CLINICAL STUDY

Thyroid cancer: is the incidence rise abating?

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Abstract

Objective: The aim of the present study was to determine recent trends in thyroid cancer incidence rates and to analyze histopathological characteristics and geographical distribution.

Methods: Histologically proven 5367 cases were collected over the period 1998–2006 in France from the Rhône-Alpes thyroid cancer registry. Geographical variations of incidence were analyzed using a mixed Poisson model.

Results: The average incidence rates, age standardized to the world population, were 3.9/100 000 in men and 12.3/100 000 in women, higher than those previously reported in France. After an initial increase during the first 3 years, a steady level of incidence was observed for the period 2001–2006. The annual incidence rate of microcarcinomas was correlated with that of all cancers in men and women ($r=0.78$ and 0.89 ; $P<0.01$) respectively. Papillary microcarcinomas represented 38% of tumors and two-thirds of them measured less than 5 mm in diameter. They were fortuitously discovered after thyroidectomy for benign diseases in 64% of cases. Histological marks of aggressiveness differed according to the size of the tumor. Despite recent advances in diagnosis, 13% of tumors were diagnosed at advanced stage especially in men. Geographical distribution of incidence based on subregional administrative entities showed lower incidence rates in rural than in urban zones in men (relative rate: 0.72; 95% CI: 0.62–0.84) and women (relative rate: 0.85; 95% CI: 0.73–0.93).

Conclusion: The present study suggests that the rise in thyroid cancer incidence is now abating. It could reflect standardization in diagnostic procedures. Further studies, performed on a more prolonged period, are necessary to confirm these data.

European Journal of Endocrinology 160 71–79

Introduction

Although thyroid cancer is relatively rare, accounting for around 1.5% of all cancers, its incidence has sharply increased over the past 30 years and to date it is the third cancer among the French women. This rise in incidence has been extensively reported, in the USA (1), Ontario (2), as well as European countries (3–5). It was associated with a change in the distribution of histological type, namely an increase in papillary cancers, accounting for more than 80% of all thyroid cancer in recent series (1, 4). A recent analysis conducted from six French cancer registries representing 13% of the French population showed an annual percent increase in the incidence of papillary cancers of 8.1% in men and 9.0% in women for the period 1983–2000 (6). The major part of the increase in papillary thyroid cancer

incidence has been related to small tumors, less than 2 cm in diameter (1), and in recent series micropapillary cancers represent 40% of cases (1, 6). The current hypothesis is that the increase in thyroid cancer incidence is mainly due to the use of more efficient diagnostic tools (7), particularly that of ultrasonography (US) and fine needle aspiration biopsy (FNAB), leading to an increased detection of small subclinical tumors. Wide variations in thyroid cancer incidence exist between countries and in the same country (8). The national estimation of incidence rates in France for the period 1998–2000 ranged from 5 to 20 per 100 000 according to administrative areas (9). These differences may reflect differential exposure to thyroid cancer environmental risk factors or differences in diagnostic practices.

Population-based cancer registries are major tools for studying incidence. They give a synthetic view of a

given pathology at a given time. The Rhône-Alpes (RA) region thyroid cancer registry (TCR) has registered 5367 histopathologically confirmed cases from 1998 to 2006, in a region accounting for 10% of the French population (six million inhabitants).

The aim of the present study was to determine recent trends in incidence rates and to analyze histopathological characteristics and geographical distribution.

Materials and methods

The TCR of the RA (TCR-RA) region is a population-based collection initiated in 1998 and is constituted of histologically proven incident cases, operated in a region that includes approximately six million inhabitants living in 8 départements and 311 cantons. The constitution of the registry was approved by the Commission Nationale de l'Informatique et des Libertés. It was performed with the help of the histopathologists, the surgeons, and the regional health agency. Patients were informed by surgeons of their inclusion in the registry according to French legislation and they were aware of the possibility to refuse. Cases were transmitted from various sources assuring satisfactory completeness: pathology reports provided by the 30 histopathology laboratories of the RA region, card index of 103 surgical wards, and hospital claims databases (10).

