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Childhood head and neck cancer in France: incidence, survival and trends from 2000 to 2015

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Brief running title: Childhood head and neck cancers

1 **Childhood head and neck cancer in France: incidence, survival and trends from 2000 to** 2 **2015**

3 **Abstract**

4 *Introduction:* Childhood head and neck cancers (HNC) are rare and represent a complex group
5 of anatomical topographies. The aim of this study is to describe the distribution, the incidence
6 and survival rates of children with malignant HNC in France.

7 *Methods:* A population-based study was conducted between 2000 and 2015 in children less
8 than 15 years with a diagnosis of HNC using the French National Registry of Childhood
9 Cancers database (RNCE). Age-standardized incidence rates (ASR) and survival analysis were
10 performed.

11 *Results:* The 1623 included HNC represented 5.6% of all cancers included in the RNCE. The
12 thyroid was the leading tumor site category (26.6%), followed by head and neck soft tissue
13 location (15.4%) and the nasopharynx (10.8%). The most common cancers were thyroid gland
14 carcinomas (26.1%), rhabdomyosarcomas (23.9%) and Burkitt Lymphomas (8.6%).
15 Nasopharynx cancers and soft-tissue sarcomas were statistically more frequent in boys, while
16 thyroid carcinomas were significantly more frequent in girls. The annual ASR was 8.6 new
17 cancer cases per million children. For all HNC combined, the 5-year overall survival (OS) was
18 87.7% [95%CI: 85.9–89.2]. There was no statistically significant variation in 5-year OS
19 between 2000-2007 and 2008-2015.

20 *Conclusions:* Epidemiological data on HNC distribution, incidence and survival contributes to
21 better understand these tumors by quantifying their impact on the French population and
22 assessing their burden. Regarding the exclusion of topographies and some histological origins
23 performed by some authors, this report proposes new recommendations to study HNC in a
24 pediatric population.

26 **1. Introduction**

27 Head and neck cancers (HNC) are rare among children under 15 years of age but some studies
28 show an increasing incidence of pediatric HNC compared to all childhood cancer [3,5]. HNC
29 account for about 12–15% of all reported pediatric cancers [1–3], because there are differing
30 opinions among authors and clinicians as to what exactly constitutes HNC regarding both
31 reported sites and histologies [1,2,4,5]. Indeed, HNC represent a complex group of anatomical
32 topographies which can be affected by a multitude of malignant tumors, the most frequent of
33 which are lymphomas, rhabdomyosarcomas (RMS), thyroid carcinomas and nasopharyngeal
34 carcinomas [4,6,7].

35 Overall, the 5-year survival in children with HNC remains high (around 80-90%) [8], but
36 analyzes by topographic and/or histological subgroup reveal some disparities: children with
37 malignant thyroid or salivary gland tumors have excellent survival, while those with high-risk
38 squamous cell carcinomas or neuroblastomas have poor survival rate [9,10].

39 The aim of the study is to describe the main characteristics of HNC, their distribution by
40 topography and histology, and to provide national estimates of the incidence and survival rates
41 of children with malignant HNC in the French population over the 2000-2015 period. Then
42 incidence and survival trends over the study period are analyzed.

43

44 **2. Material & methods**

45 *2.1. Population*

46 Study data was obtained from the French National population-based Registry of Childhood
47 Cancers (RNCE), including about 1800 cases per year [11]. Children from 0 to 14 years of age
48 living in mainland France with HNC diagnosed between January 1, 2000 and December 31,
49 2015 were identified. The diagnoses were coded using third edition of the International
50 Classification of Disease for Oncology (ICDO-3) [12] and grouped according the third version

51 of the International Classification of Childhood Cancer (ICCC-3) [13]. The HNC were selected
52 according to their specific ICDO-3 topographic codes divided in 13 groups regarding to tumor
53 location (Table 1) [12]. Staging at diagnosis was defined as metastatic (M+) or non-metastatic
54 (M0) for solid tumors and using Ann Arbor or St Jude/Murphy systems for lymphomas.
55 Only primary head and neck malignant tumors were included. The selected sites are listed in
56 Table 1, so all malignant tumors with any of these topographic ICDO-3 codes were included.
57 Nodal or extranodal lymphomas were included only if they were located in the head and neck
58 area (Waldeyer's ring, tonsils, hypopharynx, nasopharynx, ...). Retinoblastoma, central
59 nervous system (CNS) tumors, and post-transplant lymphoproliferative diseases or Langerhans
60 cell histiocytosis were excluded.
61 The RNCE provided information on child and cancer characteristics, vital status and last contact
62 date. The methods used to record cases and ensure case completeness have been described
63 previously [11]. Population data were provided by the French Institute of Statistics and
64 Economics Studies (INSEE) for each year until 2015. The number of children under the age of
65 15 years varies overall from 11,138,557 in 2000 to 11,780,105 in 2015.

66

67 *2.2. Data analysis*

68 All data were retrieved, tabulated by tumor type, and categorized using the ICCC-3
69 classification [13]. The male/female (M/F) ratio was the ratio of number of cases in males to
70 that in females.

