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ORIGINAL ARTICLE

Should familial disease be considered as a negative prognostic factor in micropapillary thyroid carcinoma?

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Abstract

Purpose An increased aggressiveness of familial papillary thyroid carcinoma (FPTC) compared with sporadic form has been reported. On the contrary, the biological behavior of familial microPTC (FmPTC) is still debated. To assess if familial diseases should be considered as a negative prognostic factor in mPTC, the clinical presentation and outcome of FmPTC and sporadic mPTC (SmPTC) were compared.

Methods We retrospectively analyzed 291 mPTC (SmPTC $n=248$, FmPTC $n=43$) patients followed for a median follow-up of 8.3 years. FmPTC was defined as the presence of PTC in two or more first-degree relatives, after excluding hereditary syndromes associated with PTC.

Results FmPTC patients had more frequently bilateral tumor (32.6% versus 16.5%, $p=0.01$) and lymph node metastases at diagnosis (30.2% versus 14.9%, $p=0.02$). At the first follow-up, FmPTC patients had a higher rate of structural disease and a lower rate of remission compared to SmPTC ($p=0.01$). Also in a multivariate model, using a "CHAID tree-building algorithm", familial disease correlated with a worse clinical presentation and outcome of mPTC patients. Familial disease was associated with a higher rate of intermediate risk patients in non incidental mPTC and with a higher rate of structural incomplete response in mPTC without lymph node metastases ($p=0.01$).

Conclusions Like in macroPTC, the familial form of the diseases has been shown to be a negative prognostic factor also in mPTC, therefore, it should be highly regarded in the management of mPTC patients.

Keywords Familial papillary thyroid carcinoma · Thyroid microcarcinoma · Prognostic factor thyroid microcarcinoma

Introduction

Thyroid microcarcinoma is defined according to the World Health Organization (WHO) classification as a tumor of ≤ 1 cm in size and is represented by papillary histotype in nearly all cases [1]. The incidence of papillary thyroid carcinoma (PTC) has increased in many countries over the past 20 years and currently the most common PTC found in the United States, in patients older than 45 years, is micropapillary thyroid carcinoma (mPTC) [2]. The prevalence of mPTC is strictly dependent on the method of detection (autoptic, surgical or clinical) and the growing incidence of mPTC is mainly related to a larger use and improvement of screening procedures such as the high-resolution sonography and fine needle aspiration cytology [3, 4].

PTC is usually sporadic, but familial clustering, in the absence of hereditary syndromes or identified predisposing mutations associated with PTC, is described in nearly 10% of cases [5, 6]. Familial PTC (FPTC) is defined by the presence of the tumor in two or more first-degree relatives and the majority of authors have reported an increased aggressiveness of FPTC, compared with sporadic form, characterized by a higher grade of multifocality, lymph-node metastases and risk of recurrence during follow-up [7–10]. On the contrary, some reports did not find differences between sporadic and familial PTC [11, 12]. As well as the incidence of mPTC has increased, also the familial form of the diseases (FmPTC) has become more common than previously reported. Although mPTC has usually an

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excellent prognosis, multifocality, cervical lymph node and distant metastases may be detected, respectively, in 30–40%, 25–43% and 1.0–2.8% of cases [13–15]. To date, only few authors have compared the clinical presentation and outcome between familial and sporadic mPTC. In 1999, Lupoli et al. [16] described familial mPTC as a "new clinical entity'' characterized by an unfavourable behavior but subsequently only few studies have confirmed this observation [17, 18]. Another study evaluating a series of 199 patients with cancer smaller than 1.5 cm, showed no differences between 18 patients with family history of thyroid cancer and patients with sporadic tumors [19].

The aim of our study was to establish if FmPTC has a different clinical presentation and outcome compared to sporadic mPTC (SmPTC) and if familial diseases should be regarded as a negative prognostic factors also in mPTC.

