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TITLE

Thyroid cancers in children and adolescents in France: Incidence, survival and clinical management over the 2000-2018 period

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2 Thyroid cancers in children and adolescents in France: Incidence, survival and clinical
3 management over the 2000-2018 period

4

5 **ABSTRACT**

6 **Introduction:** Thyroid cancer is the first cause of endocrine malignancy among children. Over
7 the past decades, an increase in the incidence rates (IR) has been observed around the world.
8 Our study aimed to describe epidemiology, therapeutic management and survival rates of
9 children and adolescents with thyroid cancer in France.

10 **Methods:** A population-based study was conducted between 2000 and 2018 in children and
11 adolescents less than 17 years with a diagnostic of thyroid cancer using the French National
12 Registry of Childhood Cancers (RNCE). Age standardized incidence rates (ASR) and survival
13 analysis were performed.

14 **Results:** A total of 774 thyroid cancers were included : 579 papillary (PTC), 83 follicular
15 (FTC), and 111 medullary carcinomas (MTC). PTC are more frequent in females and in
16 adolescents whereas MTC mainly concerned children, mostly with a familial predisposition.
17 Almost all patients underwent thyroidectomy, completed for most patients with PTC and FTC
18 by radioiodine therapy. Between 2000-2018, thyroid cancers IR in children fluctuated between
19 1.3 and 3.2 per million, without any significant trend. The median follow-up time was 11.3
20 years in children, and 5.7 years in adolescents. The 5-year-OS was greater than 98.5%.

21 **Conclusions:** The RNCE plays a critical role in surveillance, and tells us where we are in the
22 efforts to better understand thyroid cancers in pediatric and adolescent population. Considering
23 the very favorable survival, a stratification should be proposed between cases at low risk and
24 cases at high risk of relapse, in order to consider a strategy of therapeutic de-escalation in the
25 most favorable cases.

26 1. INTRODUCTION

27 Pediatric thyroid cancer is rare and counts for 1 to 3% of pediatric cancers. However, it
28 represents the first cause of endocrine malignancy among children. Thyroid cancers in children
29 have a good prognosis, especially papillary carcinoma (PTC), despite their more advanced
30 nature at diagnosis than in adults and the higher risk of recurrence [1–4]. Differentiated thyroid
31 carcinoma (DTC) is the most frequent (more than 90%) with an age-standardized incidence
32 rate (ASR) of 6.7 (95%CI: [6.5-6.8]) cases per million person-years in the United States [5].
33 Rates increase during the second decade and particularly after the age of 15 years [6,7].
34 Medullary thyroid carcinoma (MTC) is more common in children aged 0 to 4 years [7].
35 Globally, girls are more affected with a sex ratio reported at 4.4:1 among children and young
36 adults aged 0-19 years and up to 6:1 among the 15-19-year age group [6,7].

37 Over the past decades, an increase in the incidence of pediatric thyroid cancers has been
38 observed around the world. Gupta et al reported an increase, between 1998 and 2012, in
39 adolescents and young adults in more than 33 countries for women and 22 for men, among the
40 41 studied [8]. In the United States, an overall increase in the incidence rate (IR) between 1973
41 and 2013 was reported in people aged under 20 with a rate going from 0.5 (95%CI: [0.3-0.7])
42 to 1.1 (95%CI: [0.9-1.4]) per 100,000 person-years [9]. This increase concerned more
43 particularly PTC and was more marked between 2006 and 2013 with an average annual
44 percentage change in IR of 9.6% (95%CI: [5.1-14.2]) [9]. In France, a similar increase was
45 observed among children aged 0-14 years between 1978 and 2001, through general
46 departmental registers survey who have nevertheless recorded a low number of cases [10].
47 Between 2000 and 2008, according to data from the French National population-based Registry
48 of Childhood Cancers, the incidence of thyroid cancers remained stable [11].

49 The causes of this increase in the occurrence of thyroid cancers remain controversial. The
50 improvement in the recording of cases over time could be an explanation [10]. On the other

51 hand, the improvement of imaging techniques, which are more sensitive, and the evolution in
52 the diagnostic approach of thyroid nodules, particularly in children, making it possible to detect
53 localized tumors earlier, could explain an overdiagnosis of thyroid cancers [5,9,12,13].
54 However, the observation of the significant increase in cancers with an advanced stage and
55 large tumors, as reported among the 10-19-year age group in the United States, could show a
56 real increase in incidence, potentially linked to environmental exposures or to yet unknown
57 risky lifestyles [5,9,14].

58 The increasing IR of thyroid pediatric cancers observed throughout the world requires careful
59 epidemiological monitoring of this malignancy, in particular through the updating of national
60 epidemiological data. Thus, our study aimed to describe epidemiology, incidence, therapeutic
61 management, and survival rates of children and adolescents aged 0 to 17 years and diagnosed
62 with thyroid cancer between 2000 and 2018.