71 Age-standardized incidence rates (ASR) were calculated for the 16-year period, 2000–2015,
72 based on the annual age- and sex-specific population estimates provided by the INSEE. ASR
73 were estimated by the direct method using the world population age distribution. Methods based
74 on Poisson distribution were used to specify the 95% confidence interval (95%CI) for the ASR
75 [14]. The conventional average annual percent change (AAPC) was considered to test for a time

76 trend in ASR. AAPC was derived from the slope parameter estimate of a linear regression
77 model considering the natural logarithm of the ASR as a function of the calendar year [15].
78 Survival analysis was performed on a dataset containing all cases diagnosed between January
79 1, 2000 and December 31, 2015 and followed up until August 1, 2018. Median length of follow-
80 up was calculated using the inverse Kaplan-Meier method [16]. The overall survival (OS) was
81 estimated using the Kaplan–Meier method [17]. The end point of interest was death from any
82 cause, with the date of diagnosis acting as the time origin. Survival curves between groups were
83 compared using the log-rank test, and the trend in survival over time periods was estimated
84 using the log-rank test for trend [18,19]. For survival analysis conducted by ICC3-3 groups and
85 subgroups [13], and tumor stage, multiple HNC cases were counted once, considering the first
86 HNC diagnosed. Multivariate statistical analyses were performed to examine the relationships
87 between duration of survival and following variables: age groups (<1year, 1-4 years, 5-9 years,
88 10-14 years), periods of diagnosis (2000-2007, 2008-2015), metastatic disease (yes/no), and
89 gender (boys, girls). The risks of death were estimated by hazard ratios (HR) and their 95%
90 confidence intervals (95% CI) using Cox proportional hazards regression models [20].
91 Statistical tests were two-sided with a significance level of 0.05. All statistical analyses were
92 performed using the SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA, 2013).

93

94 **3. Results**

95 *3.1. Description of cases*

96 Over the 2000-2015 period, 1623 cases of HNC were identified, i.e. 5.6% of all cancers
97 included in the RNCE (28 998 malignancies). Four children were reported with multiple HNC
98 (Table 2). Two of them had diagnosis of multiple cutaneous cancers in a context of xeroderma
99 pigmentosum and two children had a post-radiation osteosarcoma after their first cancers.

100 Table 3 describes the distribution of HNC by main histologic groups and anatomic sites. The
101 thyroid was the leading tumor site category (26.6%), followed by head and neck soft tissue
102 location (15.4%) and the nasopharynx (10.8%). The most common histologic groups were
103 carcinomas (37.4%), especially affecting thyroid gland (26.1%), then rhabdomyosarcomas
104 (23.9%), and Burkitt Lymphomas (8.6%), especially involving nasopharynx (6.8%). More boys
105 were reported to have nasopharynx cancer (especially Burkitt lymphoma and undifferentiated
106 carcinoma of nasopharyngeal type (UCNT)) or soft-tissue sarcomas as compared to girls with
107 M/F ratios of 4.7 ($p<0.01$), 2.7 ($p=0.01$), and 1.4 ($p=0.01$), respectively. Conversely, thyroid
108 carcinomas were significantly more frequent in girls (M/F ratio of 0.5, $p<0.01$). The mean age
109 at diagnosis was 8.1 years (Standard deviation: 4.5). Neuroblastoma affected the youngest
110 children (mean age: 1.5 years) and UCNT was found among the oldest (mean age: 12.4 years).

111 *3.2. Incidence*

112 The annual ASR over the 2000-2015 period was estimated to be 8.6 new HNC cases per million
113 children [95%CI:7.8-9.5] (Table 4). Overall, ASRs varied from less than 1 per million for
114 neuroblastoma and malignant bone tumors, to more than 3 per million for carcinoma and
115 melanoma. HNC incidence was stable over time with an AAPC of 0.1% [95%CI: -1.1 % to 1.2
116 %, p -value = 0.94].

117 *3.3. Survival*

118 The median follow-up time in the cohort was 106 months (Interquartile Range: 55 –160
119 months), with 2.9% of cases lost to follow-up. Table 5 describes the 1-, and 5-year overall
120 survival (OS) among children with HNC from 2000 to 2015 by ICCC-3 diagnostic groups and
121 subgroups ($n=1619$).

122 For all HNC combined, OS was 95.4% [95%CI: 94.3–96.4], 90.3 [95%CI: 88.8-91.7], and
123 87.7% [95%CI: 85.9–89.2] at 1 year, 3 years and 5 years after diagnosis, respectively. The 5-
124 year OS>85% was observed for lymphomas, neuroblastomas, germ cells tumors (GCT),

125 carcinomas and melanomas, whereas 5-year OS was around 65-75% for osteosarcomas and
126 rhabdomyosarcomas. The 5-year OS was close to 29% for malignant rhabdoid tumors. There
127 was no statistically significant variation in 5-year OS between 2000-2007 and 2008-2015 for
128 all HNC combined and by diagnostic groups (Table 6).

129

130 *3.4. Stage at diagnosis*

131 *3.4.1. Lymphomas*

132 A total of 167 cases of head and neck lymphomas (66.8%) were stage I-II. The majority of
133 Hodgkin lymphoma and mature-B cell lymphoma were stage I-II (90% and 74.2%,
134 respectively), while high proportions of stage III-IV were observed for Burkitt lymphoma
135 (38.5%) and precursor-cell lymphoma (32.3%). For all lymphomas, 5-year OS rates were
136 96.2% [CI95%:91.8–98.3] for stage I-II and 92.5% [CI95%:84.0-96.6] for stage III-IV
137 (p =0.12) (Table 8A). There were no significant differences in survival by stage for all sub-
138 group lymphomas.

139 *3.4.2. Solid tumors*

140 Metastatic diseases were observed for 137 of head and neck solid tumors (10.0%), with highest
141 proportions for rhabdomyosarcomas and neuroblastomas (15.6% and 18.5%, respectively.
142 Table 7B). For all solid tumors, 5-year OS rates were 88.7% [CI95%:86.7-90.4] for non-
143 metastatic diseases and 63.0% [CI95%:54.2-70.5] for metastatic stages (p < 0.01) (Table 8B).
144 There were statistically significant differences in survival by stage for all reported sub-groups
145 of head and neck solid tumors. For metastatic diseases, the 5-year OS varied from 57.7%
146 [CI95%: 45.3–68.2] for children with rhabdomyosarcoma to 91.5% [CI95%: 69.6-97.8] for
147 those with thyroid carcinoma.