The following data were recorded: demographic information, surgical procedure, major diameter of the tumor (or the largest if multiple), histological criteria used for tumor node metastasis (TNM) classification including extrathyroidal development (ET) beyond the thyroid capsule, focality, and lymph node metastases (LNM). Histological subtypes were classified according to the World Health Organization (WHO) classifications (2004) (11) in the following categories: papillary, follicular, oxyphilic (variant of papillary and follicular), poorly differentiated (insular), anaplastic, and medullary thyroid carcinomas. There was no direct reevaluation of the pathology. However, in order to have a homogeneous diagnosis, a cautious reading of all pathological records was performed by a pathologist member of the national committee on thyroid cancer (NB-D). For staging by pTNM, the fifth edition was applied to the whole series and the sixth edition to the cases recorded from 2003 to 2006. There was no reclassification. The study of papillary variants according to the WHO 2004 classification was applied to 954 consecutive tumors, corresponding to 87% of papillary thyroid cancers removed in 2005 and 2006. The series was considered as representative since there was no choice *a priori* and since the cases were highly comparable with the whole series in terms of age, sex ratio, proportion of microcarcinomas (36 vs 38%), and pTNM staging (data not shown).

A total of 5367 incident cases of thyroid cancer were registered in the TCR-RA during the 9-year period (1998–2006). Of these, 1256 (23.4%) were diagnosed in men and

4111 (76.6%) in women. The mean age at diagnosis was 49 ± 15 years for men and 50 ± 15 years for women. Surgical procedures consisted of total (or near total) thyroidectomy in 79% of patients (mean age 49 ± 17 years). Cervical lymph node dissection was not systematically performed in cases of limited disease without evidence of lymph node involvement at clinical examination, pre and/or perioperative US and direct observation at surgery. It was performed in 24% of cases, corresponding to 1285 patients and consisted of central neck dissection in 30%, central and lateral neck dissection in 60%, and more extensive dissection in the remaining 10%.

Statistical analyses

Incidence rates were calculated for the period 1998–2006 and expressed as incidence rates per 100 000 person-years, age standardized both to the European and World populations, to ensure comparison with published data. The geographical variations of incidence (1998–2004) were analyzed on a French 'canton' basis (i.e. a French administrative entity) using a mixed Poisson model (12), and separate analysis for males and females were conducted. In the Rhône-Alpes Region, there are 311 cantons of which 56 (18%) are considered urban (INSEE classification) and 255 (82%) rural and semirural. The covariates introduced in the model with fixed effects were: age, year of diagnosis, physician density (i.e. the number of general practitioners per 1000 inhabitants), and the urban/rural characteristic of the canton. Canton was introduced in the model assuming a random effect and, for each canton, its relative rates were estimated using a shrinkage estimator (12) and mapped with software Arcview 3.1.

Results

Overall age-adjusted incidence rates

A total of 5367 incident cases of thyroid cancer were registered in the TCR-RA during the 9-year period (1998–2006). The overall incidence rates, age standardized to the European and world populations, were 4.82 and 3.9 per 100 000 men and 14.91 and 12.3 per 100 000 women respectively. Incidence rates increased during the first 3 years of the study and were, thereafter, stable over time for the period 2001–2006 (Table 1). Incidence rates by age groups at diagnosis are shown in Fig. 1 in men and women. Low rates were observed in children with a rapid increase at puberty for girls. A maximal incidence of 35/100 000 was obtained in women of 55–59 years. The world-standardized incidence rates of microcancers (≤ 1 cm) were 1.21/100 000 in men and 4.76/100 000 in women. There was a significant correlation between the annual incidence rate of microcancers and that of all cancers in men and women ($r = 0.78$ and 0.89 ; $P < 0.01$) respectively.

Table 1 Incidence rates per 100 000 person-years of thyroid cancers in the Rhône-Alpes region, by sex and year.

Year	Men		Women	
	Standard Europe	Standard world	Standard Europe	Standard world
1998	3.37	2.47	10.27	8.35
1999	4.12	3.32	11.65	9.53
2000	4.27	3.43	13.78	11.28
2001	5.16	4.19	18.82	15.25
2002	5.78	4.77	17.14	13.83
2003	5.21	4.24	15.79	12.99
2004	5.70	4.49	16.55	13.41
2005	5.32	4.19	17.09	14.53
2006	5.02	3.95	15.67	12.70

Data have been age standardized both to the European and the world population in order to allow for comparisons.