63

64 **2. MATERIALS AND METHODS**

65 **2.1 Study population**

66 The present study used data from the French National population-based Registry of Childhood
67 Cancers (RNCE) recording cases of solid pediatric tumors for children (0-14 years) since 2000
68 and extending to adolescents (15-17 years) since 2011. All incident cases of thyroid cancer
69 (group XI.b according to the third version of the International Classification of Childhood
70 Cancer (ICCC-3) occurring in children and adolescents (0-17 years) and diagnosed in France
71 between 2000 and 2018 were included [15]. Lacour et al have previously described the
72 methodology of case registration for the RNCE [16].

73

74 **2.2 Data collection**

75 The registration form included child and adolescent characteristics, information on patient
76 medical and family history, clinical data at diagnosis, initial treatment, patient pathway from
77 diagnosis to treatment, vital status and last contact date.

78 Using the third edition of the International Classification of Disease for Oncology (ICDO-3),
79 histology was tabulated as: papillary carcinomas (8260/3, 8340/3-8344/3, 8350/3), follicular
80 carcinomas (8290/3, 8330/3, 8335/3, 8337/3) and medullary carcinomas (8345/3) [17]. Stage
81 at diagnosis were standardized according to the UICC TNM classification of malignant tumors,
82 Eight edition (TNM8) [18]. Vital status was obtained at the time of analysis by active search in
83 medical records and by matching the RNCE files and the central population register (RNIPP)
84 sorted by date and place of birth to obtain the mention of death and the date of death.

85

86 **2.3 Statistical Analysis**

87 Age standardized IR per million children were calculated using direct standardization and world
88 standard population aged 0-14 years as reference [19]. Crude incidence rate (CIR) were
89 calculated for adolescents aged from 15 to 17 years. Methods based on Poisson distribution
90 were used to specify the 95% confidence interval (95%CI) for ASR and CIR [20]. The average
91 annual percent change (APC) was considered to test for a time trend in ASR and CIR. APC was
92 derived from the slope parameter estimate of a linear regression model considering the natural
93 logarithm of the ASR as a function of the calendar year [21]. To study overall survival, the time
94 origin was the date of diagnosis. The date for last follow-up was March 1, 2021. The end point
95 of interest was the occurrence of death, all causes combined. The median length of follow-up
96 was calculated using the reverse Kaplan-Meier estimator [22]. Follow-up (<5 and \geq 5 years)
97 according sex, age group and histological group over the 2000-2015 period was analyzed. 5-
98 year overall survival (5y-OS) was calculated using the Kaplan-Meier estimator [23]. Survival
99 curves were compared using log-rank test [24,25].

100

101 **3. RESULTS**

102 **3.1 Patient characteristics (Table 1)**

103 Between 2000 and 2018, 774 patients, aged 0-17 years, with thyroid cancer were included: 490
104 (63.3%) aged 0-14 years (as children group) and diagnosed from 2000 to 2018 and 284 (36.7%)
105 aged 15-17 years (as adolescent group) and diagnosed from 2011 to 2018. Mean age at
106 diagnosis was 10.6 (3.6) years for children and 16.2 (0.8) years for adolescents. Over the 2011-
107 2018 period, adolescents were more frequently female compared to children (81.3% vs 67.5%;
108 $p<0.01$) and had more frequently PTC (88.4% vs 67.5%; $p<0.01$) and less frequently follicular
109 carcinoma (FTC) (8.4% vs 15.7%; $p<0.01$) and MTC (3.2% vs 16.8%; $p<0.01$). One male
110 patient was diagnosed with a Spindle epithelial tumor with thymus-like differentiation
111 (SETTLE) at 12 years. He presented a metastatic relapse 10 months after diagnosis and died 6
112 years after diagnosis. This patient was excluded from analysis and in following results, as this
113 tumor type is extremely rare.

114

115 **3.2 Patient medical history (Table 2)**

116 A total of 88 (11.4%) patients had a family relative with thyroid cancer history, mostly (n=73,
117 83.0%) a first-degree member family (parents, brothers or sisters). Familial predisposition
118 mainly concerned patients with MTC at diagnosis (n=81, 93.1%; $p<0.01$). Predispositions of
119 patients with MTC were mostly Multiple Endocrine Neoplasia type 2 (MEN2) with 79 (74.5%)
120 MEN2A syndromes, 20 (18.9%) MEN2B, 3 (2.8%) MEN 2 (type not specified), 3 (2.8%) RET
121 mutation (syndrome type not specified) and 1 (0.9%) Familial Medullary Thyroid Carcinoma
122 (FMTC). PTC predispositions were: APC (Adenomatous Polyposis Coli) gene mutation (n=3),
123 Cowden syndrome (n=1) and RET mutation (n=1). Among patients having FTC, 1 (1.2%) had
124 a Cowden syndrome.

