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Clinical Research Article

Medullary Thyroid Cancer: Epidemiology and Characteristics According to Data From the Marne-Ardennes Register 1975-2018

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Abstract

Context: Medullary thyroid cancer (MTC) is a rare disease.

Objective: The main objective of our study was to analyze the incidence evolution of MTC with a follow-up of more than 40 years. Further, a descriptive and survival analysis was performed according to the Kaplan–Meier analysis.

Design, Setting, and Patients: This is a retrospective epidemiological study using data from the Marne-Ardennes registry from 1975 to 2018. Two hundred sixty patients with MTC were included.

Main Outcome Measures: The incidence was calculated in the territory of the register (Marne and Ardennes departments of France) and standardized on the demographic structure of France. Patient and tumor characteristics were described. An analysis in a subgroup comparing hereditary and sporadic forms was performed. An analysis of survival was performed.

Results: The standardized incidence shows an increasing trend over time. The incidence increased significantly from 0.41 to 0.57/100 000 person-years between 1986 and 1996 and 2008 and 2018. The MTC was hereditary in 21.2% of cases. The sex ratio (males:females) was 0.73. The average age at diagnosis was 53 years. Ninety-seven patients (37.3%) were N1, 26 (10%) were M1, and 56 (21.5%) developed metastases during the follow-up. Complete remission was obtained in 58.5% of patients. The disease was refractory for 18.1% of patients. The 5-year survival rate was 88.4%. Sporadic cases had a poorer prognosis than hereditary MTC.

Conclusion: Our study demonstrates a moderate increase in the incidence of MTC between 1975 and 2018. The prognosis remains worse for sporadic MTC than for hereditary MTC.

Key Words: medullary thyroid cancer, incidence, survival, hereditary cancer

Medullary thyroid carcinoma (MTC) is a rare disease representing about 5% of all thyroid cancers [1]. According to the current French Public Health agency (Santé Publique France) data, MTC accounts for 5.3% of thyroid cancers in men and 2.1% in women in 2018 [1]. Its incidence in France is 350 new cases per year [2].

Among thyroid cancers, papillary thyroid cancer is by far the most common. Its incidence has increased significantly in recent decades, due to improved detection by ultrasound and cytological and histological analyses. The incidence of MTC is less well documented, as is its evolution over the last few decades.

A distinction is made between sporadic MTC and hereditary MTC. MTC is hereditary in 25% of cases [3, 4]. Autosomal dominant transmission occurs in the case of MEN2. Genetic investigation should be performed in all MTC patients regardless of age of onset.

Mutations in the RET gene are involved in the majority of hereditary MTC oncogenesis, as well as in >50% of sporadic MTC [5-7]. Different mutations may be responsible. A genotype-phenotype relationship exists [8-12]; 918 codon mutation is associated with a poor prognosis [13, 14].

MTC's survival and prognosis are worse than those of papillary cancer. The relatively low incidence of MTC explains the lack of data in the literature regarding incidence, prognosis, survival, lymph node, and metastasis involvement.

Our study based on Marne-Ardennes registry data between 1975 and 2018 aims to analyze the evolution of MTC incidence over a recent period covering more than 40 years. Second, a descriptive analysis of MTC characteristics, patients, and treatments was performed, as well as a survival study.

Materials and Methods

Study Population

This is an epidemiological, retrospective study using data from the Marne-Ardennes registry.

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This register includes 850 000 inhabitants. This number has been stable since 1975. We included 260 patients diagnosed as MTC between 1975 and 2018 and living in the Marne or Ardennes departments. This research is in accordance with the Declaration of Helsinki. All patients have signed an informed consent for their data to be included in the registry.

Study Measures

Incidence rates were calculated in the registry area (Marne and Ardennes departments) and standardized on the demographic structure France (by age group and sex). These incidence rates were calculated per 100 000 person-years (PY) over four 11-year periods (1975-1985, 1986-1996, 1997-2007, 2008-2018).