148

149

3.5. Multivariate analysis

150 For all HNC combined, children aged 1-4 years and with metastatic disease had a significant
151 risk of death compared to those of another age group and with non-metastatic disease with
152 hazard ratios of 2.2 (CI95%: 1.6-2.9) and 2.7 (CI95%: 2.0-3.6), respectively. In metastatic
153 HNC, the proportion of children aged 1-4 years with soft tissue sarcoma, for which the lowest
154 5-year OS was observed (Table 8B), was higher compared to the other age group (<1 year:
155 3.8%, 1-4 years: 42.5%, 5-9 year: 31.2%, 10-14 year: 22.5%).

156

4. Discussion

158 This study describes the incidence and the overall survival of children with head and neck
159 cancers in France during the 2000-2015 period, based on national population-based cancer
160 registry data.

161 The study data displayed that 5.6% of all children with cancer in France were affected by HNC.
162 The HNC incidence was stable over the considered period, with an annual ASR of 8.6 cases per
163 million children. The predominant malignant entities contributing to childhood HNC were
164 thyroid carcinomas, rhabdomyosarcomas and Burkitt lymphomas. The leading tumor sites were
165 thyroid gland, soft-tissue and nasopharynx. Highest proportions of girls were found for GCT
166 and thyroid carcinoma. Differences in age groups were observed with GCT and neuroblastoma
167 especially in youngest children and carcinomas among the oldest. A high proportion of children
168 with cancer in this location survived with a 5-year OS of 87.7% [CI95%: 85.9-89.2].

169 The main strength of this study resides in the national registry-based, prospective cohort design.
170 The national coverage and the long study period enabled to estimate precisely incidence and
171 survival rates, and trends over time, based on a large number of head and neck cancer cases.

172 The comparisons with other study results are however limited by the fact that no consensual
173 definition of « head and neck cancer » exists to date. Previous studies had different inclusion

174 criteria, especially in terms of histological categories and tumor sites [1,3,5,21]. In accordance
175 to global literature delineating common pediatric head and neck malignancies as lymphomas
176 and all solid tumors [22], the present study proposes a consensus to adopt standard
177 recommendations in selection of head and neck cases, particularly in the exclusion of
178 retinoblastoma (ICCC-3 group V) and CNS tumors (ICCC-3 group III) [13], and in the
179 inclusion of the lymphomas only if they involved head and neck area. Population-based
180 registries are useful for determining cancer epidemiology, but the lack of some clinical data
181 (granularities of histological subtypes, details on treatments, responses to each line of
182 treatment) may make interpretation of their results difficult. In the future, the French Childhood
183 Cancer Observation Platform (CCOP), a nationwide infrastructure based on the National
184 population-based Registry of Childhood Cancers (RNCE) and medico-administrative databases
185 will enable in-depth survival analyses by providing complementary information on specimens
186 stored in the hospital biobanks and data on treatments, including doses of chemotherapy and
187 radiotherapy [23].

188 Our proportions of head and neck Hodgkin lymphomas (HL) and Non-Hodgkin lymphomas
189 (NHL) were lower than those observed in the United-States (US) [3,4]: 1.2% versus 13.8% and
190 5.5% versus 10.0%, respectively. But neck and lymph nodes (not included in the present study)
191 were the main anatomic topography in two American studies: 41% [1] and 61% [3]. Conversely
192 and surprisingly, our proportion of head and neck RMS was higher than those observed in the
193 US [3,4]: 23.9% versus 7.3%, respectively. Compared to 2 population-based registries in
194 European countries (Germany and Denmark) [4], most proportions were similar, except for
195 head and neck NHL in Germany (20.8% vs 5.5% in our study) [4,5]. The proportion of
196 lymphomas may be under or overestimated, since studies excluded this malignancy totally or
197 partially, because they were nonspecific HNC [4].

198 Incidence rates vary from 5.0 per million children in Denmark for 1978-2014 [21], to 16.0 in
199 the US for 2007-2009 [3], depending on the inclusion and exclusion criteria. No time variation
200 in HNC incidence was observed in the present study. In Denmark, Grønhøj et al [21] reported
201 a significant annual increase of 2.2% (95%CI, 0.8-3.7%) during 1978-2014 among children
202 with HNC, explained by a rise mainly of sarcomas, where rhabdomyosarcomas accounted for
203 61.6%. A similar trend of increasing rates of pediatric HNC has been observed in the US
204 between 1973 and 2010 [3], which is proportional to the overall cancer increase in children.

205 Sex and age variations in HNC are consistent compared to all childhood primary cancers in
206 France [24]: a female predominance is particularly seen for thyroid carcinomas and extracranial
207 and extragonadal GCT, highest proportion of young children are found for neuroblastoma and
208 extracranial and extragonadal GCT, and carcinomas occur most often in older children.

209 Considering the 5-year OS rates, our results were comparable to those reported in France during
210 the 2000-2015 period for all childhood primary cancers [24]. However, marked differences
211 between head and neck location and all sites for neuroblastomas (5-year OS: 91.0%
212 [CI95%:82.0-95.6] versus 76.1% [CI95% 74.3-77.9], respectively) and bone Ewing tumor (5-
213 year OS: 85.0% [CI95%:67.6-93.5] versus 75.1% [CI95% 71.3-78.4], respectively (Table 5)).