125 A thyroiditis history was observed in 32 patients (4.1%), all with PTC. Among them, 12
126 (37.5%) had a Basedow disease, 11 (34.4%) a Hashimoto thyroiditis, and for 9 (28.1%) the
127 autoimmune thyroid disease was not specified. A total of 20 (2.6%) patients with PTC had a
128 neck or total body irradiation history, all for treating a previous cancer. Among them, 11 (55%)
129 had irradiation before 5 years and 9 (45%) at 5 years or more. An history of cancer was observed
130 in 37 patients (4.8%): one cancer for 34 patients (91.9%), two cancers for 2 patients (5.4%) and
131 three cancers for one patient (2.7%). The most frequent primary cancer was leukemia (12
132 patients). Among the 37 patients, just one patient had a known predisposition (APC gene
133 mutation).

134

135 **3.3 Tumor characteristics (Table 2)**

136 Overall, 74.9% of patients had PTC, 10.7% FTC and 14.4% MTC. Patients having MTC were
137 younger compared to patients having PTC or FTC (mean age (SD) respectively: 7.4 years (4.9),
138 13.6 years (3.0), 13.2 years (2.6); $p < 0.01$). Most tumors were unilateral or median for DTC
139 compared to MTC (PTC: 75.0% and FTC: 90.3% vs MTC: 28.8%, $p < 0.01$) and they were more
140 frequently unifocal (PTC: 58.0% and FTC: 81.9% vs MTC: 25.2%, $p < 0.01$). Majority of MTC
141 were smaller (≤ 10 mm) compared to DTC (MTC: 77.5% vs PTC: 16.2% and FTC: 2.4%,
142 $p < 0.01$). FTC and MTC were significantly mostly located compared to PTC (% of N0:
143 90.4%, 84.7%, and 39.9%, respectively) which tended to be more regional. PTC were more
144 frequently metastatic compared to others carcinoma (PTC: 8.5% vs FTC: 1.2% and MTC:
145 2.7%). For DTC, metastases were mainly located in the lung (93.9%) and more rarely in the
146 thoracic lymph nodes (2.0%). The sites of metastases in MTC were more varied: pancreas, liver,
147 lung, bones and thoracic lymph nodes.

148

149 **3.4 Disease management (Table 2)**

150 *3.4.1 Therapeutic care*

151 Most patients underwent thyroid surgery, except 2 patients having metastatic MTC. The
152 majority of them had a total thyroidectomy. Partial surgery was more frequent in patients having
153 FTC (7.2%; $p<0.01$). Two-stage surgery (thyroidectomy in two stage or second stage for neck
154 dissection) was observed for 27.6% of patients (not specified for 10 children). Majority of one
155 stage surgery were performed in patients with MTC or PTC, respectively: 97.2% and 71.5%
156 whereas children with FTC underwent more frequently surgery in two stages (65.1%, $p<0.01$).
157 During surgery, cervical dissection was performed more frequently in patients having PTC and
158 MTC compared to the ones presenting FTC (respectively: 79.1% and 72.1% vs 56.6%; $p<0.01$).
159 Moreover, patients having PTC or MTC had more often a largest dissection (bilateral neck and
160 central compartment) compared with the ones with FTC. Most of the patients having a DTC
161 had complementary treatment by Radioactive Iodine Therapy (PTC: 83.1% and FTC: 80.7% vs
162 MTC: 0%, $p<0.01$). Only 5 patients (3 with regional or metastatic MTC, one with a metastatic
163 PTC and one with an insular carcinoma) had other treatments as targeted treatment, external
164 radiotherapy or chemotherapy.

165

166 *3.4.2 Care system*

167 Patients with MTC had mostly the first medical contact with a university hospital practitioner
168 specialized in children diseases ($p<0.01$). For DTC, the first contact was more various and
169 patients were mostly seen at diagnosis in an adult unit ($p<0.01$). Differentiated carcinomas were
170 firstly managed by endocrinologists and nuclear medicine physicians compared to MTC which
171 were more frequently managed by endocrinologists and pediatricians ($p<0.01$). For surgery,
172 similar results were observed on patient's journey.

173

174 **3.5 Incidence**

175 Age-specific incidence rates (IR) per million by sex for thyroid cancers over the 2000-2018
176 period are presented in Figure 1. IR are close for both genders between 0 and 7 years and below
177 2 per 1,000,000 person-year. For females, there is a dramatical increasing of IR with age from
178 2.1 [95%CI: 1.2-3.5] for 8 years to 35.0 [95%CI: 28.7-42.3] per 1,000,000 person-year for 17
179 years. Therefore, the sex ratio is 5:1 in the adolescent group. Between 0 and 6 years, IR are
180 higher for MTC compared to DTC (Figure 2). For PTC, there is a strong increasing of IR with
181 age, from 0.5 [95%CI: 0.2-1.1] for 7 years to 18.7 [95%CI: 15.4-22.4] per 1,000,000 person-
182 year for 17 years.