Demographic and clinical data including information regarding the diagnosis, tumor markers [calcitonin and carcinoembryonic antigen (CEA)], cytological results adapted to the Bethesda 2009 system, surgical procedure, the postoperative period, histopathology including the size of the tumor, extra-thyroidal extension, tumor focality, and the presence of mixed lesions. In the case of mixed lesions, if the prognosis was for the nonmedullary lesion, we decided not to include it in the survival analysis or consider it as refractory MTC. We included incidental microMTC.

The sporadic or hereditary nature of the disease was investigated by systematically searching for RET mutation, as well as the risk level. In hereditary MTC, the index case and screened patient were identified.

Calcitonin level at diagnosis was classified into 3 categories: calcitonin < 40 pg/mL, 40 pg/mL < calcitonin < 500 pg/mL, and calcitonin > 500 pg/mL, determined after a literature review [8, 13, 15, 16].

The 2010 TNM classification was used, as the latest 2017 edition was released 1 year before the end of the study collection. We described synchronous and metachronous metastasis and time to first metastasis appearance.

Hereditary and sporadic MTC were compared, as well as index cases and screening patients in hereditary MTC.

The disease status during follow-up was noted (remission, stabilization, progression, refractory). Complete remission is defined by the association of no clinical, biochemical, or structural evidence of disease. Refractory MTC is defined as locally advanced or metastatic MTC that is not accessible to standard treatments (surgery, interventional radiology, radiotherapy). Finally, death and its link to MTC were recorded.

Statistical Analyses

The characteristics of patients, tumors, and treatments were described using frequencies and percentages for qualitative variables: means, SDs, medians, and extremes for quantitative variables. Inference tests were performed using χ^2, Fisher's or Student's test, or ANOVA tests depending on the conditions of application.

Survival analyses used log-rank tests and Cox models. Two separate survival analyses were performed, according to sporadic or hereditary disease, including or not including the screening patients. The significance threshold was set at 5% ($P = .05$). All analyses were performed in R version 3.4.4. All figures were produced using Prism Graphpad version 9.0. and R version 3.4.4.

Results

Incidence

The incidence in the Marne-Ardennes territory standardized on the age structure of France, showed a slight increasing trend over time (Fig. 1).

The average incidence of MTC between 1975 and 1985 was 0.16/100 000 PY, between 1986 and 1996 was 0.41/100 000 PY [0.407-0.413], between 1997 and 2007 was 0.56/100 000 PY, and between 2008 and 2018 was 0.57/100 000 PY [0.567-0.573]. Thus, 95% confidence intervals do not overlap. There has been a statistically significant increase in the incidence of MTC since the mid-1980s. The increase in MTC incidence was less pronounced than that found in papillary cancers (Fig. 2) [17].

The MTC proportion among all thyroid cancer types was 3.5% from 1975 to 1985, 10.4% from 1986 to 1996, 4.3% from 1997 to 2007, and 3.7% from 2008 to 2018. Thus, there was a clear increase in the proportion of MTC between the first and second decade, followed by a decrease in the relative incidence of MTC over the last 3 decades.

Characteristics

Population

In the Marne-Ardennes registry from 1975 to 2018, 260 patients with MTC were registered (Table 1). MTC was sporadic in 205 patients (78.8%) and hereditary in 55 patients (21.2%), with no increase in the proportion of hereditary MCT over time. There was a sex ratio of 0.73, with 57.7% women and 42.3% men. The average age at diagnosis was 53 years. Women were older, with an average age at diagnosis of 56 years compared to 50 years for men ($P = .0146$).

The preoperative calcitonin level was >500 pg/mL in 46.5%. Among the 27 patients with calcitonin <40 pg/mL, only 1 had lymph node involvement at diagnosis. Of the 26 patients with metastasis at diagnosis, 2 had a calcitonin between 40 and 500 pg/mL and 22 had a calcitonin >500 pg/mL (value unknown for 2 patients). Preoperative CEA was performed in 53.8% of cases. An elevated CEA level at diagnosis was observed in 80% of cases (112/140), greater than 10 times normal in 44.3% of cases (62/140), and greater than 100 times normal in 7% of cases (10/140).