214 The best survival observed in head and neck neuroblastomas can be explained by two factors:
215 the slightly higher proportion of children aged less than one year (44.4% versus 38.5% for all
216 neuroblastomas) [24] and the lower proportion of metastatic stage (18.5%) while the metastatic
217 stages in all neuroblastomas represent 39% in a recent European study [25]. Our results are in
218 line with those reported by an American study which showed a higher disease-specific death
219 risk for adrenal locations than for head and neck location (adjusted hazard ratio= 2.9; 95%CI,
220 1.5-5.3) [26]. Compared to non-head and neck sites, we reported higher 5-year OS for children
221 with head and neck Ewing sarcoma. These survival disparities may be due to differences in
222 tumor size or metastatic rate. Ellis et al [27] have reported that head and neck Ewing sarcomas

223 were more commonly less than 5cm (61% vs 24%) and presented more commonly with
224 local/regional disease (82% vs 66%) with impact on prognosis.

225 Although there are few studies analyzing survival in children with HNC, our 5-year survival
226 rates were similar to those observed in Europe for thyroid cancer [8], in the US for head and
227 neck neuroblastoma [26] and for head and neck melanoma [28].

228 In our study, the overall survival among children with HNC incidence was stable over time.
229 Probably the number of our cohort prevents to depict some small outcome variations, as in
230 pediatric nasopharyngeal carcinoma [29]. It is already known that some tumors with
231 intermediate survivals has not outcome improvement over time as osteosarcoma [30]. Some
232 other studies have reported a stable outcome in large other series as RMS in favorable [31] or
233 unfavorable head and neck sites [32].

234

235 **5. Conclusion**

236 Childhood HNC are of varied natures, have a low incidence, are often poorly described in terms
237 of natural evolution and optimal treatment, and frequently involve functionally or vitally
238 important anatomic structures [33]. Epidemiological data on HNC distribution, incidence and
239 survival reported in this report contributes to our understanding of these tumors by quantifying
240 their impact on the French population and assessing their burden. Regarding to the exclusion
241 of topographies and some histological origins performed by some authors, we recommend that
242 HNC studies should include all locations that are part of this region, except for central nervous
243 system tumors, retinoblastomas, and all nodal or extranodal lymphomas without involvement
244 of head and neck area. Therefore, this report could become the starting point for future HNC
245 epidemiological studies.

246

247 **Authors' contributions**

248 All named authors have participated in the study to a sufficient extend to be named as authors.
249 All authors were involved in the study design and analysis plan. All authors critically reviewed
250 the study results, commented on the drafts, and approved the final manuscript.

251

252 **Declaration of Competing Interest**

253 None declared.

254

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261

262 **Ethical Approval**

263 This study was performed at the French National Registry of Childhood Cancer, CRESS Team
264 7, UMR-S 1153, Inserm, Paris-Descartes University, CHRU Nancy, France. Ethical approval
265 was granted by the French National Commission on Informatics and Freedoms (Number
266 900183 for the French National Registry of Childhood Solid Tumors and Number 998198 for
267 the French National Registry of Childhood Hematological Malignancies), providing all patients
268 have expressed their opposition before registration in the French National Registry of
269 Childhood Cancer database.

270

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396 **Table 1.** Topographic codes used to identify Head and Neck Cancer cases [12].

397 *Abbreviations:* ICD-O-3, International Classification of Diseases for Oncology, Third Edition.

398

399 **Table 2.** Characteristics of children with multiple head and neck primary cancers (France,
400 2000-2015).

401 *Abbreviations:* H&N, Head and Neck.

402

403 **Table 3.** Childhood head and neck cancer characteristics (France, 2000-2015).

404 *Abbreviations:* M/F ratio, ratio of male over female cases; SD, Standard deviation; UCNT:

405 Undifferentiated carcinoma of nasopharyngeal type; NRSTS: Non-rhabdomyosarcoma soft-
406 tissue sarcomas

407

408 **Table 4.** Annual standardized incidence rates of head and neck cancers per million children by
409 ICCC-3 diagnostic groups and subgroups in France (2000-2015) by gender.

410 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition; ASR,
411 Age-Standardized rate; 95%CI, 95% confidence interval.

412

413 **Table 5.** One-year and 5-year overall survival (OS) among children with head and neck cancers
414 by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2015 and comparison to all
415 childhood cancer.

416 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition; OS,

417 Overall Survival; 95%CI, 95% confidence interval; pPNET, peripheral primitive

418 neuroectodermal tumor.

419

420 **Table 6.** Five-year overall survival (OS) for French children diagnosed with head and neck
421 cancers, by period of diagnosis (2000-2007, and 2008-2015).

422 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition; OS,
423 Overall Survival; 95%CI, 95% confidence interval; pPNET, peripheral primitive
424 neuroectodermal tumor

425 * Logrank test

426

427 **Table 7.** Stage of childhood head and neck cancer by ICCC-3 diagnostic groups and subgroups:
428 France, 2000 to 2015.

429 (A) Lymphomas.

430 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition

431 (B) Solid tumors.

432 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition;
433 pPNET, peripheral primitive neuroectodermal tumor; M0, absence of distant metastasis; M+
434 presence of metastasis.

435

436 **Table 8.** Five-year overall survival (OS) by stage for childhood head and neck cancer: France,
437 2000 to 2015.

438 (A) Lymphomas.

439 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition;
440 95%CI, 95% confidence interval.

441 * Logrank test

442 (B) Solid tumors.

443 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition;
444 pPNET, peripheral primitive neuroectodermal tumor; 95%CI, 95% confidence interval; M0,
445 absence of distant metastasis; M+ presence of metastasis.

446 * Logrank test

Table 1

Topographic codes used to identify head and neck cancer cases [12].

