

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

Paolo Del Rio, Tommaso Loderer, Mario Giuffrida, Federico Cozzani, Matteo Rossini, Deborah Bonfili, Elena Bonati

Unit of General Surgery, Parma University Hospital, Parma, Italy

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 Thy 5 or Thy 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 $50,45 \pm 14,41$. Preoperative cytological diagnosis resulted Thy 5 in 47 cases (19,7%) and Thy 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 significantly 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 Thy 5 or Thy 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 Thy 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 Thy 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. After exclusion, 238 patients that had pathological PTC and received thyroidectomy were included in the present study.

We analyzed the following characteristics: gender, age, preoperative cytological diagnosis, presence or not of tall cell variant of papillary thyroid carcinoma, sclerosing variant of papillary thyroid carcinoma, multifocal disease, lymph vascular invasion, soft tissue invasion and lymph node metastasis after post-operative histological diagnosis.

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 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 $50,45 \pm 14,41$. Preoperative cytological diagnosis resulted Thy 5 in 47 cases (19,7%), Thy 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 $1,56 \text{ cm} \pm 0,85 \text{ cm}$ (on 8 patients data were missing). In multifocal disease, mean tumor size was $1,54 \pm 0,77 \text{ cm}$, in non-multifocal disease mean tumor size was $1,57 \pm 0,89 \text{ cm}$. We did not find a statistically significant difference between tumor size and the presence of multifocal disease.

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 $53,2 \pm 14,78$ and $48,97 \pm 14,03$ in non-multifocal disease. Older age was significantly related to multifocal papillary carcinoma ($p < 0.05$).

Out of the 191 Thy 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 Thy 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. Soft tissue invasion was reported in 40/155 (25,8%) cases without multifocal disease and in 35/83 (42,2%) cases with multifocal disease. The presence of multifocal disease was related with a higher incidence of soft tissue invasion at the histological specimen ($p < 0.05$). Lymph node metastasis were reported in 14/155 (9%) cases with no multifocal disease and in 8/83 (9,6%) 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) (83 cases)	Group 2 (unifocal) (155 cases)	P
Age	53.2±14.78	48.97±14.03	< 0.05
Gender			
Male (62 cases)	20 (24.1%)	42 (27.1%)	NS
Female (176 cases)	63 (75.9%)	113 (72.9%)	NS
Cytological Exam			
Thyr 5 (47 cases)	14 (16.9%)	33 (21.3%)	NS
Thyr 6 (191 cases)	69 (83.1%)	122 (78.7%)	NS
Preoperative bilateral nodules			
Yes (99 cases)	50 (60.2%)	49 (31.6%)	< 0.05

Table 2. Postoperative histologic reports for both groups

	Group 1 (multifocal) (83 cases)	Group 2 (unifocal) (155 cases)	P
Tumor size	1,54 cm ± 0,77 cm	1,57 ± 0,89 cm	NS
Lymph nodes metastasis			
Yes (22 cases)	8 (9.6%)	14 (9.0%)	NS
Lymph vascular invasion			
Yes (18 cases)	6 (7.2%)	12 (7.7%)	NS
Soft tissue invasion			
Yes (75 cases)	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 diagnosis 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.