In 92.7% of hereditary MTC (51/55), RET mutation was identified. The 4 remaining patients were identified by family history. The most frequent RET mutations occurred in codon 804 (17 patients), codon 618 (12 patients), and codon 634 (10 patients); 18.2% of the mutations were high or highest risk level.

The average size of the tumors was 21 mm. This size decreased over time from 23.3 mm in 1975 to 1985 to 18.9 mm in 2008 to 2018. Thus, the proportion of microMTC diagnosed increased from 13% in 1975 to 1985 to 31.2% in 2008 to 2018.

According to the 2010 TNMp classification, central and lateral lymph node involvement was present in 5.1% and 16% of T1 patients, respectively. Cervical lymph node involvement was present in 100% of patients classified as T4.

Two hundred thirty-two patients were M0, 26 were M1. One patient with a mixed tumor, with anaplastic contingent, was removed from the study of metastatic and refractory character and from the survival analysis. During the follow-up, a total of 56 patients developed metachronous metastasis.

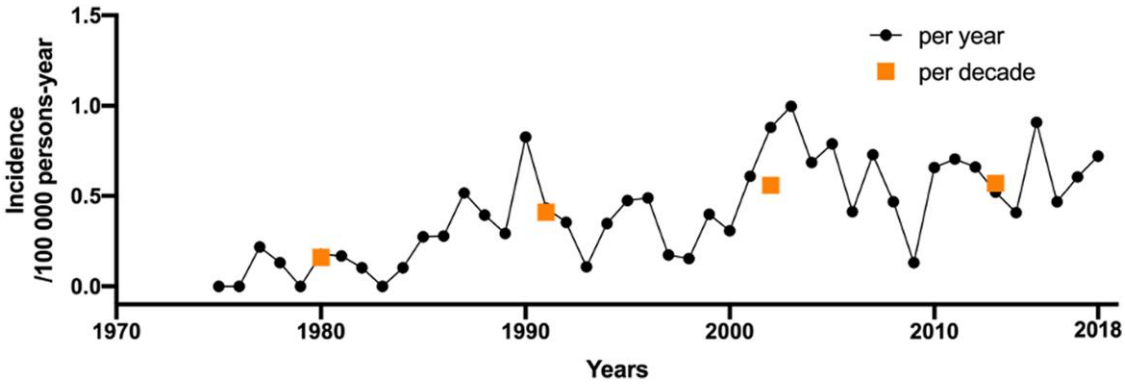

Figure 1. Evolution of MTC incidence in the Marne-Ardennes territory from 1975 to 2018, standardized on the structure of France (/100 000 person-years). Abbreviations: MTC, medullary thyroid cancer.

Among the 26 synchronous metastatic patients, 15 did not develop new metastasis.

At diagnosis, 61.5% of metastasis was extra cervical lymph nodes (16/26), 26.9% bone metastasis (7/26), 34.6% lung metastasis (9/26), and 23% liver metastasis (6/26).

Among the patients with metachronous metastasis, the involvement was lymph node metastasis in 69.6% of cases (39/56), bone metastasis in 25% of cases (14/56), lung metastasis in 23.2% of cases (13/56), liver metastasis in 30.4% of cases (17/56), and other in 10.7% of cases (1 brain, 2 breast, 1 thymus, 1 pelvis, 1 adrenal). Mean occurence time of metastasis was 8.7 months for patients with N1 lymph node involvement and 34.6 months for those with N0 involvement. The median time to metastatic disease in M0 patients at diagnosis was 38.2 months.

Differences between hereditary and sporadic MTC

We performed a subgroup study comparing sporadic and hereditary forms (Table 1).

