Multifocality in patients treated for papillary Thyroid Carcinoma: a preliminary analysis of related risk factors

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Abstract. Background: Multifocality is usually detected afterwards surgery for papillary thyroid cancer (PTC) and has been reported in 18-87% of PTC. Methods: This is a retrospective single-center study involving a series of 238 patients that underwent thyroidectomy or lobectomy after preoperative fine needle aspiration (FNA) diagnosis of Thyr 5 or Thyr 6, according to Bethesda classification, from January 2015 to December 2019 at the General Surgery Unit of the University - Hospital of Parma. We divided patients into two main groups: patients with multifocal papillary thyroid cancer at postoperative diagnosis and patients with unifocal papillary thyroid cancer. The aim of the study is to identify demographic or preoperative radiological risk factors for the presence of multifocal PTC and to verify the presence of cyto-histological features of greater aggressiveness in multifocal tumors than in unifocal ones. Results: Out of our sample, 176 patients were females (73,9%) and 62 males (26,1%) with a mean age of 50,45 ±14,41. Preoperative cytological diagnosis resulted Thyr 5 in 47 cases (19,7%) and Thyr 6 in 191 cases (80,3%). Multifocal cancer was reported in 35,8% of the females and in 32,3% of the males. Older age was significatively related to the presence of multifocal papillary carcinoma (p<0.05). Preoperative bilateral thyroid nodules were associated with a higher finding of multifocal disease at histological examination (p<0.05). The presence of multifocal disease was related with a higher soft tissue invasion at the histological specimen (p<0.05). Tumor size was not related to multifocal PTC in our study. Conclusions: Older age of patient and preoperative bilateral thyroid nodules are significantly associated to multifocal thyroid cancer. In add to this, multifocal disease is related to higher finding of perithyroidal tissue invasion at histological exam. In case of predictive factors for multifocal PTC, surgeons should take total/near-total thyroidectomy always into consideration. (www.actabiomedica.it)

Keywords: thyroid carcinoma, multifocality, thyroidectomy, lobectomy, Bethesda.

Introduction

The incidence of differentiated thyroid cancer (DTC) has increased in the last decades due to the spread use of ultrasound (EUS) and ultrasound-guided fine-needle aspiration biopsy (FNA), ranging from 0,5 to 10 cases every 100.000 habitants. Papillary thyroid carcinoma (PTC) is the main type of DTC (1-5).

EUS has been widely used to stratify the risk of malignancy in thyroid nodules and aids decision-making about whether FNAC is indicated. The use of EUS is related to an increased detection rate of PTC lower than 1 cm, defined as microcarcinoma (MPTC) (6). MPTC accounts for 39% of cases of thyroid cancer in the United States (7). PTC may occur in one focus or more. It is labeled multifocal PTC if two or more foci are detected following surgery (8). Single thyroid nodularity is rare in iodine deficient regions (9) but it is the condition to perform a lobectomy in case of T1-T2 DTC, according to international guidelines (10-11).
Multifocality has been reported in 18–87% of PTC, it has been always considered a potential risk for disease progression and local recurrence (12). The incidence of multifocal MPTC has been reported ranging from 13.4% to 36.1% of all MPTC. (13)

In this study we aimed to evaluate demographic or preoperative radiological risk factors for the presence of multifocal PTC and to verify, analyzing the specific features, the presence of cyto-histological features of greater aggressiveness in multifocal tumors than in unifocal ones.

Methods

This is a retrospective single-center study, involving a series of 289 patients that underwent curative surgery for malignant thyroid disease, with a preoperative FNA diagnosis of Thyri 5 or Thyri 6, according to Bethesda 2010–2017 classifications, at General Surgery Unit of University Hospital of Parma, over a five-year period between 2015 and 2019. Institutional review board approval was previously obtained, and the study was conducted according to Helsinki Declaration. Patients have given their informed consent for participation.

The inclusion criteria were: patients with preoperative FNA diagnosis of Thyri 5–6 nodules, according to Bethesda classification 2010–2017, patients treated with thyroidectomy, histological findings of thyroid carcinoma. The exclusion criteria were: patients with FNA diagnosis of Thyri 1–4; no histologically proven PTC; history or coexistence of other head and neck cancers. 51 cases were excluded from our study due to insufficient data or finding of benign disease after post-operative histological examination. In 238 cases out of our sample it has been possible to evaluate the presence or not of multifocal thyroid carcinoma by means of a histological diagnosis post-surgery. Among the 238 patients, 176 were females (73.9%) and 62 males (26.1%) with a mean age of 50.45 ± 14.41. Preoperative cytological diagnosis resulted Thyri 5 in 47 cases (19.7%), Thyri 6 in 191 cases (80.3%). All patients underwent preoperative ultrasound. In 132 cases no bilateral thyroid nodules were found (55.5%), in 99 bilateral thyroid nodules were detected (41.6%), in 7 cases it was not possible to assess this data (2.9%). 221 patients underwent total thyroidectomy (92.9%) and 17 lobectomy (7.1%), with the routinely use of IONM and the adoption of two stage thyroidectomy technique in case of post lobectomy signal loss. The transitory vocal palsy was found post-operatively in 5 patients (2.1%) and 1 patient (0.4%) had permanent vocal palsy. Bilateral vocal cord palsy was not documented. Two-stage thyroidectomy was performed in two cases.