Topography	ICD-O-3 site code [12]
Orbit and adnexa (lacrima gland)	C69.5, C69.6
Middle ear	C30.1
Nasal cavity	C30.0
Accessory sinuses (paranasal sinuses)	C31
Lips, oral cavity and pharynx	
- Lips	C00
- Mouth cavity	C02, C03, C04, C05, C06
- Oropharynx	C01, C09, C10
- Nasopharynx	C11
- Hypopharynx	C12, C13
- Other and ill-defined sites	C14
Larynx	C32
Trachea	C33
Head and neck	
- Soft tissues	C49.0
- Bones	C41.0-1
- Skin	C44.0-4
- Peripheral nerves	C47.0
- Other ill-defined sites	C76.0
Salivary glands	
- Parotid gland	C07
- Other and unspecified major salivary glands	C08
Thyroid gland	C73
Parathyroid gland	C75.0
Glomus (carotid body & glomus jugulare)	C75.4, C75.5 (only jugulare)

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, Third Edition.

Table 2

Characteristics of children with multiple head and neck primary cancers (France, 2000-2015).

Children	Gender	Genetic abnormalities	Age at diagnosis	Diagnoses	Follow-up: Alive or Dead (age at death)
n°1	Female	Xeroderma pigmentosum	9 years	Cutaneous basal cell carcinoma	Alive
			11 years	Cutaneous melanoma	
n°2	Male		1 year	H&N soft-tissue Rhabdomyosarcoma	Dead (11 years)
			6 years	Post-radiation maxilla osteosarcoma	
n°3	Male		5 years	H&N soft-tissue Rhabdomyosarcoma	Dead (9 years)
			11 years	Post-radiation temporal osteosarcoma	
n°4	Female	Xeroderma pigmentosum	5 years	Cutaneous squamous cell carcinoma	Alive
			8 years	Cutaneous basal cell carcinoma	

Abbreviations: H&N, Head and Neck.

Table 3

Childhood head and neck cancer characteristics (France, 2000-2015).

Anatomic site	Morphology	n	%	M/F ratio	Age (Year)	
					Mean	(SD)
Head and neck		541	33.3	1.2	6.3	(4.6)
Bone		114	7.0	1.4	8.4	(3.9)
	Ewing sarcoma	36	2.2	1.6	7.4	(3.8)
	Chordoma	25	1.5	1.1	10.2	(2.8)
	Osteosarcoma	20	1.2	1.2	10.6	(3.2)
	Other malignancies	33	2.0	1.8	6.8	(4.2)
Skin		103	6.3	1.2	8.5	(4.1)
	Melanoma	46	2.8	1.7	8.5	(4.6)
	Basal cell carcinoma	25	1.5	0.7	9.6	(2.9)
	Other malignancies	32	2.0	1.1	7.6	(3.9)
Peripheral nerve		74	4.6	0.9	2.2	(3.3)
	Neuroblastoma	69	4.3	1.0	1.5	(2.2)
	Other malignancies	5	0.3	0.0	11.0	(2.8)
Soft tissue		250	15.4	1.3	5.6	(4.3)
	Rhabdomyosarcoma	148	9.1	1.3	5.6	(3.8)
	NRSTS	82	5.1	1.2	6.2	(5.0)
	Other malignancies	20	1.2	1.0	3.3	(4.2)
Thyroid gland		431	26.6	0.5	10.5	(3.6)
	Adenocarcinomas	424	26.1	0.5	10.6	(3.6)
	Other malignancies	7	0.4	0.5	9.0	(5.6)
Pharynx		278	17.1	2.4	8.4	(3.9)
Nasopharynx		176	10.8	2.3	8.8	(4.1)
	UCNT	55	3.4	2.7	12.4	(2.2)
	Burkitt lymphomas	51	3.1	4.7	8.2	(3.4)
	Rhabdomyosarcoma	39	2.4	1.4	5.8	(3.5)
	Large B-cell diffuse lymphomas	9	0.6	0.5	7.4	(3.3)
	Other malignancies	22	1.4	1.8	7.1	(4.7)
Oropharynx		92	5.7	2.7	7.5	(3.3)
	Burkitt lymphomas	56	3.5	4.6	7.4	(2.8)
	Large B-cell diffuse lymphomas	20	1.2	1.0	8.5	(2.8)
	Other malignancies	16	1.0	2.2	6.6	(4.9)
Hypopharynx or pharynx not specified		10	0.6	2.3	8.6	(3.9)
	Burkitt lymphomas	3	0.2	2.0	8.7	(3.2)
	Hodgkin lymphomas	3	0.2	2.0	11.7	(2.3)
	Other malignancies	4	0.2	3.0	6.3	(4.3)
Orbit and adnexa		111	6.8	1.4	5.6	(4.0)
	Rhabdomyosarcoma	94	5.8	1.5	5.9	(3.9)
	Other malignancies	17	1.0	0.9	3.9	(4.1)

Table 3 (Continued)

Localization	Morphology	n	%	M/F ratio	Age (Year)	
					Mean	(SD)
Salivary glands (parotid gland and other major glands)		102	6.3	0.7	10.2	(3.3)
	Acinar cell carcinoma	22	1.4	0.2	11.9	(1.6)
	Rhabdomyosarcoma	17	1.0	1.8	6.8	(3.5)
	Adenocarcinoma	9	0.6	0.3	11.8	(2.0)
	Other malignancies	20	1.2	2.8	9.6	(4.0)
	Mucoepidermoid carcinoma	34	2.1	0.5	10.7	(2.6)
Accessory sinuses (paranasal sinuses)		57	3.5	2.0	7.0	(4.0)
	Rhabdomyosarcoma	37	2.3	2.4	7.0	(4.1)
	Burkitt lymphomas	9	0.6	8.0	6.6	(3.0)
	Other malignancies	11	0.7	0.6	7.1	(4.7)
Lips and oral cavity		51	3.1	1.0	8.0	(5.0)
	Rhabdomyosarcoma	18	1.1	1.0	5.4	(5.0)
	Mucoepidermoid carcinoma	10	0.6	1.5	12.0	(2.2)
	Other malignancies	23	1.4	0.8	8.2	(4.8)
Nasal cavity and Middle ear		47	2.9	1.8	7.6	(4.4)
	Rhabdomyosarcoma	27	1.7	2.0	6.1	(3.9)
	Esthesioneuroblastoma	8	0.5	0.3	8.8	(5.5)
	Other malignancies	12	0.7	5.0	10.3	(3.2)
Larynx and Trachea		5	0.3	1.5	10.6	(4.5)
	Rhabdomyosarcoma	2	0.1	1.0	8.0	(7.1)
	Other malignancies	3	0.2	2.0	12.3	(2.1)
Total		1623	100.0	1.1	8.1	(4.5)

