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Is multifocality a risk factor in low-risk papillary thyroid cancer?

Giulia Sapuppo[1, 2], Sonia Grasso[1], Guenda Di Benedetto[1], Ilenia Marturano[3], Gabriele Costanzo[1], Antonino Belfiore[1], Gabriella Pellegriti[3]

[1]*Endocrinology, Department of Clinical and Molecular Biomedicine, Garibaldi-Nesima Medical Center, University of Catania, Italy*
[2]*Centre of Experimental Oncology and Haematology, Department of Clinical and Experimental Medicine, Policlinico "G. Rodolico-San Marco" Medical Centre, Catania, Italy*
[3]*Endocrinology, Garibaldi-Nesima Medical Centre, Catania, Italy*

Abstract

Introduction: Multifocality in papillary thyroid cancer (PTC) is a common event, ranging from 18% to 87%. Additional multiple foci are frequently very small and generally detected in pathology specimens. The mechanisms of intrathyroidal spread, and its correlation with age, gender, tumour size, and lymph node metastases remain unclear. Moreover, studies assessing the prognostic impact of PTC multifocality have yielded non-univocal results. We aimed to evaluate the following: a) the histopathological and clinical characteristics associated with multifocal PTC; and b) the impact of multifocality on the long-term outcome.

Material and methods: We analysed a consecutive series of 2814 PTC patients without evidence of microscopic extrathyroidal extension (T1a, T1b, and T2), all of whom had undergone total thyroidectomy and were followed-up (median 4.7 years) in our thyroid clinic. Females comprised 81.3% and males 18.7% (F/M = 4.4/1), with a median age at diagnosis of 45.0 years. Patients were subdivided into 2 groups: 72.7% unifocal tumour and 27.3% multifocal tumour. Post-surgical radioiodine ablation (RAI) (30–100 mCi of 131-I) was performed in 1425 (50.6%) patients. All patients were periodically followed with thyroglobulin and anti-thyroglobulin antibodies measurements and with neck ultrasonography under L-thyroxine therapy and subjected to additional radioiodine administration or another therapeutic measure if not cured.

Results: Patients in the multifocal group were older (median age 46.4 *vs*. 44.5 years, respectively, $p < 0.05$) and presented a lower F/M ratio (F/M = 3.7/1 and 4.7/1; $p = 0.01$). T1a and T1b tumours showed no significant difference in multifocality rate whereas T2 tumours were less frequently multifocal (14.2% *vs*. 10.9%, $p < 0.05$). Multifocal tumours were more frequent in N1b (11.3% *vs*. 7.8%, $p < 0.01$) and less frequent in Nx (50.5% *vs*. 56.8%, $p < 0.01$), with no difference between the N0 and N1a groups. The clinical outcome was similar in the 2 group of patients (88.2 % in the unifocal group *vs*. 90.2% in the multifocal group).

Conclusions: Multifocality is more frequent in older and male patients, in smaller tumours, and in N1b. However, multifocality "per se" was not associated, in our study, with worse clinical outcome in PTC patients.

Key words: *papillary thyroid cancer; multifocality; multifocal tumour; thyroid cancer outcome; risk factors*

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy [1–3], and for over 85% of cases it shows a papillary histotype (PTC). The detection of multifocality in PTC is a common event, occurring in approximately 20–30% of PTCs. Multiple foci are frequently subcentrimetric and generally detected in pathology specimens following surgery. PTC frequently spreads to the lymph nodes (LN) of the neck compartment (12–81% of cases) [4, 5], and these locoregional metastases may be present even when the primary tumour is small and intrathyroidal [6].

PTC is generally associated with an excellent prognosis: the 5-year survival rate is close to 100% for localized disease, 98% for regional disease, and 55% for metastatic disease [7]. According to the American Thyroid Association (ATA) risk stratification, multifocal PTC with no other adverse features meeting criteria for upstaging are considered low-risk tumours, although the risk of local-regional recurrence is 1–2% in unifocal tumours and 4–6% in multifocal papillary microcarcinoma (ATA, Recommendation 48, B20) [8].