183 Between 2000 and 2018, there was no significant evolution in thyroid cancers IR in the children
184 age group (Figure 3). All tumor types confounded (DTC and MTC), the rates fluctuated
185 between 1.3 per 1,000,000 person-year in 2016 and 3.2 in 2005 (APC: -1.1%; 95%CI: [-5.7;
186 +3.8]; p=0.66). For DTC, it fluctuated between 1.1 per 1,000,000 person-year in 2003-2004
187 and 2.5 in 2005 (APC: +0,1%/year; 95%CI: [-1.4; +1.7]; p=0.89).

188

189 **3.6 Overall survival (Table 3)**

190 Overall, 14.2% of cases were lost to follow-up. Over the 2000-2015 period, 92.3% of cases
191 (n=550/596) had a follow-up more than 5 years after diagnosis. No significant differences were
192 observed for the follow-up (<5 years or ≥5 years) when comparing by sex, age group and
193 histological group. Over the 2000-2018 period, the median follow-up time (Interquartile range)
194 was 11.3 (6.6-15.7) years in children, and 5.7 (3.3-7.9) years in adolescents. The 5y-OS was
195 greater than 98.5%. For children diagnosed during the 2000-2010 period, we observed higher
196 survival rates for PTC (5y-OS:100%) and MTC (5y-OS: 97.1; 95%CI: [88.9-99.3]) compared
197 to FTC (5y-OS: 92.4%; 95%CI: [73.0-98.1]). Overall survival did not differ according to
198 metastasis status in both age groups or periods. No significant differences were observed when
199 comparing children and adolescent group over the 2011-2018 period.

200

201 **4. DISCUSSION**

202 This study describes the incidence, the clinical management and the overall survival of pediatric
203 thyroid cancers, in France, between 2000 and 2018, based on national population-based cancer
204 registry data.

205 As described in literature [5–7], our study confirms that DTC, compared to MTC, are more
206 frequent and affect mostly females with an increased incidence after the age of 10 years. It is
207 generally agreed that the clinical course of PTC differs between children and adults. Children
208 usually present with larger tumors and a greater incidence of lymph node metastasis and lung
209 metastasis. This is the case in our study with a majority of tumors of 10 to 40 mm, 50% of
210 lymph node involvement and 8.5% of lung metastasis. FTC were mostly located and unifocal.
211 They are reported to be less aggressive than PTC implying a less advanced disease at diagnosis
212 and fewer cases of recurrence [26,27]. Concerning risk factors, MTC were mostly associated
213 with a predisposition. MTC are known to be hereditary in 95% of cases, occurring because of
214 germline RET mutations and resulting in MEN syndrome (particularly MEN2A, more rarely
215 MEN2B) or FMTC [6,27]. Some PTC were also rarely associated with genetic mutations as
216 reported in literature like APC or Cowden syndromes [27]. Radiation exposure are an
217 environmental risk factor of DTC and particularly PTC [6,27]. In our study, we observed that
218 all patients who had a neck or total body irradiation history for a prior malignancy presented a
219 PTC at diagnosis.

220 Total thyroidectomy is the recommended treatment in PTC pediatric cancers because of the risk
221 of bilateral and multifocal disease and the increased risk of secondary tumor [6,26,27]. Total
222 thyroidectomy is also recommended for MTC which can be aggressive tumors [28]. According
223 management guidelines, we observed that almost all of the PTC and MTC patients underwent
224 total thyroidectomy with frequent lymph nodes dissection. Patients having FTC, compared to

225 other patients, underwent more frequently partial surgery with less lymph node dissection
226 performed. Indeed, FTC is known to be generally an unifocal tumor with rare spreads regional
227 lymph nodes involvement [27]. In addition to surgery, radioiodine-131 (I^{131}) therapy is
228 recognized to be an effective treatment in the prevention of recurrence in case of DTC [6,27].
229 We observed that more than 80% of patients presenting a DTC underwent this additional
230 treatment. This proportion testifies of the widespread use of this treatment. However, this
231 therapy present potential side effects which can be acute (tissues damage as xerostomia,
232 stomatitis, ocular dryness, ...) or develop on long-term basis (second malignancies, pulmonary
233 fibrosis, ...), increasing overall mortality [27]. Thus, these data invites physicians to better
234 identify patients who should benefit from this treatment, as reminded by the American Thyroid
235 Association [27]. Concerning care pathway entry, we observed that patients with MTC were
236 mostly followed in pediatric unit of University hospital due to the earlier diagnostic and the
237 hereditary character of the disease requiring specific management by specialized physicians. In
238 comparison, for patients with DTC, the type of health care services, the unit and the practitioner
239 specialty were varied. Patient care in the adult units remains the more frequent, explained by
240 the fact that patients are older at diagnosis. These results show the diversity of care pathway
241 taken by patients. This fact complicates the identification of pediatric cases for the registry,
242 even more for DTC that are mainly followed in adult units implying to continue to strengthen
243 links with the national network partners.