Histopathological subtypes

The distribution of histopathological types is given in Table 2. Papillary thyroid carcinomas (PTC) accounted for 86.5% of all cancers. The distribution of PTC variants was analyzed from a subset of 954 tumors. Among them, 36% were microcarcinomas. When analyzing tumors more than 1 cm in diameter, the proportion of classical papillary variant was 44% and that of the follicular variant was 46%, constituted in equal proportion of invasive and encapsulated tumors. In invasive forms, plurifocality was found in 30%, extrathyroid growth (ET) in 16%, and LNM in 17% whereas in the encapsulated follicular variant, plurifocality was found in only 10% and neither ET nor LNM was found. The diffuse sclerosing variant was found in 2% of cases and represented 5.8% of the 0–30 years age group. It was associated with LNM in 75% of cases. LNM were also found in 60–75% of patients with the tall cell or solid variant.

Follicular thyroid cancers represented 5.9% of cases (Table 2); they were encapsulated in 60%, and widely invasive in 40%. Twenty-eight percent of follicular thyroid cancer belonged to the oncocytic variant. Poorly differentiated (insular) carcinomas represented 1%, whether pure or associated with differentiated papillary or follicular component in 13% of them. Anaplastic and

medullary thyroid cancer represented 1.06 and 2.8% respectively.

Stage at diagnosis

The respective distribution of pTNM scores according to the fifth and sixth editions is shown in Table 3. As expected, the proportions of pT1 and pT3 were higher while those of pT2 and pT4 were lower in the sixth compared with the fifth edition. The distribution of the pTNM scores (fifth and sixth editions) by age groups is shown in Fig. 2 (A and B). The main findings were a progressive increase in pT1 with age, in both classifications, a progressive decrease with age in LNM from 40% in children to 10% in older subjects (Fig. 2B). The use of the sixth edition, resulted, in children and adolescents, in a striking decrease in pT4 counterbalanced by an increase in the proportion of pT3 tumors. Thus, extensive tumors classified as pT4 were almost exclusively observed in older subjects and mainly in men (Fig. 2B). As a whole, aggressive tumors classified as pT3 or pT4 represented 13% of thyroid cancer. The proportions of cancer types were different from those of the whole series with 59% of papillary cancers, 17% of follicular, 7% of oncocytic, 5.4% of insular, 4% of medullary, and 6.6% of anaplastic. Distant metastases led to the diagnosis of thyroid cancer in 1% of patients.

Microcarcinomas represented 38.2% of all tumors (2154 cases), 96.5% of them being papillary. A large proportion of these tumors (64%) had a diameter of ≤ 0.5 cm and 30% had a diameter of ≤ 0.2 cm. The proportions of microcancers were significantly different between men and women (33 vs 42% respectively; $P < 0.005$) and between age groups ($P < 0.004$) with the highest value of 49% in the 50–60 years group. The effect of age was similar in men and women. Seventy percent of microcancers were removed from patients older than 45 years. In the whole group of microcancers plurifocality was found in 27%, ET in 5.5%, and LNM in 5.2%. The relationship between tumor size, LNM, and ET are shown in Fig. 3. The proportion of ET and LNM

Figure 1 Incidence rates per 100 000 person-years of thyroid cancers by age groups in men and women.

Table 2 Histopathological characteristics of the 5367 incident cases of thyroid cancer diagnosed between 1998 and 2006 in the French Rhône-Alpes region.