Patients and methods

Study population

We retrospectively evaluated 291 patients (214 females/77 male; median age 47 years) with mPTC followed at the Section of Endocrinology, University of Siena (Italy) from 1978 to 2017. The median follow-up was 8.7 years (range 1–42 years). According to the WHO guidelines mPTC was defined as a tumor equal or less than 1 cm. FmPTC was defined as a tumor occurring in two or more first-degree relatives, after excluding clinical or pathological evidence of hereditary syndromes associated with non-medullary thyroid cancer, such as familial adenomatous polyposis, Gardner syndrome, Peutz–Jegher syndrome, Cowden disease. Two hundred forty-eight/291 (85.2%) patients had a SmPTC while FmPTC was found in 43/291 (14.8%) subjects. In thirty-three/43 (76.7%) cases 2 family members were affected while in the remaining cases (10/43, 23.3%) 3 or more family members were affected. Pathological reports of all family members affected were reviewed. A written consent was given by all patients to use the clinical data for research purpose.

Initial treatment of mPTC

Surgical treatment consisted in near total thyroidectomy in 283/291 (97.3%) cases and lobectomy in 8/291 (2.7%) patients. Lymph node dissection was performed in 76/291 (26.1%) patients. Twenty-six/76 (34.2%) patients were submitted to therapeutic lymph-node dissection while 50/76 (65.8%) patients received prophylactic central-compartment lymph node dissection. In 88/291 (30.2%) patients diagnosis of mPTC was obtained at histopathological examination (incidental mPTC) while in the remaining patients (203/291; 69.8%) the diagnosis of thyroid cancer was made before surgery by fine needle aspiration cytology (FNAC) (non incidental mPTC).

According to 2009 ATA risk stratification [20], 193/291 (66.3%) patients were classified at low risk and 98/291 (33.7%) patients at intermediate risk. After surgery, 191/291 patients (65.6%) received radioiodine ablation therapy at median activity of 2664 Mbq (range 555–5550 Mbq), after recombinant human TSH (rhTSH) or after levothyroxine withdrawal, respectively, in 56% and 44% of cases. Patients were followed every 6 months during the first year and subsequently the follow-up visits were scheduled based on the clinical course of the disease and the estimated risk of recurrence of each patient.

Criteria used to define the clinical status

Clinical outcome was assessed at two time intervals, 12–24 months after initial treatment (response to the initial therapy) and at last follow-up, using the same criteria. The definition of clinical response varied depending on whether the patient was treated with RAI ablation or not [21, 22]. Specifically, patients were classified as having: [1] an excellent response, [2] an indeterminate response, [3] a biochemical incomplete response and [4] a structural incomplete response.

Statistical analysis

Epidemiological data are presented as mean ± SD and median when needed. The *t* test or the Mann–Whitney test were performed to compare normal or non-normal variables, respectively. To evaluate significant differences in data frequency we analyzed contingency tables. Tables with size larger than 2×2 were examined by the Chi-squared test or a numerical approximation of the Fisher's exact test, when cell frequencies were greater than 4 or not, respectively.

The following variables were studied by univariate analysis: age at diagnosis, sex, extrathyroidal extension, multifocality, bilaterality, familial disease, incidental/non incidental mPTC, lymph node metastases at diagnosis and 2009 ATA risk class. Statistically significant variables found at univariate analysis were entered into a binary logistic regression analysis to identify those with independent prognostic significance. A CHAID (Chi-squared Automatic Interaction Detection) decision tree analysis was applied to identify prognostic factors and to determine their relationship with the clinical presentation and outcome of mPTC patients. To identify prognostic factors for clinical presentation, 2009 ATA risk class (Low and Intermediate group) was the dependent variable and significant patient/tumor characteristics at univariate analysis were included as covariate. Clinical outcome at the first control and at last follow-up was

represented by three groups: excellent response, biochemical incomplete response/indeterminate response and structural incomplete response. To identify prognostic factors for clinical outcome, the above mentioned three groups were the dependent variable and significant patient/tumor characteristics at univariate analysis were included as covariate.

Statistical analysis was performed using the software StatView for Windows version 5.0.1 (SAS Institute, Cary, NC) and the *SPSS* Statistics version 22.0. A p value < 0.05 was considered statistically significant.