The average age of diagnosis was 38.7, with a mean of 37.3 years for men and 40.4 years for women. The mean age of diagnosis was significantly younger for hereditary cases compared to sporadic cases ($P < .001$). There was an equal sex distribution with 54.5% men (30/55) and 45.5% women (25/55) for the hereditary cases. However, there was a difference in the sex distribution between hereditary and sporadic cases ($P = .046$).

Some patients had hereditary MTC in childhood, with a minimum age of 5 years old at diagnosis.

Eighty-eight percent of sporadic MTC were unifocal, but only 20% in hereditary MTC. This difference is even more marked for bilateral multifocal cases with a proportion of 54.4% for hereditary MTC vs 2.4% for sporadic ($P < .0001$).

Extra-thyroidal extension of MTC at diagnosis was present in 3.6% of patients with hereditary MTC compared to 10.2% of patients with sporadic MTC. Calcitonin levels at diagnosis were lower in hereditary MTC ($P < .0001$).

Histological results of hereditary forms highlight a preponderance of multifocal forms. There was also only 1 patient with metastatic disease at diagnosis among the hereditary forms. The time to metastasis was 31.1 months for the hereditary forms compared to 6.2 months for the sporadic forms ($P = .17$).

Differences between index cases and screening patients

The comparison in hereditary MTC of index cases and screened patients showed in index cases a predominance of women (63.2%), an average older age, and a higher average calcitonin. Thirty-six point eight percent of the index cases had at diagnosis a calcitonin >500 pg/mL, and, on the contrary, 41.7% of the screened cases had a calcitonin <40 pg/mL. Also, the TNM and AJCC stages were more severe in the index cases.

The level of risk associated with the type of RET mutation seems similar between the 2 groups for the moderate risk level, but there were more mutations associated with a high risk in the screened cases and 10% of mutations associated with the highest risk in the index cases against none in the screened cases.

Prognosis

The follow-up of the patients in the cohort varies from less than 1 year for some patients with micro carcinoma in postoperative remission to more than 20 years for some patients who were stable, in progression, or refractory. A survival analysis showed that complete remission was achieved in 58.5% of patients. The disease progressed to refractory form in 18.1% of patients. During follow-up, stabilization was achieved in 26.5% of patients, and progression was observed in 30.4% of patients. In total, 20.2% of patients with a complete postoperative remission subsequently progressed. To date, 28% of patients have died and 14.6% have died as a result of their MTC. Complete remission is the current outcome in 58.6% of M0 patients, 81.9% of N0M0 patients, 15.1% of N1M0 patients, and 15.1% of patients with a calcitonin level at diagnosis >500 pg/mL.

The 10-year survival study was performed for patients diagnosed until 2011 (at least 10 years after diagnosis), representing 202 patients. Twenty-two percent of patients died within 10 years of diagnosis, of which 13.9% died of a cause directly related to their MTC.

In M0 patients, 14.6% died within 10 years, while, in M1 patients, 81.8% died within 10 years. Among the N0M0 patients, 7.6% died within 10 years, including 2.2% due to MTC. Of the N1M0 patients, 24.1% died within 10 years, including 13.8% due to MTC.

The survival curves for hereditary and sporadic forms (Fig. 3) show a poorer prognosis in the sporadic cases of our cohort ($P = .0011$). The survival rate for hereditary MTC is 95% at 5 years and 92% at 10 years. The survival rate for hereditary MTC excluding screening patients is 88% at 5 years and 81% at 10 years. The survival rate for sporadic MCT is 82% at 5 years and 70% at 10 years. Comparing the survival of patients with sporadic MTC to hereditary MTC excluding