244 We observed that thyroid cancer IR were similar and low (below 2 per 1,000,000 person-year)
245 for both genders between 0 and 7 years. However, after 8 years IR increased dramatically for
246 females with a 4:1 Female/Male ratio by 16 years of age and 5:1 by 17. Paulson et al reported
247 a nearly 6:1 F/M ratio by 15–19 years of age [6]. Conversely, IR are higher for MTC before 6
248 years, fluctuating between 0.3 [95%CI: 0.1-0.7] and 0.8 [95%CI: 0.4-1.4] per 1,000,000 person-
249 year. During 2000-2004 period, the French ASR for all thyroid carcinomas confounded for

250 children under 15 years was 1.9 per 1,000,000 person-year [16]. The age-standardized rate per
251 1,000,000 person-year observed in France during 2000-2018, in the children group was 1.3
252 [95%CI: 1.1-1.6] for PCT 13.4 [95%CI: 11.8-15.1] for adolescent group. Our results are close
253 to the United States (US) rates. Indeed, in a study based on 39 US cancer registries during 1998-
254 2013, Bernier et al, reported for PTC an ASR of 0.5 per million person-year for children under
255 10 years, 4.7 for 10-14 years and 18.44 for 15-19 years [5]. For FTC, the ASR per 1,000,000
256 person-year observed in France during 2000-2018, in the children group was 0.2 [95%CI: 0.2-
257 0.4] and the IR was 1.3 [95%CI: 0.8-1.9] for the adolescents. Bernier et al reported for FTC an
258 ASR of 0.04 per million person-year for children under 10 years, 0.6 for 10-14 years and 1.6
259 for 15-19 years [5]. For MTC, the ASR per 1,000,000 person-year observed in France during
260 2000-2018, in children was 0.5 [95%CI: 0.3-0.7] and the IR was 0.5 [95%CI: 0.2-0.9] for the
261 adolescent group. MTC are known to be rare, explaining these low rates. Over the last years,
262 increased IR for thyroid cancer were observed worldly. In the US, IR increased from 1973 to
263 2013 (mean APC: 2.54; 95%CI: 1.69-3.40) for children under 20 years [9]. Same phenomenon
264 was observed in South Korea [8,29]. We did not observe similar trend in our study as there was
265 no significant evolution in IR in children over 2000-2018 in France. Improvement of imaging
266 techniques or overdiagnosis may be associated to the increasing IR observed worldly
267 [5,9,12,13]. This improvement in diagnostic procedures might have occurred in France prior to
268 the period of our study, thus explaining the absence of an observed increase in incidence.
269 Finally, our data confirm, as reported in literature, that pediatric thyroid cancer has an excellent
270 prognosis, as the 5-year overall survival was superior to 98.5% [1-4]. The challenge in these
271 tumors is to limit the long-term effects such as second cancers linked to irradiation. We will be
272 able to study this soon by linking the RNCE cases with the medico-administrative databases to
273 get information about late effects or second cancers [30].

274 Our study presents several limitations. First, 14.2% of cases were lost to follow-up due to
275 missing birth data (8.5%). Indeed, place of birth is required for linking the registry data to the
276 RNIPP and this information were sometimes missing, especially in adolescent population.
277 However, over the 2000-2015 period, the major part of the cohort (92.3%) had a follow-up
278 more than 5 years after diagnosis allowing us to have a mid-term view of patient medical
279 history. Then, detection of death predictors was limited due to the low occurrence of the death
280 event.

281 But our study also has some notable strengths. First, we studied a large case series as this study
282 used data from a national pediatric cancer registry. The registry relies on a wide network of
283 national partners. Indeed, cases are identified actively within the hematology-oncology and
284 pediatric surgery departments. In complementary, the registry collaborates with the medical
285 information departments of University Hospital Centers and cancer centers, and with the
286 general cancer registries, allowing to pursue an exhaustive collection of cases. The confirmation
287 and documentation of cases are carried out by the network of clinical research associates of the
288 registry. Then, for this study, to update the quality of our data, for the 774 cases, tumors
289 histological type was verified through the reading of each pathology report and coded and
290 classified using the ICD-O-3 by a single physician. Also, all data regarding tumoral extension
291 were standardized according the TNM8 classification by the same specialist.

