to the increased diagnosis of papillary thyroid cancers (PTCs), particularly micropapillary thyroid cancers (mPTCs).[2-4] These are defined as PTCs less than 10 millimeters and are associated with an excellent prognosis and long term survival rate above 96%.[4, 5] This overdiagnosis results invariably in overtreatment. For low-risk tumors, hemithyroidectomy has proven not to reduce survival but it may be associated with a higher local recurrence. Even though, support is growing for more conservative, risk-tailored strategies for TC management (including watchful waiting).[2, 4, 6] However, the risk factors such as multifocality,

extrathyroidal extension, and lymphovascular invasion, contributing to higher recurrence risk, are not infrequent in mPTCs.[7] This study aimed to compare patients with mPTCs vs. PTCs regarding overall survival and disease-free survival, and identify clinical and pathological risk factors for prognosis.

METHODS

A retrospective, unicentric, cohort study was carried between 2012 and 2016. All consecutive patients with (micro)papillary thyroid carcinoma was enrolled and divided in two groups: microcarcinoma group (<10 millimeters) and control group (≥ 10 millimeters). Exclusion criteria were loss to follow-up, previous thyroid surgery and non-operative treatment. Primary endpoints were to compare overall survival and disease-free survival between groups. Secondary endpoints were to assess which variables were associated to higher stages and recurrence rate. In this study aggressive histology was defined as tall cell, hobnail variant, columnar cell carcinoma, squamous differentiation, diffuse sclerosing variant or solid/trabecular variant. The risk of recurrence was catalogued as high in the presence of previous radiation exposure, family history of thyroid cancer, posterior location (near recurrent nerve, esophagus or trachea), aggressive histology, multifocality or extrathyroidal extension, according to ESMO Guidelines.[2] Tumour stage was catalogued by the eighth edition of the Union for International Cancer Control (UICC) Tumour, Node and Metastasis (TNM) classification.

Statistical analysis was performed using SPSS 26 (International Business Machines Corporation). Continuous variables were presented as mean $\pm$ SD, whereas qualitative data were presented as number and percentage. Categorical variables were presented as the number of patients and its corresponding proportion with respect to the group under study. Patient characteristics were compared with Mann Whitney tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Overall cumulative survival and disease-free survival were obtained by the Kaplan-Meyer method and compared by log rank test. Significance was assumed whenever p values were less than 0.05. This work has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Approval of ethical commission of our hospital was dismissed because it was an observational study that granted confidentiality of data.

RESULTS

Patient's Demographics

Records of 93 patients (37 mPTCs and 56 PTCs) were analyzed (table 1). Yearly distribution of cases was 7.4 and 11.2 cases for mPTCs and PTCs, respectively. There were only 5 male patients, 2 in mPTC and 3 in PTC group (5.4 vs. 6.9%, $p=1$). Patients in mPTC group were significantly older (45.4 vs. 54.3 years, $p=0.003$) and had significantly smaller nodules (11 ± 7 vs. 23 ± 11 millimeters; $p=0.000$). There were no differences regarding family history (0 vs. 3.5%) of TC, radiation exposure (0 vs. 1.8%) and symptomatic clinical presentation ($p=0.148$) between groups. The most frequent clinical presentations were asymptomatic thyroid nodule (70.3 vs. 55.4%), goiter (10.8 vs. 17.9%), dysphagia (8.1 vs. 7.2%), globus sensation (0 vs. 8.9%), lymph node (5.4 vs. 0%) and dysphonia (2.7 vs. 3.6%). Diagnosis was incidental following thyroidectomy for presumably benign thyroid lesions in 6 cases (5.4 vs. 7.1%, $p=0.739$). Hemithyroidectomy (lobectomy and isthmusectomy) was performed in 18.9% of patients with