Table 1 Clinical and pathological features of sporadic and familial mPTC patients

Parameters	Familial mPTC ($n=43$)	Sporadic mPTC ($n=248$)	p
Gender: *n* (%)			0.8**
Male	11 (25.6)	66 (26.6)	
Female	32 (74.4)	182 (73.4)	
Age at diagnosis (years)			0.4*
Mean ± SD	45.0 ± 14.0	47.4 ± 14.5	
Range	16–73	14–78	
Median	45	48	
Lymphadenectomy: *n* (%)			**0.007
No	27 (62.8)	188 (75.8)	
Therapeutic	9 (20.9)	17 (6.9)	
Prophylactic	7 (16.3)	43 (17.3)	
Lymph-node metastases: *n* (%)			**0.002
Yes	13 (30.2)	37 (14.9)	
Not	30 (69.8)	211 (85.1)	
Tumor diameter (mm)			0.29**
Mean ± DS	0.95 ± 1.43	0.74 ± 0.65	
Median	0.9	0.8	
Range	0.1–10	0.1–10	
Multicentricity: *n* (%)			0.1**
Yes	17 (39.5)	73 (29.4)	
Not	26 (60.5)	175 (70.6)	
Bilaterality: *n* (%)			**0.01**
Yes	14 (32.6)	41 (16.5)	
Not	29 (67.4)	207 (83.5)	
Minimal extrathyroidal extension: *n* (%)			0.08**
Intrathyroidal	27 (62.8)	189 (76.2)	
Extrathyroidal	16 (37.2)	59 (23.8)	
Incidental tumor: *n* (%)			0.8**
Yes	12 (27.9)	76 (30.6)	
Not	31(72.1)	172 (69.4)	
2009 ATA risk: *n* (%)			**0.03
Low	21 (48.8)	172 (69.4)	
Intermediate	22 (51.2)	76 (30.6)	
Radioiodine ablation: *n* (%)			0.2**
Yes	32 (74.4)	159 (64.1)	
Not	11 (25.6)	89(35.9)	
Follow-up (years)			0.8*
Median	8.6	8.3	
Range	(2.4–18)	(1–42)	

The results with p values < 0.05 have been indicated in bold

*By Mann–Whitney U test

**By χ^2 test

Results

Clinical presentation in familial and sporadic mPTC

The clinical–pathological features of familial ($n=43$) and sporadic mPTC patients ($n=248$) are shown in Table 1. The rate of therapeutic lymph node dissection was significantly higher in FmPTC than SmPTC ($n=9/43$, 21% versus $n=17/248$, 6.8%, $p=0.007$) due to the higher rate of presurgical diagnosis of lymph node metastases in FmPTC patients. Conversely, the rate of prophylactic lymphadenectomy was similar in FmPTC and SmPTC ($n=7/43$, 16.3% versus $n=43/248$,17.3%). At final histology, the rate of lymph node metastases was significantly higher in patients with FmPTC (30.2%) when compared with SmPTC (14.9%; $p=0.002$). In addition, FmPTC patients had more frequently bilateral tumor (32.6% in FmPTC and 16.5% in SmPTC; $p=0.01$). Minimal extrathyroidal extension, defined as the extension of tumor to perithyroid soft tissue and/or sternothyroid muscle (T3 category according to AJCC TNM 7th edition), was more common in FmPTC (37.2% in FmPTC and 23.8% in SmPTC) although this difference was not statistically different ($p=0.08$). Using the 2009 ATA risk stratification [16], FmPTC patients were more frequently classified at intermediate risk (22/43; 51.2%) than SmPTC patients (76/248, 30.6%; $p=0.03$). No difference between familial and sporadic mPTC was found for sex, age at diagnosis, diameter of tumor, incidental or not incidental tumor, I-131 remnant ablation and length of follow-up.