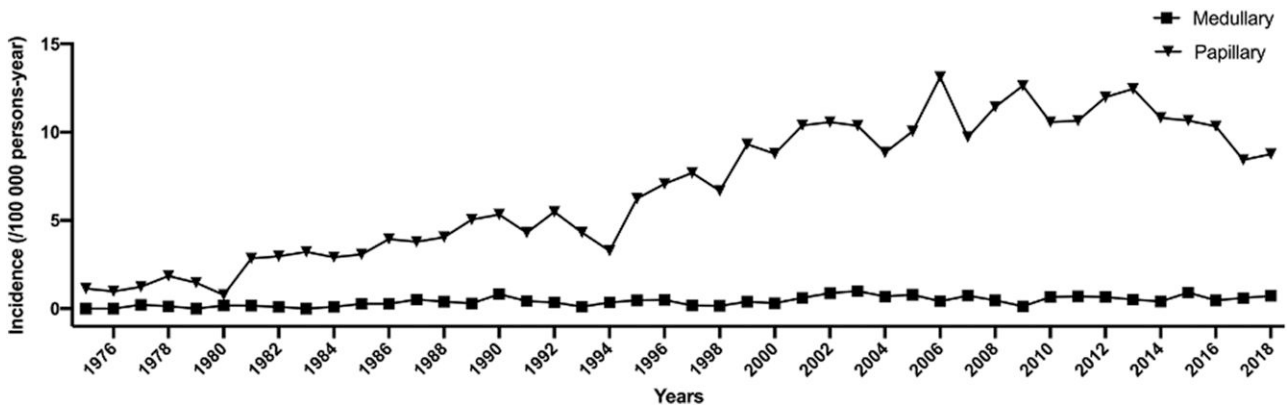

Figure 2. Evolution of MTC and papillary cancer incidence in the Marne-Ardennes territory from 1975 to 2018, standardized on the structure of France (/100 000 person-years). Abbreviations: MTC, medullary thyroid cancer.

screening patients shows a prognosis that remains worse for sporadic MTC ($P < .01$).

Discussion

Key Findings of This Study

Our retrospective study shows a statistically significant moderate increase of MTC's incidence over the last decades. This increase may be explained by the development of ultrasound-fine needle aspiration, the improvement of calcitonin assay, and the anatomopathological advances allowing the discovery of micro-cancers.

In the literature, the proportion of MTC compared to other thyroid cancers is between 5% and 8% [18]. A recent analysis of the United States registry revealed a decrease in this proportion with a current rate of 1% to 2% of all thyroid cancers [8]. A decreasing trend is also found in our study. Also, the French Public Health agency (Santé Publique France) describes this decrease with a proportion of 6.1% in 1990-1994, 6% in 1995-1999, 5.8% in 2000-2004, 4.8% in 2005-2009, and 3.7% in 2010-2015 [1]. The main cause is the significant increase of papillary carcinomas, especially small cancers ≤ 10 mm [17]. In our study, a proportion of 4.7% of MTC among all thyroid cancers was found in 2018.

Comparison/Contrast With Major Recognized Published Studies

The sex ratio is 0.73. There was a nonsignificant female predominance. However, follicular thyroid cancer shows a significant female predominance. This difference in MTC can be explained by the significant proportion of hereditary forms. An American study analyzing the SEER (Surveillance, Epidemiology, and End Results) program from 1992 to 2006 has found no significant sex difference in MTC [19]. In the Marne-Ardennes registry, MTC was hereditary for 21.2% of the cohort, which is consistent with literature reporting 25% of hereditary cases [4, 20]. The description of nodules in the literature focuses mainly on the ultrasound and pathological features. We did not find any publication that investigated the presence of MTC within a multinodular goiter or as an isolated nodule. Our study found a clear predominance of isolated MTC at 53.8% compared to 26.5% as a multinodular goiter. In 99% of cases, if the preoperative plasma calcitonin is < 40 pg/mL, then there is no lymph node involvement. If the calcitonin is >500 pg/mL, advanced disease should be investigated [15, 17]. In our study, 27 patients had a calcitonin <40 pg/mL and 1 of them had lymph nodes at diagnosis. Thus, a calcitonin at diagnosis <40 pg/mL is associated with the absence of lymph node metastasis in 96.3% of cases. Of the 26 patients M1 at diagnosis, 22 had a calcitonin >500 pg/mL. The hereditary nature of MTC can also be guided by histological examination [21]. In an international multicenter study, there was a prevalence of 5.6% of bilateral lesions in 313 sporadic MTCs [22]. Our study reports 2.4% bilateral multifocal forms in sporadic MTC compared to 54.5% in hereditary MTC. Thus, the bilateral character points to a hereditary MTC but does not rule out a sporadic form.