	Number and proportion	Mean age at diagnosis (year) $\pm$ s.d.	LNM	ET
Total	5367			
Men	1256 (23.4%)	49 $\pm$ 15		
Women	4111 (76.6%)	50 $\pm$ 15		
Papillary	4642 (86.5%)			
Men	1012 (80.5%)	48 $\pm$ 15	176 (17%)	162 (16%)
Women	3630 (88.2%)	49 $\pm$ 15	434 (12%)	494 (13%)
Follicular	321 (5.9%)			
Men	106 (8.4%)	52 $\pm$ 16	6 (5.6%)	16 (15.6%)
Women	215 (5.2%)	51 $\pm$ 19	13 (6%)	32 (15%)
Oncocytic	104 (1.9%)	60 $\pm$ 15	4 (0.3%)	32 (30%)
Poorly differentiated	52 (1%)	62 $\pm$ 16	10 (20%)	23 (44%)
Medullary	154 (2.8%)	51 $\pm$ 18	53 (34%)	22 (14.2%)
Anaplastic	57 (1.06%)	72 $\pm$ 13	26 (46%)	53 (95%)
Papillary variants	954			
Variant $\leq$ 1 cm	342 (36%)		5.2%	5.5%
Variant $>$ 1 cm	612 (64%)			
Classical	266 (28%)		40%	30%
Follicular	286 (30%)		8%	8%
Tall cell	4 (0.4%)		75%	75%
Diffuse sclerosing	20 (2.1%)		75%	30%
Solid	10 (1%)		60%	70%
Focal insular	7 (0.7%)		0%	45%
Oncocytic	16 (1.67%)		0%	6.25%

increased as a function of tumor size. It was lower than 5% in tumors less than 5 mm in diameter. The microcancers were classified as 'clinical', expected after US or FNAB or observed by the surgeon (36%), or fortuitously discovered (64%). The mean size of 'clinical' microcancers was higher than that of fortuitous cancers: 0.64 ± 0.26 cm vs 0.35 ± 0.22 cm; $P < 0.01$. In 'clinical' microcarcinomas, ET and LNM were seen in 12% and multifocality in 35%, whereas in fortuitous cancers the ET and LNM were noted in 1% and multifocality in 19%. Globally, fortuitous cancers, 93% of them being microcarcinomas were found in thyroids removed for benign disease: hyperthyroidism in 11%, in the vicinity of adenomas in 32%, and in multinodular goiters in 57%. The contribution of fortuitously discovered microcancers dramatically decreased with age (Fig. 2A). The proportions of cancers discovered in goiters varied with age from 7% in patients younger than 25 years, to 22% in patients 25–50 years, to 31% in patients 50–60 years, and to 34% in patients older than 60 years.

Table 3 Distribution of pTNM staging according to the fifth and sixth editions.

	Fifth edition		Sixth edition	
	Men (%)	Women (%)	Men (%)	Women (%)
pT1	31.7	40.5	45.9	61.7
pT2	38.2	40.2	26.2	20
pT3	12.1	4.5	22.4	14.6
pT4	16.8	14.6	4.8	2.9

Time trend in the distribution of thyroid cancer

As shown in Fig. 4, there was a strong parallelism between the number of thyroid cancer over the study period and the number of papillary tumors with a rapid increase between 1998 and 2001 and further stabilization. A similar pattern was observed for small tumors, especially less than 1 cm in diameter. As shown in Fig. 5, this increase with time was mainly related to an increase in the number of microcancers fortuitously discovered, and mainly concerned the group of the smallest (< 0.5 cm) in which fortuitous cancers represented 72% in 2002 (vs 35% for the 0.5–1 cm for the same period). By contrast, there was no change over time in the number of non-papillary tumors nor in the number of large tumors more than 4 cm in diameter (T3 or T4) observed in 9.8% of patients ($n = 506$; Fig. 4).

Geographical variations of incidence rates

Table 4 shows the number of cases and the incidence rates per 100 000 person-years according to the urban/rural characteristic of the cantons. The incidence in rural cantons was 28% lower than in urban cantons in men (relative rate $4.3/6 = 0.72$) and 15% in women (relative rate $14.4/17 = 0.85$). The Poisson mixed model with adjustment on all covariates confirmed these results. Indeed, the rural/urban characteristic was found statistically significant: the ratio was estimated at 0.72 (95% CI: 0.62–0.84) in men and 0.82 (95% CI:

Figure 2 Distribution of pTNM stages (fifth and sixth edition) by age. (A) pTNM fifth edition, 5310 cases (1998–2006): 0–14 years, 40 cases; 15–19 years, 80 cases; 20–29 years, 437 cases; 30–40 years, 979 cases; 41–50 years, 1188 cases; 51–60 years, 1329 cases; >60 years, 1257 cases. pT1 results are presented as all cases, cases pT1 'clinical', and cases pT1 'fortuitous'. (B) sixth edition, 2548 cases (2003–2006): 0–14 years, 13 cases; 15–19 years, 35 cases; 20–29 years, 231 cases; 30–40 years, 456 cases; 41–50 years, 530 cases; 51–60 years, 650 cases; >60 years, 633 cases. N+ (=N1a+N1b).