Short and long-term outcome of familial and sporadic mPTC

At the time of the first follow-up (1–2 years after initial therapy) the clinical status was significantly different between the two groups ($p=0.01$). In particular, 30/43 (69.8%) patients with FmPTC and 196/248 (79.0%) patients with SmPTC fulfilled the criteria of excellent response. Biochemical incomplete/indeterminate response was found in 6/43 (13.9%) patients with FmPTC and in 40/248 (16.1%) patients with SmPTC. Structural incomplete response was observed in 7/43 (16.3%) patients with FmPTC and in 12/248 (4.9%) patients with SmPTC (Table 2, panel A). As expected, patients with structural disease had only loco-regional disease detected by neck ultrasound and confirmed by FNAC. In the following years, patients with structural diseases were submitted to surgery and/or additional radioiodine therapy. In particular, 5/7 (71.4%) patients with FmPTC and 9/12 (75%) patients with SmPTC received radioiodine therapy while 2/7 (28.6%) patients with FmPTC and 3/12 (25%) SmPTC received additional surgical therapy. In the group of patients treated with radioiodine therapy,

Table 3 Risk factors associated with 2009 ATA risk class in mPTC (univariate analysis)

	Low risk ($n=193$)	Intermediate risk ($n=98$)	p
FmPTC			**0.008**
Yes ($n=43$)	21 (48.8%)	22 (51.2%)	
No ($n=248$)	172 (69.4%)	76 (30.6%)	
Incidental mPTC			**<0.0001**
Yes ($n=90$)	81 (90.0%)	9 (10.0%)	
No ($n=201$)	112 (55.7%)	89 (44.3%)	
Age			0.13
<55 years ($n=203$)	129 (63.5%)	74 (36.5%)	
>55 years ($n=88$)	64 (72.7%)	24 (27.3%)	
Sex			0.57
Male ($n=77$)	49 (63.6%)	28 (36.4%)	
Female ($n=214$)	144 (67.3%)	70 (32.7%)	

The results with p values < 0.05 have been indicated in bold

Table 2 Clinical outcomes of familial and sporadic mPTC patients

Parameters	Familial mPTC	Sporadic mPTC	p
Panel A			
Response to initial therapy: n (%)	$n=43$	$n=248$	**0.01***
Excellent response	30 (69.8)	196 (79.0)	
Structural Incomplete response	7 (16.3)	12 (4.9)	
Biochemical incomplete/indeterminate response	6 (13.9)	40 (16.1)	
Panel B			
Clinical outcomes at the end of follow-up: n (%)	$n=38$	$n=235$	0.72*
No evidence of disease	31 (81.6)	203 (86.4)	
Structurally persistent disease	3 (7.9)	13 (5.5)	
Biochemical incomplete/indeterminate response	4 (10.5)	19 (8.1)	

The results with p values < 0.05 have been indicated in bold

*By χ^2 test

Table 4 Risk factors associated with response to initial therapy in mPTC (univariate analysis)

	Excellent response $n=226$	Biochemical incomplete/indeterminate response $n=46$	Structural incomplete response $n=19$	p
Age				0.64
< 55 years ($n=203$)	157 (77.3%)	31 (15.3%)	15 (7.4%)	
> 55 years ($n=88$)	69 (78.4%)	15 (17.0%)	4 (4.6%)	
Sex				**0.04**
Male ($n=77$)	53 (68.8%)	15 (19.5%)	9 (11.7%)	
Female ($n=214$)	173 (80.8%)	31 (14.5%)	10 (4.7%)	
FmPTC				**0.01**
Yes ($n=43$)	30 (69.8%)	6 (13.9%)	7 (16.3%)	
No ($n=248$)	196 (79.0%)	40 (16.1%)	12 (4.9%)	
Incidental mPTC				**0.003**
Yes ($n=90$)	69 (76.7%)	20 (22.2%)	1 (1.1%)	
No ($n=201$)	157 (78.1%)	26 (12.9%)	18 (9.0%)	
Lymph node metastases at diagnosis				**< 0.0001**
Yes ($n=50$)	28 (56.0%)	9 (18.0%)	13 (26.0%)	
No ($n=241$)	198 (82.2%)	37 (15.3%)	6 (2.5%)	
Multifocal disease				0.52
Yes ($n=90$)	69 (76.7%)	13 (14.5%)	8 (8.8%)	
No ($n=201$)	157 (78.1%)	33 (16.4%)	11 (5.5%)	
Bilateral disease				**0.01**
Yes ($n=55$)	40 (72.7%)	6 (10.9%)	9 (16.4%)	
No ($n=236$)	186 (78.8%)	40 (17.0%)	10 (4.2%)	
Minimal extrathyroidal extension				0.06
Yes ($n=75$)	60 (80.0%)	7 (9.3%)	8 (10.7%)	
No ($n=216$)	166 (76.9%)	39 (18.0%)	11 (5.1%)	
2009 ATA risk class				**0.0007**
Low ($n=193$)	156 (80.8%)	32 (16.6%)	5 (2.6%)	
Intermediate ($n=98$)	70 (71.4%)	14 (14.3%)	14 (14.3%)	