mPTC and 21.4% in PTC group ($p=0.769$), and later totalization was performed in 71.4 vs. 83.3%, respectively ($p=0.603$). Lymph node dissection (LND) was performed in 8.1% of patients of mPTC group vs. 8.9% of PTC group ($p=0.890$) and later LND was performed in 8.3 vs. 12.5% of cases, respectively. Central LND was performed in 4 cases (mPTC 2.7 vs. 5.4% PTC) and lateral LND in 4 cases (mPTC 3.6 vs. PTC 5.4%), with no significant differences between groups. Postoperative complications occurred in 19.4% of cases but there were no differences between groups (dehiscence 2.7 vs. 0%; dysphonia 13.5 vs. 7.2%, hypocalcemia 5.4 vs. 10.7%, $p=0.653$). The presence of postoperative complications documented significant differences according to the type of thyroidectomy performed. In this study total thyroidectomy was associated to higher rate of complications, independent of the type of carcinoma (24.3 vs. 0%, $p=0.017$). Morbidity was verified in 2 totalized patients (1 mPTC and 1 PTC). There were no differences regarding aggressive histology (0 vs. 1.8%) and extrathyroidal extension (24.3 vs. 21.4%) between groups. This study documented that the rate of multifocal tumours was higher in mPTC (24.3 vs 7.1%, $p=0.019$). As a matter of fact, the 4 cases of bilaterality were all patients of mPTC group, all of them younger than 50 years old. Preoperatively only 2 patients in PTC group and no patient in mPTC group were classified as having high-risk of recurrence. Postoperatively 59.5% of mPTC and 73.2% of PTC patients were classified as high-risk ($p=0.165$). There were no differences in lymph node invasion between groups, but patients of mPTC group had significantly lower staging (stage II 13.5 vs. 32.1%, $p=0.042$). Therapy with iodine (70.3 vs. 78.6%, $p=0.364$) and kinase inhibitors (2.7 vs. 0%, $p=0.398$) was equally frequent between groups.

Primary Endpoints

In mPTC group, recurrence was identified in 5 patients, 4 of them lymph node metastasis (3 in lateral and 1 in both central and lateral compartments). The other patient had pulmonary and lymph node recurrence (in both central and lateral compartments). In PTC group, recurrence was identified in 7 patients, 6 of them lymph node metastasis (4 in lateral and 2 in central compartment). The other patient presented pulmonary and lymph node metastasis (lateral compartment). There were no differences regarding recurrence (13.5 vs. 12.5%, $p=0.887$) and mortality (0 vs. 1.8%, $p=1$) between groups (table 1). Disease free survival was 92 (77.5; 105.5) and 87 (79.25; 100) months ($p=0.575$) (figure 1).

Secondary Endpoints

Older patients presented significantly higher stages (stage II 3.2 <55 vs. 68% ≥55 years) and recurrence was only significantly influenced by lymph node invasion (6 vs. 66.7%, $p=0.001$) and non-low-risk mPTC (26.7 vs. 6.3%, $p=0.006$). Sex, nodule size, family history, radiation exposure, aggressive histology, multifocality and extrathyroidal extension did not significantly influenced staging or recurrence rate. On the other hand, lymph node invasion was only significant related with extrathyroidal extension (60 vs. 40%, $p=0.003$) and non-low-risk mPTC (70 vs. 30%, $p=0.007$).

DISCUSSION

The peak age of patients in this study was 45-55 years for both mPTC and PTC which is slightly older than other references. Older patients presented significantly higher stages and there was no significant association between lymph node metastasis of mPTC and patients' age, sex, multifocality and extrathyroidal invasion. These findings disagree with a Chinese study that found that lymph node invasion was significantly associated with younger age, multifocality

and capsular invasion.[8] However, both studies agree that lymph node invasion is significant correlated with extrathyroidal extension and that it is highly recommended to pay close attention to mPTC.

In this study no differences regarding extrathyroidal extension and lymph node invasion were observed between groups, but mPTC presented significantly higher rate of multifocality. These findings are not in agreement with those of a Turkish study that found that the rate of multicentricity of the PTC was significantly higher in patients with tumors >1 centimeter. [7] However, both studies agree that, although mPTCs are generally associated with high survival rates, risk factors such as multifocality, extrathyroidal extension, and lymph node invasion (increasing the recurrence risk) are not rare and these patients should be followed more carefully. In fact, according to this study, patients of mPTC group presented a higher rate of bilaterality. These results are in concordance with Pitt and colleagues that found a high incidence of multifocality and bilaterality in patients with mPTC, [9] although it may not imply a worse prognosis according with some evidence.[10] In this study only one of the four patients presenting bilaterality recurred.

Most of the patients of mPTC group submitted to hemithyroidectomy were thereafter totalized, which make us ponder if it is still a good option as some authors defend, [11] although total thyroidectomy implies a non-negligible morbidity rate comparing with posterior totalization as observed in this study (24.3 vs. 13.3%). In mPTC group the rate of lymph node invasion in central area was 33.3% which is in concordance with Chinese literature, [11] but six times higher than some other studies.[7]

In this study, 59.5% of patients in mPTC group were classified as having high-risk of recurrence, which is almost twice the risk described in some series.[5] Many patients classified as having high-risk of recurrence postoperatively were not identified as such in the preoperative work-up. This handicap was already identified in the literature and is associated with incomplete response.[12] Moreover, about one third of PTC and most of mPTC recurrences were central lymph node metastasis, what makes us think about prophylactic central compartment LND as some studies advise.[13] Although some evidence shows that this methodology detects more lymph node metastases, it does not appear to affect recurrence. [14, 15] However, other studies currently on going (NCT03570021—ESTIMABL3) may show other conclusions. It is becoming increasingly clear that an improvement of preoperative work-up for identification of high-risk patients is crucial to determine what subset of patients benefit from a more aggressive surgical management.[16, 17]

Patients in mPTC group presented better stages at the expense of younger age but similar recurrence rate and time to recurrence. This make us ponder if a staging system more focused on lymph node invasion, extrathyroidal extension and multifocality would be more adequate.