The disease-specific 10-year survival rate for patients with MTC is approximately 75% [23]. In our study, the 10-year disease-specific survival rate is 86.1%. Roman et al, in a prognostic study of MTC, found no significant increase in patient survival over the last few decades and noted that 50% of MTC patients are stage III or IV at diagnosis [24, 25]. In our study, 33% of MTC are stage III or IV at diagnosis. Our study shows a difference in survival between hereditary and sporadic MCT, even after excluding patients with hereditary MCT from family screening. Our hypothesis is that the disease may be less aggressive in hereditary MCT. Also, patients with familial MCT may be more amenable to long-term monitoring. In a GETC (Calcitonin Tumor Study Group) study of 899 patients, follow-up revealed 5% relapse after complete postoperative remission [26]. In our study, it is 20.2%. These results highlight the importance of lifelong follow-up although normalization of calcitonin after surgery determines overall survival and relapse-free survival [15, 27, 28]. In the GETC study, the 10-year survival rate of patients with complete postoperative remission was >95% to 97%. In our study, it is 94.2%. According to Hadoux et al, curative surgery confers a 10-year survival rate of 96% in case of localized disease. In the presence of advanced MTC, unresectable regional disease, or distant metastasis, survival is significantly reduced [4, 29]. According to 2 German studies and a GTE study, undetectable calcitonin postoperatively was found in 30% of M0 patients, in 75% to 90% of N0 patients, and in 20% to 30% of N1 patients [15, 16, 30]. In our study, the 10-year survival rate, directly related to MTC, in localized disease at diagnosis is 93.3%. Also, complete remission without further outcome during follow-up is observed in 58.6% (136)

Table 1. Characteristics of the 260 patients with MTC in the Marne-Ardennes register from 1975 to 2018