292

293 **5. CONCLUSION**

294 The RNCE, by providing robust demographic, diagnostic, clinical and therapeutic data on
295 thyroid cancers over a 19-year period, plays a critical role in surveillance, and tells us where
296 we are in the efforts to better understand these cancers in pediatric and adolescent
297 population. Contrary to some data observed in other countries, we did not observe a significant
298 increase in incidence since 2000. In France, pediatric thyroid cancers are treated as

299 recommended with primary surgery and radioactive iodine in most cases. The prognosis of
300 these cancers is very favorable with a global survival greater than 98%. In view of this very
301 favorable survival, a stratification should be proposed between cases at low risk and cases at
302 high risk of relapse, in order to consider a strategy of therapeutic de-escalation in the most
303 favorable cases. This would limit the adverse effects of treatment, particularly in the case of I¹³¹
304 irradiation.

305

306 **AUTHORS' CONTRIBUTION**

307 All named authors have participated in the study to a sufficient extent to be named as authors.
308 All authors were involved in the study design and analysis plan. All authors critically reviewed
309 the study results, commented on the drafts, and approved the final manuscript.

310

311 **ETHICAL APPROVAL**

312 This study was performed at the RNCE, CRESS Team 7, UMR-S 1153, INSERM, Paris-
313 Descartes University, CHRU Nancy, France.

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317

318 **DECLARATION OF COMPETING INTEREST**

319 The authors declare that they have no known competing financial interests or personal
320 relationships that could have appeared to influence the work reported in this paper.

321

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429

430 **Table 1** Patient socio-demographic characteristics, thyroid cancer histological type and

431 incidence rates per million children by age group (France, 2000-2018)

432 ^a Period of thyroid cancer diagnosis

433 Abbreviations: 95%CI, 95% confidence interval; ASR, age specific incidence rate; CIR, crude

434 incidence rate

435

436 **Table 2** Patient and tumor characteristics, treatment and disease management by histological

437 type (France, 2000-2018)

438 ^a Chi-square test

439 ^b Size of the largest lesion

440 ^c Post-surgical data or clinical data when post-surgical data is unknown

441 ^d Genetic, Internal medicine, Hepato-Gastro-Enterology, Pneumology

442

443 **Table 3** Five-year overall survival by age group and period of thyroid cancer diagnosis (France,

444 2000-2018)

445 ^a Period of thyroid cancer diagnosis

446 ^b p-value logrank test

447 Results in bold translate a p-value<0.05

448 Abbreviations: 95%CI, 95% confidence interval; 5y-OS, five-year overall survival

449

450 **Figure 1** Thyroid cancer incidence rates per million children and adolescents (0-17 years) by
451 gender (France, 2000-2018)

452

453 **Figure 2** Thyroid cancer incidence rates per million children and adolescents (0-17 years) by
454 tumor type (France, 2000-2018)

455

456 **Figure 3** Incidence trends in children (0-14 years) with thyroid cancer (France, 2000-2018)

Table 1 Patient socio-demographic characteristics, thyroid cancer histological type and incidence rates per million children by age group (France, 2000-2018)

	0-14 years (2000-2018 ^a) n=490				15-17 years (2011-2018 ^a) n=284		
	n (%)	Mean (SD)	ASR ^b	95%CI	n (%)	Mean (SD)	CIR ^b [95%CI]
Gender							
Female	490 (100.0)				284 (100.0)		
Male	330 (67.3)				231 (81.3)		
	160 (32.7)				53 (18.7)		
Mean age (years)	490 (100.0)	10.6 (3.6)			284 (100.0)	16.2 (0.8)	
ICD0-3 Tumor histological type							
Papillary	328 (66.9)		1.3	[1.1-1.6]	251 (88.4)		13.4 [11.8-15.1]
Classical	189 (57.6)				144 (57.4)		
82603							
83413							
82603	9 (2.7)				3 (1.2)		
82603	0 (0.0)				2 (0.8)		
83403	78 (23.8)				67 (26.7)		
83423	3 (0.9)				3 (1.2)		
83433	14 (4.3)				14 (5.6)		
83443	7 (2.1)				4 (1.6)		
83503	28 (8.5)				14 (5.6)		
Follicular	59 (12.0)		0.2	[0.2-0.4]	24 (8.4)		1.3 [0.8-1.9]
83303							
83353	9 (15.2)				3 (12.5)		
83353	39 (66.1)				20 (83.3)		
83373	8 (13.6)				1 (4.2)		
82903	3 (5.1)				0 (0.0)		
83453	102 (20.8)		0.5	[0.3-0.7]	9 (3.2)		0.5 [0.2-0.9]
Medullary							
85883							
SETTLE tumor	1 (0.2)				0 (0.0)		

^a Period of thyroid cancer diagnosis

Abbreviations: 95%CI, 95% confidence interval; ASR, age specific incidence rate; CIR, crude incidence rate; SD, standard deviation