The results with p values < 0.05 have been indicated in bold

the cumulative activity administered in FmPTC was 13,571.6 ± 4576.9 MBq (range 660–18537, median 13,801 MBq) significantly higher ($p < 0.001$) than in SmPTC [11,114.8 ± 11,921.4 MBq (range 3700–41,033, median 5550 mCi)].

Clinical data on the last follow-up (median 8.4 years) were available in only 273/291 (93.8%) patients. The clinical outcome at this time was not different between familial and sporadic mPTC ($p = 0.72$). In particular, 31/38 (81.6%) patients with FmPTC and 203/235 (86.4%) patients with SmPTC fulfilled the criteria of excellent response. Biochemical incomplete response was found in 4/38 (10.5%) patients with familial mPTC and 19/235 (8.1%) patients with sporadic mPTC. Structural incomplete response was observed in 3/38 (7.9%) patients with FmPTC and in 13/235 (5.5%) patients with SmPTC (Table 2, panel B).

Risk factors associated with clinical presentation and outcome of mPTC (univariate analysis)

At univariate analysis, risk factors significantly associated with the clinical presentation (defined according to 2009 ATA risk classification in low and intermediate risk) were FmPTC ($p = 0.008$) and non incidental mPTC ($p < 0.0001$), but not age ($p = 0.13$) and male sex ($p = 0.57$) (Table 3).

Significant risk factors associated with the response to initial therapy (1–2 years after initial treatment) were FmPTC ($p = 0.01$), non incidental mPTC ($p = 0.003$), lymph node metastases at diagnosis ($p < 0.0001$), bilateral tumors ($p = 0.01$) and male sex ($p = 0.04$). No significant association with the response to initial therapy was found with age ($p = 0.64$), multifocal disease ($p = 0.52$) and minimal extrathyroidal extension ($p = 0.06$) (Table 4). The only significant risk factor associated with the final outcome of

mPTC patients was the presence of lymph node metastases at diagnosis ($p = 0.0002$).

Identification of patients' subgroups with different clinical outcome using a "CHAID tree-building algorithm"

We analyzed whether familial disease was associated with the clinical presentation and outcome of mPTC patients also in a multivariate model, using a "CHAID tree-building algorithm", integrating different prognostic factors significantly associated at univariate analysis. A CHAID (Chi-squared Automatic Interaction Detection) decision tree analysis was applied to identify independent prognostic factors and to establish their relationship with clinical presentation and outcome of mPTC patients. To evaluate whether the familial disease was associated with the clinical presentation, prognostic factors significantly associated at univariate analysis such as non incidental diagnosis and familial diseases, were analyzed. The CHAID algorithm first split the patients exclusively according to the incidental/non incidental tumors. The rate of intermediate risk rose from 33.7% in the whole cohort to 44.3% in patients with non incidental mPTC ($p = 0.000$, $\chi^2 = 34.1$). FmPTC was predictor of a higher rate of intermediate risk patients only in non incidental mPTC. The rate of intermediate risk patients rose from 44.3% in the whole cohort to 64.5% in patients with non incidental FmPTC ($p = 0.01$, $\chi^2 = 6.038$) (Fig. 1).