0.73–0.93) in women. General practitioner density did not appear to have a significant effect on incidence whether in men or in women. Figure 6 shows canton variability of the incidence in women after adjustment

Figure 3 Relationship between size of carcinomas, extrathyroidal extension (ET), and lymph node metastases (LNM): ≤0.2 cm, N=658; >0.2–≤0.3 cm, N=276; >0.3–≤0.4 cm, N=195; >0.4–≤0.5 cm, N=263; 0.5–≤1 cm, N=762; >1–≤2 cm, N=1320; >2–≤4 cm, N=1323; >4 cm, N=506. Mean tumor sizes were 2.4 ± 2.0 cm in men and 1.7 ± 1.0 cm in women.

in women's age and in the rural/urban characteristic of the canton.

Discussion

The RA-TCR provides an overview of the presentation of thyroid cancer as it was diagnosed during the past decade from a six million French population. After an initial rise, observed for the first 3 years, steady incidence rates were observed, both in men and women for the following 6 years. During the first 3 years, there was mainly an increase in small papillary tumors less than 1 cm in diameter whereas large tumors more than 4 cm in diameter were stable. The difference between 1998 and 2001 was constituted for 53% of tumors fortuitously discovered. Changes with time in the practice of pathologists with more careful examination of whole surgical specimens and changes with time in the consideration of *in situ* tumors as declarable cancers were probably the main determinants of the increase. Satisfactory completeness was reached after 2000 as shown by the comparison with hospital discharge databases (10). The incidence rates of the last 6 years are elevated, slightly higher than those reported for the more recent years, whether observed (4, 13–15) or estimated from French cancer registries covering 13% of the national population (9, 16). The fact that the changes in papillary tumors and small-size tumors less than 1 cm in diameter parallel those of the general incidence suggest the major influence of small papillary cancers on incidence rates (1, 6, 13, 15). The present study shows a near

Figure 4 Number of cases per year, of papillary tumors, and of tumors classified by size.

stabilization in incidence rates, and in the proportions of all groups of tumors classified by size and histopathology. To our knowledge, such steadiness in thyroid cancer incidence rates has not yet been reported. It could be the reflection of the standardization in diagnostic procedures in the region. However, the study period is relatively short, and more prolonged observations in our region and other areas are mandatory to ascertain the existence of a plateau in the incidence of thyroid cancer. It must be noticed that a similar tendency toward stabilization in incidence was recently reported for prostate cancer for the 1999–2003 period, after an initial sharp increase during the eighties and nineties (17).

As previously reported, the great majority of tumors were papillary. The microscopic criteria for the diagnosis

Figure 5 Number of cases per year of micropapillary cancers subclassified by size and by conditions of discovery.

Table 4 Number of cases and incidence rates per 100 000 person-years according to the urban/rural characteristic of the cantons.

	Urban canton		Rural or semi-rural cantons	
	Number of cases	Incidence rate	Number of cases	Incidence rate
Men	473	6.0	493	4.3
Women	1472	17	1667	14.4
Total	1945	11.8	2160	9.4