Abbreviations: M/F ratio, ratio of male over female cases; SD, Standard deviation; UCNT: Undifferentiated carcinoma of nasopharyngeal type; NRSTS: Non-rhabdomyosarcoma soft-tissue sarcomas

Table 4

Annual standardized incidence rates of head and neck cancers per million children by ICCC-3 diagnostic groups and subgroups in France (2000-2015) by gender.

ICCC-3 diagnostic groups and subgroups	Both genders			Boys			Girls		
	N	%	ASR (10 ⁶) [95%CI]	N	ASR (10 ⁶) [95%CI]	N	ASR (10 ⁶) [95%CI]	N	ASR (10 ⁶) [95%CI]
II. Lymphoma	250	15.4	1.3 [1.1-1.6]	183	1.9 [1.4-2.4]	67	0.7 [0.5-1.1]		
IIa. Hodgkin lymphoma	20	1.2	0.1 [0.0-0.2]	16	0.2 [0.1-0.4]	4	0.0 [0.0-0.2]		
IIb. Non-Hodgkin lymphoma	90	5.5	0.5 [0.3-0.7]	53	0.5 [0.3-0.9]	37	0.4 [0.2-0.7]		
IIc. Burkitt lymphoma	140	8.6	0.7 [0.6-1.0]	114	1.2 [0.9-1.7]	26	0.3 [0.1-0.6]		
IV. Neuroblastoma	81	5.0	0.5 [0.3-0.7]	38	0.5 [0.3-0.9]	43	0.5 [0.3-0.9]		
VIII. Malignant bone tumors	94	5.8	0.5 [0.3-0.7]	53	0.5 [0.3-0.9]	41	0.4 [0.2-0.7]		
IX. Soft tissue sarcomas	512	31.5	2.9 [2.4-3.4]	296	3.3 [2.6-4.1]	216	2.5 [1.9-3.2]		
IXa. Rhabdomyosarcoma	388	23.9	2.2 [1.8-2.7]	232	2.6 [2.0-3.3]	156	1.8 [1.3-2.4]		
X. Germ-cell tumors	27	1.7	0.2 [0.1-0.3]	7	0.1 [0.0-0.3]	20	0.3 [0.1-0.6]		
XI. Carcinomas and melanomas	656	40.4	3.3 [2.8-3.8]	258	2.5 [2.0-3.2]	398	4.0 [3.4-4.8]		
XIb. Thyroid carcinomas	424	26.1	2.1 [1.8-2.5]	140	1.4 [1.0-1.9]	283	2.9 [2.3-3.5]		
XIc. Nasopharyngeal carcinomas	58	3.6	0.3 [0.2-0.4]	42	0.4 [0.3-0.7]	16	0.2 [0.1-0.4]		
XIfi. Carcinomas of salivary glands	66	4.1	0.3 [0.2-0.5]	18	0.2 [0.1-0.4]	48	0.5 [0.3-0.9]		
Total	1623	100.0	8.6 [7.8-9.5]	837	8.8 [7.7-10.1]	786	8.5 [7.3-9.7]		

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; ASR, Age-Standardized rate; 95%CI, 95% confidence interval.

Table 5

One-year and 5-year overall survival (OS) among children with head and neck cancers by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2015 and comparison to all childhood cancer.