To evaluate whether the familial diseases was associated with the response to initial therapy (evaluated 1–2 years after initial therapy), prognostic factors significantly associated at univariate analysis such as non incidental diagnosis, bilateral tumor, familial diseases, lymph node metastases, male sex and 2009 ATA risk class, were analyzed. The CHAID algorithm first split the patients exclusively according to the presence/absence of lymph node metastases at diagnosis. The rate of structural incomplete response rose from 6.5% in the whole cohort to 26.0% in patients with lymph node metastases ($p = 0.000$, $\chi^2 = 38.8$). In mPTC patients without lymph node metastases, the presence of familial disease

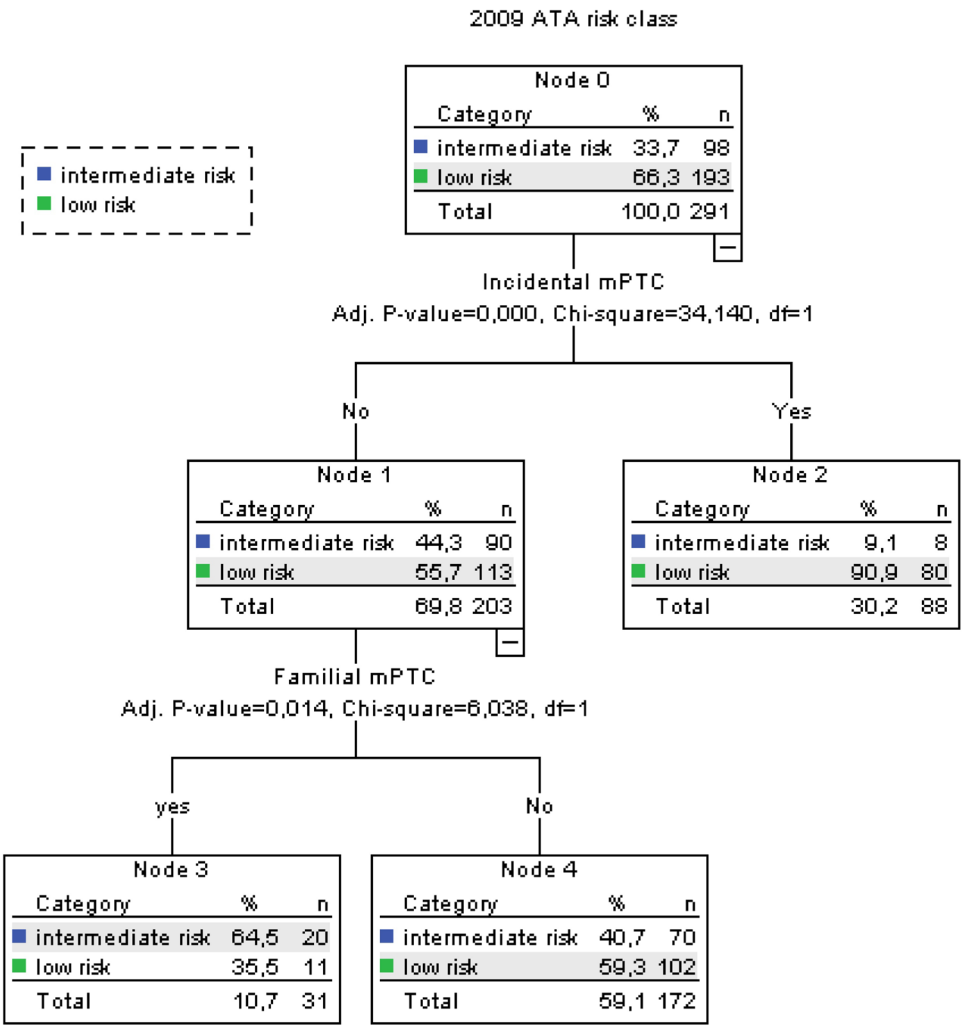

Fig. 1 Tree diagram based on CHAID analysis evaluating prognostic factors significantly associated with the clinical presentation of mPTC defined according to 2009 ATA risk class