of PTC have changed over the last four decades and its morphologic spectrum has varied considerably. Variants of PTC have been described in the last WHO classification and differ in marks of aggressiveness, i.e. extrathyroidal invasion and LNM. In the present study, variants of papillary cancers were carefully examined in a large number of papillary tumors, representative of the whole series in terms of sex ratio, proportion of microcarcinomas, and pTNM stages. Except for a higher proportion of microcarcinomas, the distribution was comparable with that reported in a retrospective study including 652 tumors diagnosed over a 30-year period (18). Conventional papillary carcinomas accounted for 28% of PTC and for 44% of PTC more than 1 cm in diameter, and were associated with LNM in 40% of cases. This proportion may be, however, underestimated since lymph node dissection was not systematic in patients without suspicious lymph node at preoperative clinical or US examination. As previously reported, macroscopic LNM was nearly constant in the diffuse sclerosing, tall cell, and solid variants, which are considered as aggressive and prone to recurrences (19, 20). The more frequent variant was follicular, observed in the present series in 46% of cases with an equal distribution of invasive and encapsulated forms, who differed markedly in terms of aggressiveness. If diagnosis of invasive FVPTC is easy, that of the encapsulated form is only defined by its nuclear features that can be subtle and necessitates caution in its interpretation (21). The diagnosis of these forms may overlap either with adenoma or with minimally invasive follicular carcinoma. Molecular biology of thyroid cancer is now expanding and it is likely that it will help in the near future for the distinction between cancer subtypes and for the determination of prognosis (22).

Large tumors, more than 4 cm in diameter, represented 10% of the whole series without any change with time over a 9-year period. As expected, men presented more often than women with such large size cancers and patients were older at diagnosis. The proportion of the various histopathological types differed from that of the whole series with a higher proportion of follicular, poorly differentiated, and undifferentiated cancers. Taken together, tumors with limited (pT3) or extensive (pT4), extrathyroidal

Figure 6 Incidence rates in women after adjustment on women's age and on the urban/rural characteristic of the canton.

extension were still found in 13% of cases despite recent advances in the early diagnosis. Since most invasive tumors of young people quoted as pT4 in the fifth edition pTNM classification were reclassified as pT3 in the sixth edition; pT4 stages were only observed in older subjects. This is in agreement with the poor prognosis of extensive thyroid cancer in the elderly.

In the present study, there was a strong relationship between the annual incidence of microcarcinomas and that of thyroid cancer. Papillary microcancers represented 2540 cases, i.e. 38% of the series. This proportion is of the same order of that reported in French (6) and North American series (1). The proportion of microcancers was higher in women, and increased with age to attain 60% in the fifties. In the present series, the overall proportion of aggressive microcancers with ET growth or LNM was lower than that reported in other studies (23, 24). Lymph node dissection was systematically performed when potentially metastatic lymph nodes were found before or during surgery, but prophylactic dissection of the central compartment was not the rule in the case of small tumors without clinical or ultrasonographic evidence of lymph node involvement (25). This attitude probably leads to an underestimation of microscopic LNM (26). However, considering the group of 'clinical' microcancers, the respective proportions of LNM and multifocality are comparable with those recently reported (27, 28). The lower proportion of aggressive microcancers may be due to the high proportion of very small cancers less than 0.5 cm in diameter. Most of them have been fortuitously discovered, by extensive pathological study, in multinodular goiters, submitted to total thyroidectomy for non-cancer purposes. The high proportion of incidental cancer, observed in the present

study, may be explained by the high prevalence of goiters in the RA region. Thyroid surgery is frequently indicated for large multinodular goiters and the incidence of thyroid surgery in the RA region has been estimated with 58/100 000 inhabitants in 2002 (data not shown). A previous report has suggested that incidental discovery of microcarcinoma was a favorable prognostic factor (29). Accordingly, fortuitously discovered microcancers were of smaller size than clinical forms with fewer stigmas of aggressiveness. Whatever the circumstances of diagnosis, histological marks of aggressiveness clearly differed according to the size of the tumor. This was even more evidenced when both criteria of aggressiveness were combined in the same tumor. A threshold of 0.5 cm for developing ET growth and LNM appears reasonable as previously suggested (30). It must be noticed that, despite these clear differences in tumor aggressiveness in relation to tumor size, all tumors up to 2 cm in diameter without ET are now equally considered as pT1 stage in the sixth edition of the pTNM classification.

Variations in incidence rates were observed between subregional administrative entities. Incidence rates were higher in urban cantons than in rural zones. There was no influence of the density of general practitioners. One hypothesis to explain such a disparity between urban and non-urban zones could imply differences in care offered and accessibility to specialists involved in thyroid cancer, namely endocrinologists and surgeons who are more likely to have their practice in urban zones. Other epidemiological studies are needed to explore potential differential effects of risk factors on incidence rates of thyroid cancers in the RA region.