Histological examination showed multifocal papillary carcinoma in 83 cases (34.9%) and 155 cases of non-multifocal disease (65.1%). The mean tumor size was described at postoperative histological exam in 230 cases and it was 1.56 cm ± 0.85 cm (on 8 patients data were missing). In multifocal disease, mean tumor size was 1.54 ± 0.77 cm, in non-multifocal disease mean tumor size was 1.57 ± 0.89 cm. We did not find a statistically significant difference between tumor size and the presence of multifocal disease.

Patients were divided into two main groups, based on the presence at the definitive histological examination of multifocal PTC or unifocal PTC. Data were analyzed using a chi-square test and Fisher’s exact test. P values of <0.05 were defined as statistically significant.

Results

A total of 289 patients were initially enrolled in our study but 51 cases were subsequently excluded due to insufficient data or finding of benign disease after post-operative histological examination. In 238 cases out of our sample it has been possible to evaluate the presence or not of multifocal thyroid carcinoma. Among the 238 patients, 176 were females (73.9%) and 62 males (26.1%) with a mean age of 50.45 ± 14.41. Preoperative cytological diagnosis resulted Thyri 5 in 47 cases (19.7%), Thyri 6 in 191 cases (80.3%).

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Multifocal tumor was reported in 35.8% of females and in 32.3% of the males. We found no statisti-
cally significant differences in the incidence between genders. The mean age in multifocal disease was 53.2 ± 14.78 and 48.97 ± 14.03 in non-multifocal disease. Older age was significantly related to multifocal papillary carcinoma (p < 0.05).

Out of the 191 Thyr 6 cases at the histological examination, multifocal disease was found in 69 cases (36.1%) and non-multifocal disease in 122 cases (63.9%). Among the 47 Thyr 5 cases, multifocal disease was found in 14 (29.8%) cases and non-multifocal disease in 33 (70.2%) cases. Comparing preoperative ultrasound and histology, multifocal disease was found in 30 patients (22.7%) without preoperative diagnosis of bilateral thyroid nodules (30/132). Among the 99 patients with preoperative diagnosis of bilateral thyroid nodules, multifocal disease was reported in 50 cases (50.5%). Preoperative bilateral thyroid nodules were associated with a higher finding of multifocal disease at histological examination (p < 0.05) (Table 1).

We evaluated the correlation between the papillary thyroid carcinoma tall cell and sclerosing variants and multifocal disease. Among the 20 cases of sclerosing papillary carcinoma variant, multifocal disease was found in 4 cases (20%) and 16 were non-multifocal (80%). Among the 218 cases without sclerosing papillary carcinoma variant, multifocal were 79 (36.2%) and unifocal were 139 (63.8%). 22 cases with tall cell papillary carcinoma variant were reported and 9 were multifocal (40.9%), 13 were unifocal (59.1%). No statistically significant correlations were found both for papillary thyroid carcinoma tall cell and sclerosing variants with multifocal disease.

We evaluated the correlation between multifocal disease and lymph vascular invasion, assessed at the histological specimen. Lymph vascular invasion was confirmed histologically in 12/155 (7.8%) patients without multifocal disease and in 6/83 (7.2%) patients with multifocal disease. No statistically significant difference was found in the two groups (Table 2).

### Discussion

The increase of DTC diagnosis is related to the spread worldwide of cervical ultrasound, fine needle aspiration biopsy and a better knowledge of thyroid disease. (1,2) PTC, generally, has a good prognosis and the surgical treatment remains controversial. The 10-year disease-free survival rate for PTC is approximately 96–98%. (14) The 2015 ATA guidelines (10) have defined thyroid lobectomy as sufficient surgical treatment for DTC lower than 1 cm, defined T1. Unilateral lobectomy can lead to misdiagnosis of a contralateral occult PTC that would cause recurrence and even require re-operation, with increased surgical risks, including hypoparathyroidism and recurrent laryngeal

**Table 1.** Patients characteristics.

|                | Group 1 (multifocal) | Group 2 (unifocal) | P     |
|----------------|----------------------|--------------------|-------|
| Age            | 53.2±14.78           | 48.97±14.03        | < 0.05|
| Gender         |                      |                    |       |
| Male           | 20 (24.1%)           | 42 (27.1%)         | NS    |
| Female         | 63 (75.9%)           | 113 (72.9%)        | NS    |
| Cytological Exam|                     |                    |       |
| Thyr 5         | 14 (16.9%)           | 33 (21.3%)         | NS    |
| Thyr 6         | 69 (83.1%)           | 122 (78.7%)        | NS    |
| Preoperative bilateral nodules | |                     |       |
| Yes            | 50 (60.2%)           | 49 (31.6%)         | < 0.05|