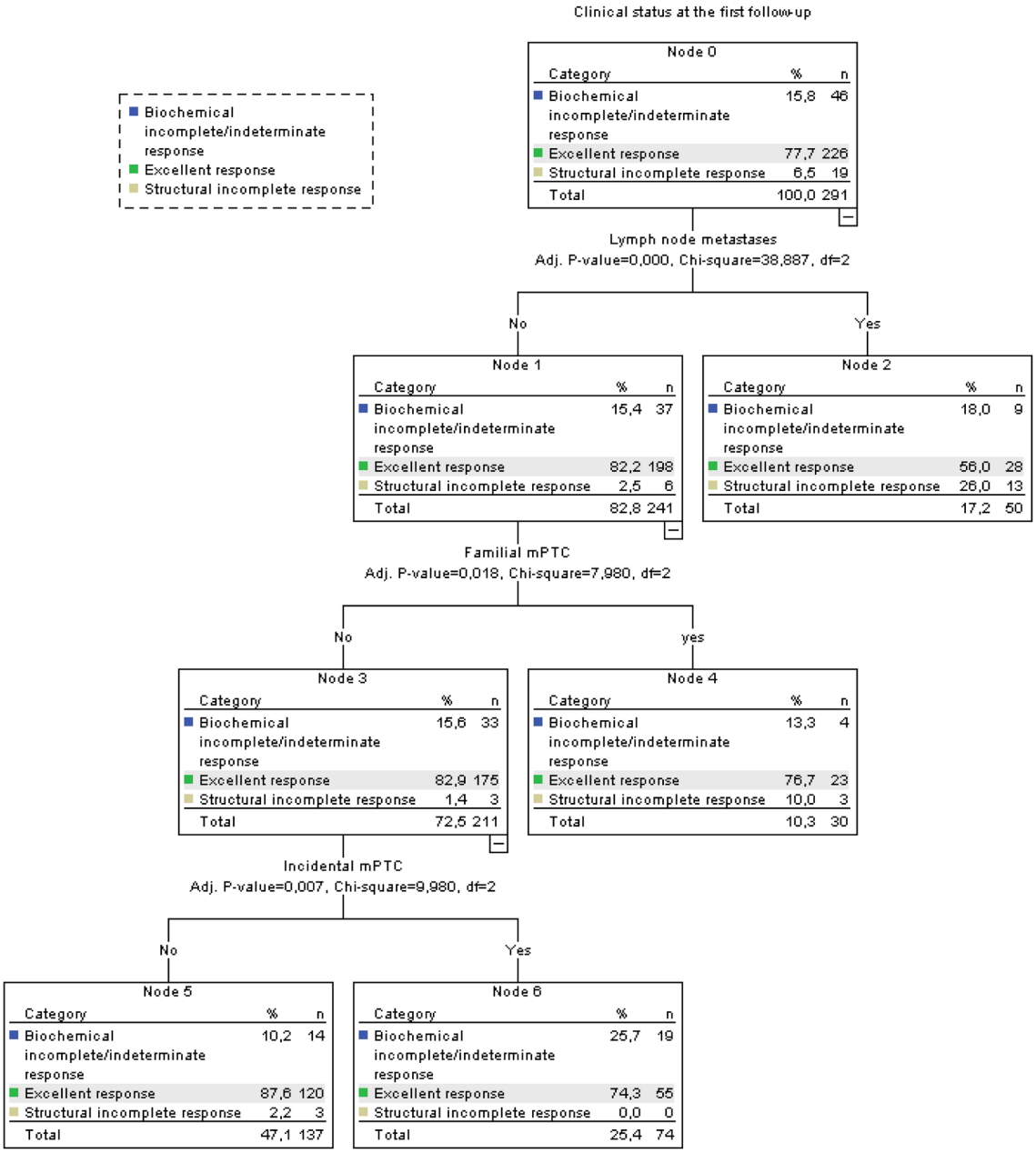

Fig. 2 Tree diagram based on CHAID analysis evaluating prognostic factors significantly associated with the response to initial therapy in mPTC patients

increased the rate of structural incomplete response from 2.5% in the whole cohort to 10.0% in patients with familial mPTC ($p = 0.01$; $\chi^2 = 7.98$) (Fig. 2).