Some retrospective studies reported a worse outcome in multifocal *vs*. unifocal tumours [9] while other studies found no differences [10]. In fact, in most cases multifocality occurs incidentally as microscopic foci found on histopathological sampling, while in other cases it is associated with a more spread disease. To date, the prognostic significance of multifocality in PTC remains controversial due to conflicting results in the literature.

Sapuppo Giulia, MD, PhD, Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Centre, Via Palermo 636, 95122 Catania, Italy, fax: +39 095 472988; e-mail: giuliasapuppo@hotmail.it

The objective of the present study was to evaluate the effect of multifocality on the outcome in a retrospective large series of PTC patients, without microscopic extrathyroidal extension, avoiding its influence as a confounding factor in the analyses, all followed up in our thyroid clinic according to a standardized protocol.

Because of the indolent progression of most PTCs, in this study persistence/recurrence (the most used endpoint for PTC) and the presence of distant metastases (the best surrogate indicator of cancer-specific death) [11] have been chosen as endpoints.

Material and methods

A consecutive series of 2814 PTC patients, all of whom had undergone total thyroidectomy, T1a (≤ 1 cm), T1b (> 1.0–2.0 cm), and T2 (> 2.0–4.0 cm) without evidence of microscopic extrathyroidal extension, followed up (median 4.7 years, IQR 2.0–8.7) in our thyroid clinic, were included: 2289 female (81.3%) and 525 male (18.7%) (F/M = 4.4/1) with median age at diagnosis of 45.0 years [interquartile range (IQR): 36.3–54.6].

Patients with evidence of microscopic extrathyroidal extension were excluded from the study because, especially in the past, they were considered an independent risk factor for disease recurrence or aggressiveness.

The clinical characteristics of these patients are shown in Table 1. Tumours were staged according to the 8th TNM edition: T (the maximum extent of the primary tumour) and N (regional LN metastases) were assessed at pathological examination. Patients with known distant metastases at surgery were excluded from the study because multifocality was considered to have little relevance in the context of advanced disease. According to multifocality, we subdivided the patients into 2 groups: 2047 unifocal (72.7%) and 767 multifocal (27.3%), and evaluated clinical and histopathological characteristics associated with multifocality and its role on the long-term outcome.

Postsurgical radioactive iodine treatment (RAI) was given to patients with one or more of the following characteristics: tumour size > 1.0 cm, nodal metastases (N1), postoperative evidence of large thyroid remnant and/or high postoperative thyroglobulin (Tg) levels, and when host risk factors (familial thyroid cancer, previous neck external beam radiotherapy) were present.

RAI treatment (30–100 mCi of ^{131}Iodine [^{131}I]) was performed in 1425 (50.6%) patients while 1389 (49.4%) were not ablated.

All patients were periodically followed with Tg and AbTg measurements and with neck ultrasonography under L-thyroxine therapy; in addition to this, RAI patients were evaluated 12–18 months later with TSH stimulation. If the patient was not cured, additional ^{131}I therapy or other therapeutic procedures were carried out. The frequency of follow-up controls, every 6 or 12 months, was modulated on the basis of the initial risk evaluation and the response to first treatment.

At the last control visit, persistent/recurrent disease was defined by one or more of the following criteria: (1) serum Tg, either under suppressive L-T4 therapy or after TSH stimulation, at detectable levels and/or higher than the value defined on the basis of the assay sensitivity at the time of measurement; (2) metastatic LN identified at ultrasound and confirmed by fine needle aspiration (FNAB) with Tg measurement in the aspirate washout; and (3) positive ^{131}I-WBS. All patients presenting persistent/recurrent disease during follow-up underwent additional diagnostic imaging procedures and surgery and/or RAI treatment and/or other therapies as required [31, 32].