ICCC-3 diagnostic groups and subgroups	N	1-year OS		5-year OS		5-year OS for all sites [24]	
		%	[95%CI]	%	[95%CI]	%	[95%CI]
II. Lymphoma	250	97.2	[94.2-98.6]	94.6	[90.9-96.8]	94.2	[93.3-95.0]
IIa. Hodgkin lymphoma	20	100.0	[-]	93.3	[61.3-99.0]	97.6	[96.6-98.3]
IIb. Non-Hodgkin lymphoma	90	94.4	[87.1-97.6]	92.0	[84.0-96.1]	89.6	[87.4-91.4]
IIb1. Precursor-cell lymphoma	34	97.1	[80.9-99.6]	97.1	[80.9-99.6]		
IIb2. Mature B-cell lymphoma (except Burkitt)	40	95.0	[81.5-98.7]	92.4	[78.3-97.5]		
IIc. Burkitt lymphoma	140	98.6	[94.4-99.6]	96.3	[91.4-98.5]	94.0	[92.0-95.5]
IV. Neuroblastoma	81	98.8	[91.6-99.8]	91.0	[82.0-95.6]	76.1	[74.3-77.9]
VIII. Malignant bone tumors	94	91.3	[83.4-95.6]	77.9	[67.8-85.1]	73.8	[71.3-76.2]
VIIIa. Osteosarcoma	20	85.0	[60.4-94.9]	65.0	[40.3-81.5]	71.0	[67.1-74.5]
VIIIc. Ewing tumor and related sarcomas of bone	36	97.1	[80.9-99.6]	85.0	[67.6-93.5]	75.1	[71.3-78.4]
VIII d. Other malignant bone tumors	30	96.7	[78.6-99.5]	86.0	[66.9-94.5]		
VIII d2. Chordoma	25	96.0	[74.8-99.4]	83.1	[60.9-93.3]		
IX. Soft tissue sarcomas	512	90.4	[87.5-92.6]	72.7	[68.6-76.4]	72.5	[70.3-74.6]
IXa. Rhabdomyosarcoma	388	91.2	[87.9-93.6]	74.1	[69.3-78.2]	72.9	[69.9-75.6]
IXd. Other specified soft tissue sarcomas	86	85.9	[76.5-91.7]	64.2	[53.0-73.5]	70.7	[66.6-74.4]
IXd2. pPNET of soft tissue	26	96.0	[74.8-99.4]	83.6	[62.0-93.5]		
IXd3. Extrarenal rhabdoid tumor	24	62.5	[40.3-78.4]	28.6	[12.4-47.2]		
X. Head and Neck Germ-cell tumors	27	100.0	[-]	100.0	[-]	94.0	[92.3-95.3]
XI. Carcinomas and melanomas	654	98.8	[97.5-99.4]	96.8	[95.1-97.9]	93.2	[91.3-94.6]
XIb. Thyroid carcinomas	423	99.5	[98.1-99.9]	98.8	[97.1-99.5]	99.0	[97.2-99.6]
XIc. Nasopharyngeal carcinomas	58	96.6	[86.9-99.1]	91.3	[80.3-96.3]		
XId. Malignant melanomas	48	97.9	[86.1-99.7]	88.7	[74.9-95.2]	88.0	[82.0-92.1]
XIe. Skin carcinomas	32	100.0	[-]	100.0	[-]		
XIf. Other and unspecified malignant carcinomas	94	96.8	[90.3-98.9]	94.6	[87.5-97.7]		
XI f1. Carcinomas of salivary glands	66	100.0	[-]	98.4	[89.4-99.8]		
XII. Other malignant neoplasms	3	66.7	[5.4-94.5]	66.7	[5.4-94.5]		
Total	1619	95.4	[94.3-96.4]	87.7	[85.9-89.2]	82.8	[82.4-83.3]

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; OS, Overall Survival; 95%CI, 95% confidence interval; pPNET, peripheral primitive neuroectodermal tumor.

Table 6

Five-year overall survival (OS) for French children diagnosed with head and neck cancers, by period of diagnosis (2000-2007, and 2008-2015).

ICCC-3 diagnostic groups and subgroups	2000-2007			2008-2015			P-value*
	N	5-year OS		N	5-year OS		
		%	[95%CI]		%	[95%CI]	
II. Lymphoma	127	93.7	[87.7-96.8]	123	95.4	[89.1-98.1]	0.32
IIa. Hodgkin lymphoma	7	100.0	[-]	13	87.5	[38.7-98.1]	
IIb. Non-Hodgkin lymphoma	53	92.4	[81.0-97.1]	37	91.0	[74.2-97.0]	0.95
IIb1. Precursor-cell lymphoma	17	94.1	[65.0-99.2]	17	100.0	[-]	
IIb2. Mature B-cell lymphoma (except Burkitt)	27	92.6	[73.5-98.1]	13	92.3	[56.6-98.9]	
IIc. Burkitt lymphoma	67	94.0	[84.9-97.7]	73	98.6	[90.4-99.8]	0.11
IV. Neuroblastoma	36	97.2	[81.9-99.6]	45	85.8	[71.0-93.4]	0.29
VIII. Malignant bone tumors	44	81.8	[66.9-90.5]	50	74.1	[58.8-84.5]	0.26
VIIIa. Osteosarcoma	7	71.4	[25.8-92.0]	13	61.5	[30.8-81.8]	
VIIIc. Ewing tumor and related sarcomas of bone	16	87.5	[58.6-96.7]	20	83.3	[56.8-94.3]	
VIII d. Other malignant bone tumors	18	83.3	[56.8-94.3]	12	91.7	[53.9-98.8]	
VIII d2. Chordoma	15	80.0	[50.0-93.1]	10	90.0	[47.3-98.5]	
IX. Soft tissue sarcomas	249	73.1	[67.1-78.1]	263	72.4	[66.3-77.5]	0.91
IXa. Rhabdomyosarcoma	196	74.5	[67.7-80.0]	192	73.8	[66.7-79.8]	0.79
IXd. Other specified soft tissue sarcomas	34	64.7	[46.3-78.2]	52	63.8	[48.7-75.5]	0.89
IXd2. pPNET of soft tissue	10	90.0	[47.3-98.5]	16	79.0	[47.9-92.7]	
IXd3. Extrarenal rhabdoid tumor	9	22.2	[3.4-51.3]	15	32.0	[10.9-55.7]	
X. Head and Neck Germ-cell tumors	11	100.0	[-]	16	100.0	[-]	1.00
XI. Carcinomas and melanomas	330	95.4	[92.4-97.2]	324	98.3	[96.1-99.3]	0.08
XIb. Thyroid carcinomas	213	98.6	[95.6-99.5]	210	98.9	[95.8-99.7]	0.43
XIc. Nasopharyngeal carcinomas	28	89.3	[70.4-96.4]	30	93.3	[75.9-98.3]	0.62
XId. Malignant melanomas	28	81.5	[61.2-91.9]	20	100.0	[-]	
XIe. Skin carcinomas	17	100.0	[-]	15	100.0	[-]	
XIf. Other and unspecified malignant carcinomas	45	91.1	[77.9-96.5]	49	97.9	[85.8-99.7]	0.14
XIf1. Carcinomas of salivary glands	29	100.0	[-]	37	97.2	[81.9-99.6]	0.81
XII. Other malignant neoplasms	3	66.7	[5.4-94.5]	0	-	[-]	-
Total	800	87.3	[84.8-89.5]	819	87.6	[85.0-89.7]	0.72

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; OS, Overall Survival; 95%CI, 95% confidence interval; pPNET, peripheral primitive neuroectodermal tumor

* Logrank test

Table 7

Stage of childhood head and neck cancer by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2015. (A) Lymphomas. (B) Solid tumors.