	All (n = 260)	Sporadic (n = 205)	Hereditary	
			Index case (n = 19)	Screening (n = 36)
Sex				
Men, n (%)	110 (42.3)	80 (39.0)	7 (36.8)	23 (63.9)
Women, n (%)	150 (57.7)	125 (61.0)	12 (63.2)	13 (36.1)
Age All (min-max)	53 (5-97)	57.4 (19-97)	48 (6-79)	33 (5-69)
Nodules at diagnosis				
MNG, n (%)	69 (26.5)	56 (27.3)	10 (52.6)	3 (8.3)
Isolated nodule, n (%)	140 (53.8)	126 (61.5)	6 (31.6)	8 (22.2)
Signs of compression, n (%)	10 (3.8)	9 (4.4)	1 (5.3)	0
Cytology				
Noncontributory, n (%)	14 (8.8)	10 (4.9)	2 (10.5)	2 (5.6)
Benign, n (%)	10 (6.3)	8 (3.9)	2 (10.5)	0
Cellular atypia or vesicular lesions, n (%)	16 (10.1)	16 (7.8)	0	0
Malignant and suspected malignancy, n (%)	119 (74.8)	105 (51.2)	7 (36.8)	7 (19.4)
Incidental finding				
Histological, n (%)	38 (14.6)	36 (17.6)	2 (10.5)	0 (0)
Calcitonin				
Mean pg/mL	5332	5357	1042	709
<40 pg/mL, n (%)	27 (10.4)	10(4.9)	2 (10.5)	15 (41.7)
40-500 pg/mL, n (%)	57 (21.9)	44 (21.5)	5 (26.3)	8 (22.2)
>500 pg/mL, n (%)	121 (46.5)	106 (51.7)	7 (36.8)	8 (22.2)
RET mutation				
Number identified, n (%)	51 (19.6)	0	17 (89.5)	34 (94.4)
RET mutation risk level				
Moderate, n (%)	39 (15)		13 (68.4)	26 (72.2)
High, n (%)	10 (4.9)		2 (10.5)	8(22.2)
Highest, n (%)	2 (0.8)		2 (10.5)	0
Type of surgery				
Total thyroidectomy, n (%)	246 (97.6)	183 (89.3)	19(100)	35 (97.2)
Thyroid lobectomy, n (%)	13 (5.0)	13 (6.3)	0	0
Cervical dissection				
All n (%)	197 (75.8)	152 (74.1)	16 (84.2)	29 (80.6)
Central n (%)	197 (75.8)	152 (74.1)	16 (84.2)	29 (80.6)
Unilateral lateral, n (%)	44 (22.3)	39 (19.0)	0	5 (13.9)
Bilateral lateral, n (%)	93 (47.2)	62 (30.2)	12 (63.1)	19 (52.8)
Surgical morbidity				
Recurrent nerve paralysis, n (%)	65 (26.7)	51 (24.9)	5 (26.3)	9 (25.0)
Early postoperative hypocalcemia, n (%)	135 (55.5)	105 (51.2)	10 (52.6)	20 (55.6)
Lymphorea, n (%)	14 (5.8)	11 (5.4)	1 (5.3)	2 (5.6)
Horner's syndrome, n (%)	3 (1.2)	3 (1.5)	0	0
Focality				
Unifocal, n (%)	192 (73.8)	181 (88.3)	2 (10.5)	9 (25.0)
Unilateral multifocal, n (%)	22 (8.5)	9 (4.4)	4 (21.1)	9 (25.0)
Bilateral multifocal, n (%)	35 (13.5)	5 (2.4)	13 (68.4)	17 (47.2)
T category				
T1a, n (%)	82 (31.5)	48 (23.4)	7 (36.8)	27 (75)
T1b, n (%)	55 (21.2)	47 (18.1)	5 (26.3)	3 (8.3)
T2, n (%)	63 (24.2)	53 (20.4)	6 (31.6)	4 (11.1)
T3, n (%)	43 (16.5)	41 (20.0)	1 (5.26)	1 (2.8)

(*continued*)

Table 1. Continued

	All (n = 260)	Sporadic (n = 205)	Hereditary	
			Index case (n = 19)	Screening (n = 36)
T4, n (%)	9 (3.5)	9 (4.4)	0	0
N category				
N0 N (%)	101 (38.9)	66 (32.2)	10 (52.6)	25 (69.4)
N1a % (n)	10.8 (28)	12.7 (26)	5.3 (1)	2.8 (1)
N1b % (n)	26.5 (69)	29.3 (60)	26.3 (5)	11.1 (4)
M status				
M0% (n)	88.8 (231)	87.3 (178)	94.7 (18)	97.2 (35)
M1% (n)	10 (26)	12.2 (25)	5.3 (1)	0

Abbreviations: MNG, multinodular goiter; MTC, medullary thyroid carcinoma.