Table 1. *Clinical and histopathological characteristics of 2814 patients operated for papillary thyroid cancer*

	n	(%)
Patients (n)	2814	
Age [y]		
Median (IQR range)	45.0 (36.3–54.6)	
Gender		
Female	2289	(81.3)
F/M ratio	4.4/1.0	
TNM		
T status (T)		
T1a	1694	(60.2)
T1b	745	(26.5)
T2	375	(13.3)
N status (N)		
N0	592	(21.1)
Nx	1549	(55.1)
N1a	425	(15.1)
N1b	246	(8.7)
Multifocality	767	(27.3)

IQR — interquartile range; TNM — tumour–node–metastasis

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of the institutional Research Committee and with the Helsinki declaration as revised in 2013. Informed consent of the present retrospective study was waived.

Statistical analysis

Categorical variables were expressed as frequencies and percentages (%). Quantitative normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with IQR. The normality of quantitative variables was tested by the Kolmogorov-Smirnov test. Categorical variables were analysed using the chi-square test with Yates's correction or Fisher's test. Quantitative variables were assessed by Kruskal-Wallis test followed by Dunn's multiple comparison test. Multivariate analysis was carried out using logistic regression including only variables identified as being significant at univariate analysis. A p value < 0.05 was considered statistically significant for all analyses. Data analysis was performed using the SPSS statistical software version 13.0 for windows.

Results

Clinical and histopathological characteristic according to unifocal or multifocal tumour are shown in Table 2. Age at diagnosis was significantly higher in the multifocal group *vs*. unifocal (median age 46.4 *vs*. 44.5 and ≥ 55 years 27.0% *vs*. 23.3%, respectively, in the multifocal and unifocal group, $p < 0.05$), and the F/M ratio was lower in the multifocal than in the unifocal group (F/M = 3.7/1 and 4.7/1, respectively; $p = 0.01$).

Table 2 *Clinical and histopathological characteristic according to unifocal or multifocal tumour*

	Unifocal		Multifocal	
	n	(%)	n	(%)
N	2047	(72.7)	767	(27.3)
Age [y]				
< 55 years	1571	(76.7)	560	(73.0)*
Gender				
F/M	1686/361		603/164 *	
Ratio	4.7/1		3.7/1	
T status				
T1a	1228	(60.0)	466	(60.8)
T1b	528	(25.8)	217	(28.3)
T2	291	(14.2)	84	(10.9)*
N status				
N0	416	(20.3)	176	(22.9)
Nx	1162	(56.8)	387	(50.5)*
N1a	308	(15.1)	117	(15.3)
N1b	159	(7.8)	87	(11.3)*
Post-surgical RAI				
Yes	838	(40.9)	587	(76.5)*
Distant metastases				
Present	49	(2.4)	16	(2.1)
Clinical outcome				
Disease free	1820	(88.9)	692	(90.2)

*p < 0.05; RAI — radioidine ablation

In the T1a and T1b tumour groups no significant differences in multifocality frequency were found; instead, patients with tumour > 20 mm (T2 group) less frequently presented with multifocal tumours (10.9 *vs.* 14.2% p ≤ 0.05).

Analysing the lymph node status, multifocal tumours were more frequent in N1b regarding the unifocal group (11.3% *vs.* 7.8%, p < 0.01); the opposite result was found in Nx (unifocal 56.8% and multifocal 50.5%; p ≤ 0.01) with no difference in the N0 and N1a groups.

Post-surgical RAI was administered more frequently in multifocal *vs.* unifocal tumours (76.5% *vs.* 40.9%; p ≤ 0.01).

Clinical outcome was similar in the 2 groups of patients (88.9% were disease free at last control visit in the unifocal group *vs.* 90.2% in the multifocal group; p = 0.33). No difference was found when analysing data separately by gender (Tab. 3).

Evaluating patients' outcomes in relation to the ablation, we found a statistically significant difference only in T1a/T1b/T2 without lymph node metastasis, while no difference was found analysing only multifocal tumours, highlighting no impact of ablation in multifocality (Tab. 4).