A

ICCC-3 diagnostic groups and subgroups	Missing		Stage I		Stage II		Stage III		Stage IV	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
II. Lymphoma	1	(0.4)	71	(28.4)	96	(38.4)	40	(16.0)	42	(16.8)
IIa. Hodgkin lymphoma	0	(0.0)	6	(30.0)	12	(60.0)	1	(5.0)	1	(5.0)
IIb. Non-Hodgkin lymphoma	0	(0.0)	27	(30.3)	36	(40.4)	16	(18.0)	10	(11.2)
IIb1. Precursor-cell lymphoma	0	(0.0)	6	(17.6)	17	(50.0)	6	(17.6)	5	(14.7)
IIb2. Mature B-cell lymphoma except Burkitt	1	(2.6)	17	(43.6)	12	(30.8)	7	(17.9)	3	(7.7)
IIc. Burkitt lymphoma	0	(0.0)	38	(27.1)	48	(34.3)	23	(16.4)	31	(22.1)

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition

B

ICCC-3 diagnostic groups and subgroups	Stage M0		Stage M+	
	N	(%)	N	(%)
IV. Neuroblastoma	66	(81.5)	15	(18.5)
VIII. Malignant bone tumors	88	(93.6)	6	(6.4)
VIIIa. Osteosarcoma	18	(90.0)	2	(10.0)
VIIIc. Ewing tumor and related sarcomas of bone	32	(88.9)	4	(11.1)
VIIId. Other malignant bone tumors	30	(100.0)	0	(0.0)
VIIId2. Chordoma	25	(100.0)	0	(0.0)
IX. Soft tissue and other extraosseous sarcomas	432	(84.4)	80	(15.6)
IXa. Rhabdomyosarcoma	316	(81.4)	72	(18.6)
IXd. Other specified soft tissue sarcomas	79	(91.9)	7	(8.1)
IXd2. pPNET of soft tissue	24	(92.3)	2	(7.7)
IXd3. Extrarenal rhabdoid tumor	20	(83.3)	4	(16.6)
X. Head and Neck Germ-cell tumors	26	(96.3)	1	(3.7)
XI. Carcinomas and melanomas	621	(94.7)	35	(5.3)
XIb. Thyroid carcinomas	396	(93.6)	27	(6.4)
XIc. Nasopharyngeal carcinomas	52	(89.7)	6	(10.3)
XId. Malignant melanomas	46	(95.8)	2	(4.2)
XIe. Skin carcinomas	33	(100.0)	0	(0.0)
XIf. Other and unspecified	94	(100.0)	0	(0.0)
XIf1. Carcinomas of salivary glands	66	(100.0)	0	(0.0)
XII. Other and unspecified malignant neoplasms	3	(100.0)	0	(0.0)
Total	1236	(90.0)	137	(10.0)

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; pPNET, peripheral primitive neuroectodermal tumor; M0, absence of distant metastasis; M+ presence of metastasis.

Table 8

Five-year overall survival (OS) by stage for childhood head and neck cancer: France, 2000 to 2015. (A) Lymphomas. (B) Solid tumors.

A

ICCC-3 diagnostic groups and subgroups	Stage I-II 5-year OS		Stage III-IV 5-year OS		P-value*
	%	[95%CI]	%	[95%CI]	
II. Lymphoma	96.2	[91.8-98.3]	92.5	[84.0-96.6]	0.12
IIa. Hodgkin lymphoma	92.9	[59.1-99.0]	100.0	[-]	0.79
IIb. Non-Hodgkin lymphoma	95.0	[85.2-98.4]	88.5	[68.4-96.1]	0.40
IIb1. Precursor-cell lymphoma	100.0	[-]	90.9	[50.8-98.7]	0.15
IIb2. Mature B-cell lymphoma (except Burkitt)	96.6	[77.9-99.5]	90.0	[47.3-98.5]	0.71
IIc. Burkitt lymphoma	97.6	[90.9-99.4]	94.3	[83.4-98.1]	0.12

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; 95%CI, 95% confidence interval.

* Logrank test

B

ICCC-3 diagnostic groups and subgroups	Stage M0 5-year OS		Stage M+ 5-year OS		P-value*
	%	[95%CI]	%	[95%CI]	
IV. Neuroblastoma	98.5	[89.7-99.8]	60.0	[31.8-79.7]	<0.01
VIII. Malignant bone tumors	80.6	[70.3-87.7]	66.7	[19.5-90.4]	0.25
IX. Soft tissue and other extraosseous sarcomas	76.3	[71.9-80.1]	53.1	[41.5-63.4]	<0.01
IXa. Rhabdomyosarcoma	77.8	[72.7-82.1]	57.7	[45.3-68.2]	<0.01
X. Head and Neck Germ-cell tumors	100.0	[-]	100.0	[-]	-
XI. Carcinomas and melanomas	97.5	[95.9-98.5]	85.3	[68.1-93.6]	<0.01
XIb. Thyroid carcinomas	98.9	[97.2-99.6]	91.5	[69.6-97.8]	0.02
XII. Other and unspecified malignant neoplasms	66.7	[5.4-94.5]	-	[-]	-
Total	88.7	[86.7-90.4]	63.0	[54.2-70.5]	<0.01

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third Edition; pPNET, peripheral primitive neuroectodermal tumor; 95%CI, 95% confidence interval; M0, absence of distant metastasis; M+ presence of metastasis.

* Logrank test