Table 2 Patient and tumor characteristics, treatment and disease management by histological type (France, 2000-2018)

	Papillary n=579		Follicular n=83		Medullary n=111		p-value ^a
	n	(%)	n	(%)	n	(%)	
PATIENT CHARACTERISTICS							
Gender							
Female	449	(77.6)	60	(72.3)	52	(46.8)	<0.01
Male	130	(22.4)	23	(27.7)	59	(53.2)	
Age (years)							
[0 ; 5[7	(1.2)	0	(0.0)	37	(33.3)	<0.01
[5 ; 10[58	(10.0)	7	(8.4)	32	(28.8)	
[10 ; 15[263	(45.4)	52	(62.7)	33	(29.7)	
[15 ; 18[251	(43.4)	24	(28.9)	9	(8.1)	
Unknown							
Patient medical history							
Patient relatives having thyroid cancer history							
No	539	(93.1)	78	(94.0)	18	(16.2)	<0.01
Yes	26	(4.5)	4	(4.8)	58	(52.3)	
Unknown	14	(2.4)	1	(1.2)	35	(31.5)	
Patient relatives having thyroid cancer predisposition							
No	560	(96.7)	82	(98.8)	17	(15.3)	<0.01
Yes	5	(0.9)	1	(1.2)	81	(73.0)	
Unknown	14	(2.4)	0	(0.0)	13	(11.7)	
Patient Thyroid cancer predisposition							
No	560	(96.7)	82	(98.8)	4	(3.6)	<0.01
Yes	7	(1.2)	1	(1.2)	106	(95.5)	
Unknown	12	(2.1)	0	(0.0)	1	(0.9)	
Patient Thyroiditis history							
No	536	(92.6)	83	(100.0)	111	(100.0)	<0.01
Yes	32	(5.5)	0	(0.0)	0	(0.0)	
Unknown	11	(1.9)	0	(0.0)	0	(0.0)	
Patient having Neck or total body irradiation history							
No	548	(94.7)	83	(100.0)	111	(100.0)	<0.01
Yes	20	(3.5)	0	(0.0)	0	(0.0)	
Unknown	11	(1.9)	0	(0.0)	0	(0.0)	
TUMOR CHARACTERISTICS							
Tumor laterality							
Bilateral	132	(22.8)	7	(8.4)	75	(67.6)	<0.01
Unilateral or median	434	(75.0)	75	(90.3)	32	(28.8)	
Unknown	13	(2.3)	1	(1.2)	4	(3.6)	
Multifocal							
Yes	219	(37.8)	11	(13.3)	79	(71.2)	<0.01
No	336	(58.0)	68	(81.9)	28	(25.2)	
Unknown	24	(4.2)	4	(4.8)	4	(3.6)	
Size of tumor (mm)^b							
[0 ; 10]	94	(16.2)	2	(2.4)	86	(77.5)	<0.01
]10 ; 20]	176	(30.4)	10	(12.1)	8	(7.2)	
]20 ; 40]	220	(38.0)	48	(57.8)	6	(5.4)	
> 40	68	(11.7)	22	(26.5)	2	(1.8)	
Unknown	21	(3.6)	1	(1.2)	9	(8.1)	

	Papillary n=579		Follicular n=83		Medullary n=111		p-value ^a
	n	(%)	n	(%)	n	(%)	
Extension^c							
Located (N0)	231	(39.9)	75	(90.4)	94	(84.7)	
Regional (N1)	292	(50.4)	5	(6.0)	14	(12.6)	
Metastatic (M1)	49	(8.5)	1	(1.2)	3	(2.7)	
Unknown	7	(1.2)	2	(2.4)	0	(0.0)	<0.01
DISEASE MANAGEMENT							
Therapeutic care							
Thyroid Surgery							
No	0	(0.0)	0	(0.0)	2	(1.8)	
Partial thyroidectomy	18	(3.1)	6	(7.2)	0	(0.0)	
Total thyroidectomy	552	(95.3)	77	(92.8)	109	(98.2)	
Type of surgery not precized	2	(0.4)	0	(0.0)	0	(0.0)	
Unknown	7	(1.2)	0	(0.0)	0	(0.0)	<0.01
Lymph node surgery							
No	94	(16.2)	33	(39.8)	28	(25.2)	
Yes	458	(79.1)	47	(56.6)	80	(72.1)	
Central compartment	63	(13.8)	11	(23.4)	18	(22.5)	
Unilateral neck	56	(12.2)	11	(23.4)	1	(1.3)	
Unilateral neck and central compartment	96	(21.0)	8	(17.0)	4	(5.0)	
Bilateral neck	84	(18.3)	11	(23.4)	25	(31.3)	
Bilateral neck and central compartment	159	(34.7)	6	(12.8)	32	(40.0)	
Unknown	27	(4.7)	3	(3.6)	3	(2.7)	<0.01
Radioactive Iodine Therapy							
No	65	(11.2)	12	(14.5)	111	(100.0)	
Yes	481	(83.1)	67	(80.7)	0	(0.0)	
Unknown	33	(5.7)	4	(4.8)	0	(0.0)	<0.01
Other treatment							
No	571	(98.6)	82	(98.8)	108	(97.3)	
Yes	1	(0.2)	1	(1.2)	3	(2.7)	
Unknown	7	(1.2)	0	(0.0)	0	(0.0)	0.02
Care system							
First medical contact							
Health care services							
University hospital	229	(39.5)	36	(43.4)	76	(68.5)	
Cancer center	110	(19.0)	15	(18.1)	11	(9.9)	
Private practitioner	93	(16.1)	15	(18.1)	8	(7.2)	
Peripheral hospital	64	(11.1)	9	(10.8)	7	(6.3)	
Private clinic	27	(4.7)	4	(4.8)	2	(1.8)	
Unknown	56	(9.7)	4	(4.8)	7	(6.3)	<0.01
Units							
Adult	369	(63.7)	56	(67.5)	48	(43.2)	
Child	156	(26.9)	22	(26.5)	55	(49.6)	
Unknown	54	(9.3)	5	(6.0)	8	(7.2)	<0.01