CONCLUSION

Patients with mPTCs presented greater rate of multifocality and similar lymph node invasion rate, LND rate and adjuvant iodine therapy. These observations make us ponder if hemithyroidectomy is still a good option. These patients presented better stages but similar recurrence rate and time to recurrence. Moreover, staging was only significantly influenced by (older) age of presentation. These results make us question if this staging system is adequate.

A better preoperative work-up is needed to identify high-risk mPTC that should be managed more aggressively. Larger studies with longer follow-up are needed to confirm these results.

Finantial support: none.

This study was conducted in accordance with Helsinki declaration.

The authors declare that they have no conflict of interest.

This work has been presented as an electronic poster in ESSO (European Society of Surgical Oncology) Congress, 8-11 november 2021 and published in the form of an abstract in European Journal of Surgical Oncology, volume 48, issue 2, E120, february 01, 2022

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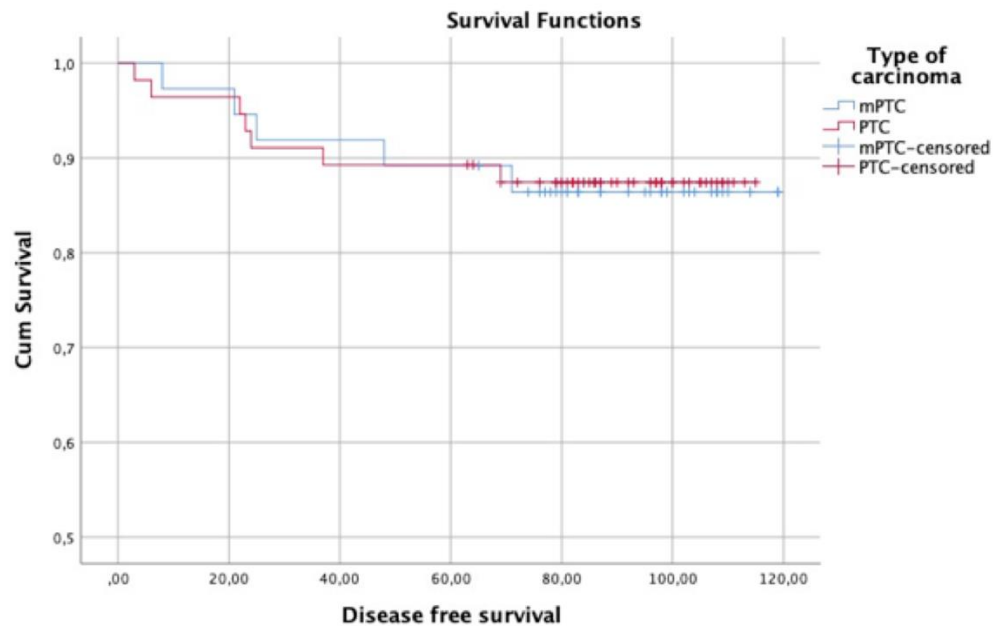


Figure 1. Comparison of curves of disease-free time documented no significant differences between the two groups of patients ($p=0.575$)

Table 1. Patient's characteristics

Variable	mPTC (n=37)	PTC (n=56)	P value
Mean age (years)	45.4+/-11.9	54.3+/-15.3	0.003***
Mean size (mm)	10.9+/-7	28.8+/-11.1	0.000***
Family history	0	2 (3.6%)	NS**
Radiation exposure	0	1 (1.8%)	NS**
Aggressive histology	0	1 (1.8%)	NS**
Multifocality	9 (24.3%)	4 (7.1%)	0.019*
Extrathyroidal extension	9 (24.3%)	12 (21.4%)	NS*
Iodine therapy	26 (70.3%)	44 (78.6%)	NS*
Kinase inhibitor therapy	1 (2.7%)	0	NS**
Lymph node invasion	4 (10.8%)	6 (10.7%)	NS*
Asymptomatic nodule	11 (29.7%)	25 (44.6%)	NS*
Stage II	5 (13.5%)	18 (32.1%)	0.042*
Recurrence	5 (13.5%)	7 (12.5%)	NS*
Cancer-related death	0	1 (1.8%)	NS**

*Qui square test; **Fisher's test; *** Man-Whitney test