Persistent/recurrent disease at last control visit was observed in 302 patients (10.7%). Its frequency was 11.1% in the unifocal group (227/2047) and 9.8% in the multifocal group (75/767), which was not statistically significant (p = 0.3); also, the rate of persistent or recurrent disease was not statistically significant in the unifocal group *vs.* the multifocal group (68.7% *vs.* 76.0%, respectively, p = 0.24).

In most cases, disease event was structural (lymph node or distant metastases or both) with no difference between the 2 groups (52.0% *vs.* 60.0% in the unifocal *vs.* multifocal group; p= 0.08).

Distant metastases were observed in 65 patients (2.3%). Their frequency was 2.4% in unifocal (49/2.047) and 2.1% in multifocal tumours (16/767); these differences were not statistically significant (p = 0.6).

We did not find multifocality a statistically significant predictor of worse prognosis at univariate analysis when considering the whole cohort of patients or only Nx/N0 patients (Tab. 5 and 6). Instead, at multivariate analysis, we confirmed male gender, and T and N status as predictors of persistent/recurrent disease and age at diagnosis, T status, the presence of LN metastases, and radioiodine ablation as significant predictors of distant metastases (Tab. 5). N1b had the highest OR for both persistent/recurrent disease and distant metastases [odds ratio (OR): 6.8 and 9.9, respectively].

When analysing only lymph node-negative patients (n = 2141), age at diagnosis, T status, and ablation were significant predictors of persistent/recurrent disease and of distant metastases (Tab. 6).

Discussion

Multifocality in PTC is a common event with a wide range of frequencies reported in the literature (18–87%) [12, 13].

Table 3. Outcome according to unifocal or multifocal tumour and gender

	Female (n = 2289)			Male (n = 525)		
	Unifocal (n = 1686)	Multifocal (n = 603)	p	Unifocal (n = 361)	Multifocal (n = 164)	p
Disease free	1508 (89.4%)	552 (91.5%)	0.14	312 (86.4%)	140 (85.4%)	0.74

Table 4. Outcome according ablation treatment and N status in all patients and only in multifocal cases

All patients					
		Whole cohort	**RAI**	**No RAI**	**p**
T1a/b/T2, N0/Nx	Disease free	2141 1969 (92.0%)	806 726 (90.1%)	1335 1243 (93.1%)	0.01
T1a/b/T2, N1a/N1b	Disease free	671 541 (80.6%)	618 502 (81.2%)	53 39 (73.6%)	0.17
Only multifocal tumours					
		Multifocal cohort	**RAI**	**No RAI**	**p**
T1a/b/T2, N0/Nx	Disease free	563 518 (92.0%)	396 368 (92.9%)	167 150 (89.8%)	0.21
T1a/b/T2, N1a/N1b	Disease free	204 174 (85.3%)	191 164 (85.9%)	13 10 (76.9%)	0.37

RAI — radioidine ablation

Table 5. *Multivariate analysis of risk factors for predicting persistent/recurrent disease and distant metastases in all patients*

Risk factor	**Persistent/recurrent disease**		**Distant metastases**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Male gender	0.8 (0.6-1.1)	0.14	Not significant at univariate	
Age				
< 55	Not significant at univariate		1.0	
≥ 55			2.7 (1.6–4.6)	< 0.01
T status				
T1a	1.0		1.0	
T1b	1.7 (0.9—1.6)	0.19	1.6 (0.8–2.9)	0.2
T2	2.1 (1.5–2.9)	< 0.01	4.1 (2.2–7.7)	< 0.01
N status				
N0	1.0		1.0	
Nx	2.1 (1.4–3.2)	< 0.01	2.1 (0.7–6.5)	0.16
N1a	3.0 (1.8–4.9)	< 0.01	3.2 (1.0–10.1)	0.05
N1b	6.8 (4.1–11.1)	< 0.01	9.9 (3.3–29.9)	< 0.01
Multifocality	Not significant at univariate		Not significant at univariate	
Ablation	1.1 (0.8–1.5)		2.7 (1.3–5.8)	< 0.01

OR — odds ratio; CI — confidence interval

In the present study, multifocal disease was diagnosed in 27.3% of the whole cohort; it was more frequent in older, male, and N1b patients. The clinicopathological characteristics of our cohort are in agreement with previous findings in the literature, and we found a clear association between multifocal disease and older age and male gender as previously reported [13–17].