**Table 2.** Postoperative histologic reports for both groups

|                | Group 1 (multifocal) | Group 2 (unifocal) | P     |
|----------------|----------------------|--------------------|-------|
| Tumor size     | 1.54 cm ± 0.77 cm    | 1.57 ± 0.89 cm     | NS    |
| Lymph nodes metastasis |          |                    |       |
| Yes            | 8 (9.6%)             | 14 (9.0%)          | NS    |
| Lymph vascular invasion |        |                    |       |
| Yes            | 6 (7.2%)             | 12 (7.7%)          | NS    |
| Soft tissue invasion |         |                    |       |
| Yes            | 35 (42.2%)           | 40 (25.8%)         | < 0.05|
nerve paralysis. (15) The presence of multifocality and multicentricity are poor prognostic factors. (12) On the other hand, the percentage of complications for total thyroidectomy, compared to lobectomy, is not irrelevant and so the extension of thyroidectomy for patients with DTC is still an important matter of debate.

In our study, multifocality was observed in 34.9% of patients. Our results are stackable to literature findings, where multifocal PTC rate has been reported ranging from 10% to 87%. (12,16-18) Literature findings on occult multifocal papillary thyroid cancer, recurrence and prognosis related to surgical procedure are controversial. Several studies have reported that only few patients are really candidate to thyroid lobectomy. Ritter et al have reported that during the follow-up of 168 patients, 18 patients (10.7%) underwent completion thyroidectomy with diagnosis of contralateral PTC in 12 cases. (19)

Haigh et al. analyzed 4,612 total thyroidectomy and 820 lobectomies and did not found differences in 10-year overall survival and 10-year recurrence rate between the two groups (20) while in another study including a huge sample of 52,173 patients, the 10-year recurrence rate for patients who received a total/subtotal thyroidectomy was lower than patients who received thyroid lobectomy (21). The latest guidelines about definitive surgical management of thyroid disease in adults from the American Association of Endocrine Surgeons, suggest that patients with DTC 1 to 4 cm in size, without aggressive cytologic or US features, such as evidence of local invasion, nodal or distant metastases, multiple bilateral nodules, or evidence of MTC, and no other identified reason for initial total thyroidectomy, such as previous head and neck radiotherapy or family history of thyroid cancer, may be offered ipsilateral lobectomy and isthmusectomy. (22)

Several studies have reported tumor size, lymph node metastasis, capsular invasion, extrathyroidal extension as poor prognostic factors and these are more often described in multifocal PTC than in the unifocal one. (23-25) Our findings suggest that multifocal PTC is more common in older age, in patients with multiple or bilateral thyroid nodules at the preoperative EUS and it is associated to a higher risk of soft tissue invasion. Tumor size, assessed at postoperative histological examination, was not related to multifocal PTC in our study. In add to this, it has been reported that multifocality is associated to a higher risk of lymph node metastasis and to a higher rate of positive VI level. Multifocal PTC can be considered an independent prognostic factor for metastatic nodules after central node dissection (CND). (26-28) Nevertheless, other studies have yielded different results. Yossi et al. reported that multifocality is not an independent factor for the patient’s outcome (29) and Harris et Al. (30) added that multifocality alone is not an indication for thyroid completion surgery. We did not find an association between multifocality and lymph node metastases in our study, probably due to the small size of the sample analyzed. The preliminary evaluation would benefit from a new analysis with a larger sample of patients, evaluated in a prospective setting.

As confirmed by Limberg et Al., in our study the histological variant of PTC is not related to multifocal disease (27). Some authors reported that histological multifocality is associated with PTC at a T3B stage. (31)

These controversial data represent a challenge for the surgeon to choose between lobectomy or total thyroidectomy. Some authors showed that multifocal MPTC is frequently associated with a worse prognosis and greater aggressiveness. Secondary tumors are often smaller than the primary, preoperatively diagnosed with ultrasound is often difficult then thyroidectomy should be carefully considered. A correct preoperative staging is mandatory for the correct risk stratification. If well conducted, it allows planning the right tailored treatment.

**Conclusions**

In our preliminary experience, older age of patients and preoperative bilateral thyroid nodules are significantly associated to multifocal thyroid cancer, but not tumor size. In add to this, multifocal disease is related to higher incidence of perithyroidal tissue invasion. A prospective analysis with a larger sample could improve these results. In the pre-operative staging of PTC, contralateral occult lesions and small multifocal lesions could be missed. The misdiagnosis can lead to tumor recurrence and re-operation in case of lobecto-
my. Therefore, an accurate assessment of patient’s age and thyroid ultrasound characteristics is mandatory for a correct planning of surgical strategy.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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