Discussion

The incidence of mPTC has considerably increased over the past years and several studies have hypothesized that mPTC is overdiagnosed and overtreated [23, 24]. The 2015 American Thyroid guidelines and the 2018 Italian consensus suggest a less aggressive therapy in mPTC, since the excellent outcome of mPTC is more related to the indolent nature of the disease rather than to the effectiveness of treatment [21, 25]. Specifically, an active surveillance management approach can be considered as an alternative to immediate surgery in mPTC without clinically evident metastases or local invasion and no convincing cytologic evidence of aggressive disease. If surgery is chosen for patients with mPTC without extrathyroidal extension and clinical lymph

node metastases, the initial surgical procedure should be a thyroid lobectomy, except for patients with prior head and neck radiation or familial thyroid carcinoma [21].

As well as the incidence of mPTC has increased, also FmPTC has become more common than previously reported. The aggressiveness of FPTC compared to sporadic PTC has been well documented in several papers [26–29]. On the contrary, it is controversial if FmPTC has a different clinical behavior than SmPTC. For this reason and to better understand what is the role of familial form in the clinical presentation and in the short and long term follow-up of mPTC, we retrospectively evaluated 291 mPTC patients followed for a median follow-up of 8.4 years. According to previous studies [18–31] we found that FmPTC had more advanced disease at diagnosis, including bilaterality and lymph node metastases. Consequently, a significant higher rate of persistent structural or biochemical disease at the time of the first control after initial therapy was observed in FmPTC. The clinical impact of familial disease in mPTC patients has been also confirmed at multivariate analysis. Specifically, although a non incidental diagnosis of mPTC was found to be the strongest predictor for the clinical presentation of mPTC, the rate of mPTC at intermediate risk was even higher in non incidental mPTC patients with familial disease (64.5% in FmPTC and 44.3.4% in SmPTC). Moreover, the rate of persistent structural disease after initial therapy was significantly increased by the presence of familial disease in patients without lymph node metastases (10% in FmPTC and 1.4% in SmPTC). This latter evidence suggests that familial disease might represent an independent negative prognostic factor for the response to initial therapy, also in low risk mPTC patients. Nevertheless, the clinical outcome at the long term follow-up was similar between familial and sporadic mPTC suggesting that the familial form of mPTC has the same probability of SmPTC to be definitively cured regardless the presence of minimal extrathyroidal extension. This latter evidence confirms the results of our previous study in which no association between minimal extrathyroidal extension and poor outcome was observed in small tumors [32]. However, we observed that more radioiodine treatments were necessary to obtain a complete remission in FmPTC with persistent structural disease when compared with SmPTC. Indeed, a significant higher cumulative activity of radioiodine was administered in FmPTC in the presence of persistent structural disease after initial therapy. A more aggressive disease behavior of FmPTC than SmPTC due to a higher rate of central lymph node metastases has been recently reported in a large cohort of mPTC patients [18]. However, in this study, conversely to our results, the local recurrence rate during follow-up was higher in FmPTC than in SmPTC (4.5% vs. 0.6%, $p < 0.001$) [18]. These discrepancy can be related to the more extensive initial surgery performed in our patients (total thyroidectomy 97.6% versus 67% in the Lee cohort), which may have improved the clinical outcome of FmPTC patients. Based on our results, we conclude that familial mPTC is a clinically distinct entity with an aggressive nature, therefore, in the presence of pre-surgical diagnosis of mPTC, familial disease should be highly regarded to better tailor the therapeutic approach and the follow-up. Therefore, large-scale trials and long-term follow-up data are required to confirm the impact of an aggressive approach on the clinical outcome of FmPTC.

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Compliance with ethical standards

Conflict of interest The authors state the absence of any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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