References

- Pellegriti G, Frasca F, Regalbutto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol* 2013;2013:965212.
- Del Rio P, Montana Montana C, Mingardi G et al. Thyroid micro-carcinoma: only a diagnostic epidemic? *Minerva Endocrinol* 2017 Sep;42(3):203-212.
- Cibas ES, Ali SZ, Cibas ES et al. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2017 Nov;27(11):1341-1346.
- Fadda G, Basolo F, Bondi A et al. Cytological classification of thyroid nodules. Proposal of the SIAPEC-IAP Italian Consensus Working Group, SIAPEC-IAP Italian Consensus Working Group *Pathologica* . 2010 Oct;102(5):405-8.
- NCCN clinical practice guidelines in oncology. *Thyroid Carcinoma* 2014
- Del Rio P, Montana Montana C, Cozzani F et al. Is there a correlation between thyroiditis and thyroid cancer? *Endocrine* 2019 Dec;66(3):538-54.
- Davies L, Welch HG Current thyroid cancer trends in the United States *JAMA Otolaryngol Head Neck Surg* 2014;140:317-322.
- Castro MR, Gharib H Continuing controversies in the management of thyroid nodules. *Ann Intern Med* 2005; 142:926-931.
- Ceresini G, Corcione L, Michiara M et al. Thyroid cancer incidence by histological type and related variants in a mildly iodine-deficient area of Northern Italy, 1998 to 2009. *Cancer* 2012 Nov 15;118(22):5473-80.
- Haugen BR, Alexander EK, Bible KC et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016 Jan;26(1):1-133.
- Pacini F, Basolo F, Bellantone R et al. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. *J Endocrinol Invest* 2018 Jul;41(7):849-876.
- Iacobone M, Jansson S, Barczy ski M, Goretzki P Multifocal papillary thyroid carcinoma--a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* 2014 Feb;399(2):141-54.
- Xue S, Wang P, Liu J, Chen G Total thyroidectomy may be more reasonable as initial surgery in unilateral multifocal papillary thyroid microcarcinoma: a single-center experience. *World J Surg Oncol* 2017 15 (1):62
- Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National multidisciplinary guidelines. *J Laryngol Otol* 2016; 130:150-160.
- Unalp HR, Erbil Y, Akguner T et al. Does near total thyroidectomy offer advantage over total thyroidectomy in terms of postoperative hypocalcemia? *Int J Surg* 2009;7:120-5.
- Feng JW, Qu Z, Qin AC, Pan H, Ye J, Jiang Y. Significance of multifocality in papillary thyroid carcinoma. *Eur J Surg Oncol* 2020 Oct;46:1820-1828
- Vorasubin N, Nguyen C, Wang M. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a meta-analysis. *Ear Nose Throat J*, 2016;95:73-77.
- Gur EO, Karaisli S, Haciyanli S et al. Multifocality related factors in papillary thyroid carcinoma. *Asian J Surg* 2019 Jan;42(1):297-302.
- Ritter A, Mizrachi A, Bachar G et al. Detecting Recurrence Following Lobectomy for Thyroid Cancer: Role of Thyroglobulin and Thyroglobulin Antibodies. *J Clin Endocrinol Metab* 2020;105:152.
- Haigh PI, Urbach DR, Rotstein LE. Extent of thyroidectomy is not a major determinant of survival in lower high-risk papillary thyroid cancer. *Ann Surg Oncol* 2005;12:81-9.
- Bilimoria KY, Bentrem DJ, Ko CY et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* 2007;246:375-81.
- Patel KN, Yip L, Lubitz CC et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. *Ann Surg* 2020 Mar;271(3):21-93.
- Del Rio P, Viani L, Montana CM, Cozzani F, Sianesi M. Minimally invasive thyroidectomy: a ten years experience. *Gland Surg* 2016 Jun;5(3):295-9.
- Miccoli P, Fregoli L, Rossi L et al. Minimally invasive video-assisted thyroidectomy (MIVAT). *Gland Surg* 2020 Jan;9:1-5.
- Dionigi G, Dralle H, Materazzi G, Kim HY, Miccoli P. Happy 20th birthday to minimally invasive video-assisted thyroidectomy! *J Endocrinol Invest* 2020 Mar;43(3):385-388.
- Janlu Song, Ting Yan , Wangwang Qiu, Youben Fan, Zhili Yang. Clinical analysis of risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a retrospective study of 3686 patients. *Cancer Management and research* 2020;12:2523-2530.
- Limberg J, Ullmann TM, Stefanova D et al. Does Aggressive Variant Histology Without Invasive Features Predict Overall Survival in Papillary Thyroid Cancer?: A National Cancer Database Analysis. *Ann Surg* 2019 Oct 9.
- Yuan J, Li J, Chen X et al. Identification of risk factors of central lymph node metastasis and evaluation of the effect of prophylactic central neck dissection on migration of staging and risk stratification in patients with clinically node-neg-

- ative papillary thyroid microcarcinoma. *Bull Cancer* 2017 Jun;104(6):516-523.
29. Geron Y, Benbassat C, Shteinshneider M et al. Multifocality Is not an Independent Prognostic Factor in Papillary Thyroid Cancer: A Propensity Score-Matching Analysis. *Thyroid* 2019 Apr;29(4):513-522.
30. Harries V, Wang YL, McGill M et al. Should multifocality be an indication for completion thyroidectomy in papillary thyroid carcinoma? *Surgery* 2020;167:10-17.
31. Sun R, Zhang H, Liu K et al. Clinicopathologic Predictive Factors of Cervical Lymph Node Metastasis in Differentiated Thyroid Cancer. *Acta Otorrinolaringol Esp* 2018 May-Jun;69(3):149-155.

Correspondence:

Received: 1 June 2021

Accepted: 13 June 2021

Dr Tommaso Loderer

Unit of General Surgery, Department of Medicine and Surgery,
University Hospital of Parma, Gramsci 14 street, 43125, Italy,
Email: tommasoloderer@gmail.com.