Although several studies have investigated the prognostic value of multifocality on disease outcomes, the clinical relevance of multifocality in PTC remains a matter of debate [13, 18, 19].

Discordant data in the literature could be due to the origin of the different tumours' foci, i.e. if multifocality is the result of multiple independent tumours (multicentricity) or intraglandular spread from a single tumour. This might represent an important issue in patient treatment.

Colombo et al. showed that some cases of multifocal PTC were the result of true multicentricity (microscopic foci of PTC widely separate from each other), whereas others are the consequence of intrathyroidal spread by an originally single tumour mass (multiple ipsilateral foci of PTC within vascular spaces, often accompanied

Table 6. *Multivariate analysis of risk factors for predicting persistent/recurrent disease and distant metastases in 2141 T1a-T1b-T2/Nx-N0 patients*

Risk factor	Persistent/recurrent disease		Distant metastases	
	OR (95% CI)	p	OR (95% CI)	p
Male gender	Not significant at univariate		0.58 (0.3–1.3)	0.19
Age				
< 55	1.0		1.0	
≥ 55	1.5 (1.1–2.1)	0.016	4.8 (2.2–10.6)	< 0.01
T status				
T1a	1.0		1.0	
T1b	1.3 (0.9–1.9)	0.15	3.2 (1.2-8.8)	0.02
T2	1.8 (1.2–2.9)	0.006	7.7 (2.9–20.7)	< 0.01
Multifocality	Not significant at univariate		Not significant at univariate	
Ablation	1.3 (0.9–1.8)		2.7 (1.1–6.4)	0.03

OR — odds ratio; CI — confidence interval

by multiple lymph node metastases, suggesting intrathyroidal spread) [20, 21].

Nowadays multifocality has less impact on risk stratifications than before. According to the 2009 ATA guidelines, the presence of multifocality slightly increased the risk of persistence/recurrent disease in PTC patients from very low to low [22].

Instead, in the 2015 ATA risk stratification [8], patients with intrathyroidal PTCs of all sizes were included in the ATA low-risk category, even if the risk of structural disease recurrence reported was 1–2% in unifocal papillary microcarcinomas and 4–6% in multifocal papillary microcarcinomas [23, 24].

In our study, an excellent response (about 90%) was recorded in the whole cohort with no difference in the two groups. In our study we found that T and N status were significant predictors of persistent/recurrent disease and that T status, the presence of LN metastases, and radioiodine ablation are predictors of distant metastases while multifocality was not. When excluding from the analysis patients with lymph node metastases, we found that age at diagnosis, T status, and radioiodine ablation (but not multifocality) were significant predictors of persistent/recurrent disease and of distant metastases.

In a recent study on 1039 consecutive PTC patients, Geron et al. [25] showed that multifocal PTC patients had more persistence of disease at one year, more recurrence during follow-up, and a higher overall mortality rate. However, there were no significant differences in recurrence, last-visit persistency, and mortality rates when adjusting for confounding variables by using propensity score matching. Therefore, they concluded that multifocality in PTC patients is not an independent prognostic factor for long-term outcomes. Accordingly, Zhang et al. [26] found no significant differences between unifocal and multifocal PTC patients in terms of age, gender, tumour size, and extrathyroidal extension (ETE).

However, conflicting data on the role of multifocality as a risk factor for persistent disease are present in the literature [26].

In a paper by Leenhardt et al. [27], lymph node involvement, multifocality, and male gender were significantly associated with the risk of recurrence at multivariate analysis, and a scoring system based on these risk factors was developed. Furthermore, they found that total foci size of multifocal tumours > 20 mm was significantly associated with recurrence. Also, Chow et al. [4] found that the risk of cervical lymph node recurrence increased 6.2-fold and 5.6-fold when LN metastases and multifocal disease were present at diagnosis, respectively. These data are consistent with the findings of many other authors [13, 18, 28–32].