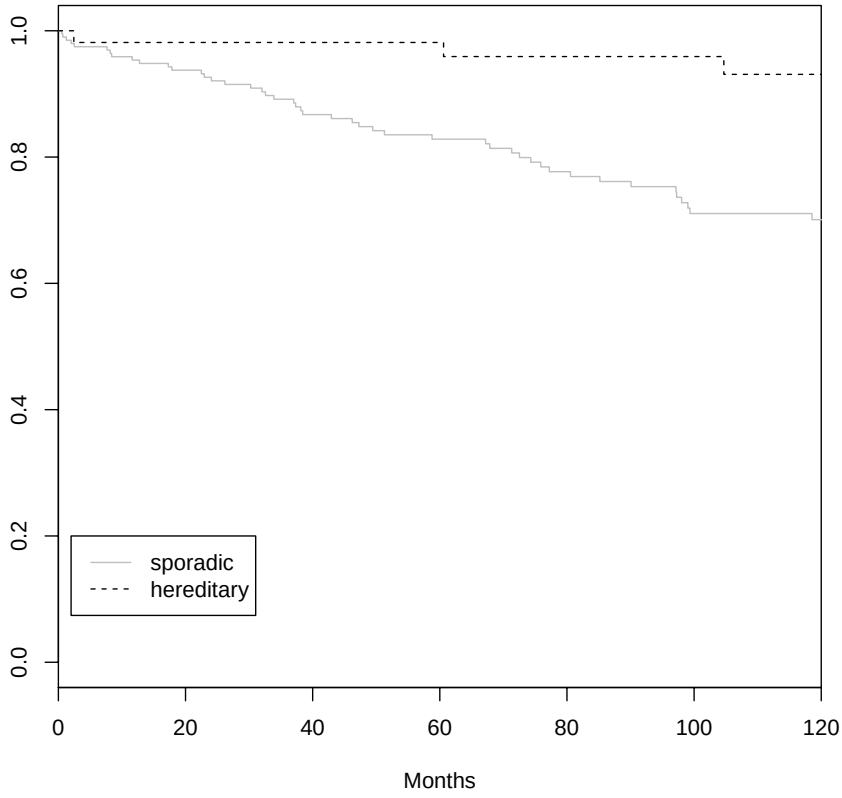

Figure 3. Survival curves at 10 years, according to sporadic and hereditary character.

of M0 patients, 81.9% (86) of N0M0 patients, and 15.1% [11] of N1M0 patients. Thus, lymph node metastasis at diagnosis is a prognostic factor for MTC. According to a meta-analysis, the median overall survival of patients with metastatic disease at diagnosis does not exceed 3 years [29, 31]. In our study, for the 26 M1 patients, the median survival is also less than 3 years. According to the European Thyroid Association, survival after the discovery of distant metastasis is about 25% at 5 years and 10% at 10 years [32]. In our study, it is 38% at 5 years and 18% at 10 years.

Strengths

The main strength of our study is that it is a longitudinal study spanning more than 40 years, involving a substantial number of MCT patients (260) from one of the main MCT registries in France.

We were able to highlight a significant difference in survival between sporadic and hereditary MCT.

Limitations

Our study describes more than 40 years of longitudinal study with patients included from 1975 to 2018. Thus, in 2023, we had 5 years of follow-up for the entire cohort, ie, 260 patients; 10 years of follow-up for patients included before 2013, ie, 226 patients; and 20 years of follow-up for patients included before 2003, ie, 148 patients. In order to present high-quality results, we have chosen not to carry out a survival study beyond 10 years.

Conclusion

Our retrospective study shows an increase in the incidence of MTC over the last decades from 0.41/100 000 PY [0.407-0.413], between 1986 and 1996, to 0.57/100 000 PY [0.567-0.573] between 2008 and 2018. That may be explained by the development of ultrasound and/or ultrasound-guided fine-needle aspiration. Twenty to 25% of MTC are hereditary forms. Genetic screening should be systematic and lead to family screening if necessary. The prognosis remains good but less than for follicular-derived tumors. Sporadic disease has a worse prognosis. Further studies should be carried out to try to explain this difference in survival between hereditary and sporadic MCT.

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Author Contributions

S.C. researched data for the article, made contributions to the discussion of the content, wrote the article, and reviewed/edited the manuscript before submission. A.D.T. made all statistical analysis, made contributions to the discussion of the content, and reviewed/edited the manuscript before submission. G.V. reviewed the manuscript before submission. S.D. reviewed the manuscript before submission. L.L.M. reviewed the manuscript before submission. M.Z. researched data for the article, made contributions to the discussion of the content, wrote the article, and reviewed/edited the manuscript before submission.

Disclosures

S.C., A.D.T., G.V., S.D., L.L.M., and M.Z. declare no competing financial interests.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Prior Presentation

This work was presented at the 38th Congress of the SFE (French Society of Endocrinology), in Nantes, at the Congress Center, on October 13, 2022.

Clinical Trial Information

CNIL number: 448676.

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