In conclusion, stabilization in the incidence of thyroid cancer, which may reflect standardization in diagnostic

procedures, was observed during the study period. Higher incidence rates were observed in urban zones suggesting differences in care access. Further studies, performed on a more prolonged period, are necessary to confirm these data.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research received funding from the Commission Epidemiologie du Conseil de Radioprotection D'EDF (Electricité de France; 2001, 2002, 2004), Ligue National Contre le Cancer, Comité du Rhône (2003), Canceropole Rhône-Alpes-Auvergne (CLARA 2003), and from Region Rhône-Alpes (2006–2008).

Acknowledgements

We would like to thank Pr Jacques Estève for his continuous inspiring support, Registre du Cancer de l'Isère (Dr François Menegoz (deceased), Dr Marc Colonna), Registre Rhône-Alpes des cancers de l'enfant (Dr Claire Berger), Thyroid cancer group of Institut de Veille Sanitaire (Dr Laurence Chérie-Challine, Pr Laurence Leenhardt), Dr Anne-Marie Schott, Dr Elisabeth Adjaj, Dr Florent de Vathaire, Pr Martin Schlumberger for their valuable advice and support, and the pathologists, surgeons, and endocrinologists of the Rhône-Alpes region for their collaboration. The following laboratories of histopathology contributed to this work: Service d'anatomie pathologique, Centre Hospitalier Lyon Sud, 69495 Pierre Bénite Cedex. Laboratoire central d'anatomie et cytologie pathologiques, Hôpital Edouard Herriot, 69437 Lyon Cedex 03. Service de pathologie du nord, Groupe Hospitalier du Nord, Centre de biologie et pathologie, 69317 Lyon Cedex 04. Service d'anatomie et cytologie pathologiques, Hôpital d'instruction des armées Desgenettes, 69275 Lyon cedex 03. Département d'anatomie et cytologie pathologiques, Centre Léon Bérard, 69373 Lyon Cedex 08. Cabinet d'anatomie et cytologie pathologiques, 69760 Limonest. Centre d'anatomie et de cytologie pathologiques, 69658 Villefranche sur Saone Cedex. Cy-Path-cabinet médical de pathologie, 69007 Lyon. Centre de pathologie ACP, 69287 Lyon Cedex 02. Département d'anatomie et cytologie, UF de pathologie Gastro-enterologique, hépatique et endocrinienne, CHU de Grenoble, 38043 Grenoble Cedex 09. Cabinet de pathologie médicale, Anatomie et cytologie pathologiques, 38100 Grenoble. Centre médical d'anatomie et de cytologie pathologiques, 38200 Vienne. Centre d'anatomie et de cytologie pathologiques, 38302 Bourgoin Jallieu Cedex. Service d'anatomie et cytologie pathologiques, Centre Hospitalier de Valence, 26953 Valence Cedex 09. Centre de pathologie, 26201 Montélimar Cedex. Cabinet d'anatomie pathologique et de cytologie, 26006 Valence Cedex. Service d'anatomie et cytologie pathologique, CHU Saint-Étienne, Hôpital Nord, 42055 Saint Etienne Cedex 2. Anatomie et cytologie pathologiques, Centre Hospitalier de Roanne, 42328 Roanne Cedex. Département d'anatomie et de cytologie pathologiques, 42234 Roanne Cedex. Institut de pathologie du Forez, 42001 Saint Etienne Cedex 1. Centre de pathologie, 42270 Saint-Priest-en-Jarez. Groupe d'anatomie pathologique et de cytologie, 42952 Saint Etienne Cedex 09. Laboratoire d'anatomie et de cytologie pathologiques, Hôpital de Fleyriat, 01012 Bourg en Bresse Cedex. Cabinet d'anatomie pathologique et cytologie, 01000 Bourg en Bresse. Service d'anatomie et de cytologie pathologiques, Centre Hospitalier Chambéry, 73011 Chambéry. Cabinet de pathologie, 73003 Chambéry Cedex. Cabinet d'anatomie et de cytologie pathologiques, 74007 Annecy Cedex. Centre de pathologie du Mont-Blanc, 74105 Annemasse Cedex.

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Received 12 October 2008

Accepted 22 October 2008