Recently Kim et al. [33], performing a meta-analysis of 26 studies comprising 33,976 patients, found that recurrence rates were significantly higher in patients with multifocal PTC than in those with unifocal PTC, while cancer-specific survival was comparable between the groups. In subgroup analyses, the HRs of multifocality for recurrence were associated with primary tumour size (> 1 cm), number of tumour foci, and patient age (paediatric *vs*. adult).

However, in our previous paper on a consecutive series of 4292 DTC patients [15], we found that multifocality was significant only at univariate analysis, while only male gender, older age, follicular histotype, T status, and lymph node metastases were significant predictors of persistent/recurrent disease at multivariate analysis.

Also, Wang et al. [34] evaluated a total of 2638 patients with PTC from 11 medical centres in 6 countries and found that patients with multifocal cancers did not have a higher rate of cancer recurrence or cancer spread outside of the neck and did not have a higher death rate. Furthermore, they replicated and validated their results in an analysis of 89,680 patients with PTC from the SEER database.

Clarifying the possible prognostic impact of multifocality in PTC has obvious clinical implications, including the choice of the type of surgery and whether or not to proceed to radioiodine ablation.

Regarding the type of surgery, the 2015 ATA guidelines consider thyroid lobectomy as an adequate treatment for PTC ≤ 4 cm confined to one lobe of the thyroid gland [8, 35–37], and they do not take into account multifocality in its risk stratification system. However, it is underlined that some patients "may require completion thyroidectomy to provide complete resection of multicentric disease and to allow for efficient RAI therapy" (ATA, RECOMMENDATION 38) [8].

On one hand, some studies have demonstrated a lower risk of loco-regional disease recurrence following total thyroidectomy as compared to thyroid lobectomy [38, 39], given the propensity for PTC to be multifocal (often bilateral, mostly in familial disease) [40, 41]. While on the other hand, loco-regional recurrence occurs in less than 1–4% of patients and has no impact on survival; therefore, completion thyroidectomy would be needed in < 10% of patients treated with thyroid lobectomy [29, 36, 42, 43].

Finally, some studies recommend level VI prophylactic dissection for patients with some prognostic features associated with an increased risk of metastasis and recurrence including multifocality (older or very young age, larger tumour size, multifocal disease, extrathyroidal extension, known lateral node metastases) because a better post-surgery staging affects the team-based decision-making for the individual patient [44–46], but it remains a matter of debate. Afif et al. [47] showed that there is a significant association between multifocal PTC and level VI lymph node positivity, increasing proportionally with the number of foci, recognizing multifocality as a sign of tumour aggressiveness, due to a higher propensity for lymph node metastasis.

Post-surgery I-131 ablation is not routinely recommended for patients with multifocal papillary microcarcinoma in the absence of other adverse features, because the majority of the available observational evidence suggests that RAI adjuvant therapy is unlikely to improve disease-specific or disease-free survival in PTC < 1 cm, uni- or multifocal, without other higher-risk features [30, 48–50]. Instead, there is conflicting evidence on the effect of I-131 ablation on tumour recurrence. Of note, in the past I-131 ablation has been given mostly routinely. In our study, patients with multifocal disease received I-131 therapy more frequently (76.5% *vs.* 40.9%), but no difference was found when analysing patients' outcomes only in multifocal tumours, highlighting the lack of impact of ablation in multifocality.

Overall, our present results are in agreement with several other studies [16, 25, 51]. The major strengths of our study include the relatively large cohort recruited in a single centre and subjected to a homogeneous protocol.

Conclusion

In our cohort of low-risk PTC patients multifocality is not a prognostic factor for the risk of recurrence/persistence and distant metastases**.**

Conflict of interests

No competing financial interests exist for all authors. The authors declare no conflict of interest.

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Institutional review board statement

All procedures involving human participants were in accordance with the ethical standards of the institutional Research Committee and with the Helsinki declaration as revised in 2013.

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