	Papillary n=579		Follicular n=83		Medullary n=111		p-value ^a
	n	(%)	n	(%)	n	(%)	
Physician specialties							
Endocrinologist	234	(40.4)	43	(51.8)	65	(58.6)	
Nuclear medicine physician	157	(27.1)	21	(25.3)	4	(3.6)	
Pediatrician	49	(8.5)	10	(12.1)	15	(13.5)	
Oncologist	58	(10.0)	1	(1.2)	7	(6.3)	
ENT (ear, nose and throat)	13	(2.2)	2	(2.4)	1	(0.9)	
Other ^d	9	(1.6)	1	(1.2)	10	(9.0)	
Unknown	59	(10.2)	5	(6.0)	9	(8.1)	<0.01
First stage surgery							
Health care services							
University hospital	373	(64.4)	45	(54.2)	96	(86.5)	
Cancer center	50	(8.6)	14	(16.9)	9	(8.1)	
Peripheral hospital	50	(8.6)	5	(6.0)	0	(0.0)	
Private clinic	92	(15.9)	18	(21.7)	4	(3.6)	
Military hospital	1	(0.2)	0	(0.0)	0	(0.0)	
Unknown	13	(2.2)	1	(1.2)	2	(1.8)	<0.01
Units							
Adult	452	(78.1)	62	(74.7)	54	(48.6)	
Child	113	(19.5)	20	(24.1)	55	(49.5)	
Unknown	14	(2.4)	1	(1.2)	2	(1.8)	<0.01

^a Chi-square test

^b Size of the largest lesion

^c Post-surgical data or clinical data when post-surgical data is unknown

^d Genetic, Internal medicine, Hepato-Gastro-Enterology, Pneumology

Table 3 Five-year overall survival by age group and period of thyroid cancer diagnosis (France, 2000-2018)

	0-14 years				p-value					
	2000-2010 ^a n=292	2011-2018 ^a n=197	15-17 years 2011-2018 ^a n=284	2011-2018 ^b						
	n	5y-OS (%)	95%CI	n	5y-OS (%)	95%CI	n	5y-OS (%)	95%CI	
Overall	292	98.6	[96.3-99.5]	197	99.5	[96.4-99.9]	284	99.5	[96.5-99.9]	0.79
Gender										
Female	197	99.0	[95.9-99.7]	133	99.2	[94.7-99.9]	231	100.0	-	0.19
Male	95	97.9	[91.7-99.5]	64	100.0	-	53	97.6	[84.3-99.7]	0.30
Tumor type										
Papillary	195	100.0	-	133	99.4	[94.7-99.9]	251	99.4	[96.0-99.9]	0.64
Follicular	28	92.4	[73.0-98.1]	31	100.0	-	24	100.0	-	-
Medullary	69	97.1	[88.9-99.3]	33	100.0	-	9	100.0	-	-
Metastasis at diagnosis										
No	270	98.9	[96.5-99.6]	178	99.4	[96.0-99.9]	267	99.5	[96.2-99.9]	0.78
Yes	22	95.5	[71.9-99.3]	18	100.0	-	13	100.0	-	-
Unknown	0	-	-	1	100.0	-	4	100.0	-	-

^a Period of thyroid cancer diagnosis

^b p-value logrank test

Results in bold translate a p-value < 0.05

Abbreviations: 95%CI, 95% confidence interval; 5y-OS, five-year overall survival





