

# TUMOURS OF THE CENTRAL NERVOUS SYSTEM

**100%**  
OF CENTRAL NERVOUS SYSTEM TUMOURS ARE RARE

## INCIDENCE

**3 725**

ESTIMATED NEW CASES  
ITALY, 2015

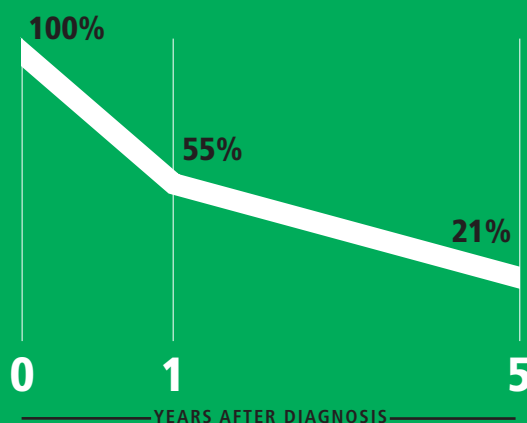
**3 588** TUMOURS OF THE CENTRAL NERVOUS SYSTEM  
**137** EMBRYONAL TUMOURS OF THE CENTRAL NERVOUS SYSTEM

## PREVALENCE

**26 610**

ESTIMATED PREVALENT CASES  
ITALY, 2010

## SURVIVAL





# INCIDENCE

**TUMOURS OF THE CENTRAL NERVOUS SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	AIRTUM POOL (period of diagnosis 2000-2010)														ITALY	
	RATE	95% CI	OBSERVED CASES (No.)	RARE CANCERS BY SITE (%)	SEX				AGE							ESTIMATED NEW CASES 2015
					MALE		FEMALE		0-54 yrs		55-64 yrs		65+ yrs			
					RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI		
<b>TUMOUR OF THE CENTRAL NERVOUS SYSTEM (CNS)</b>	<b>5.89</b>	<b>5.79-6.00</b>	<b>13 071</b>	<b>100%</b>	<b>6.99</b>	<b>6.84-7.15</b>	<b>4.87</b>	<b>4.74-4.99</b>	<b>3.17</b>	<b>3.08-3.26</b>	<b>11.64</b>	<b>11.24-12.05</b>	<b>11.67</b>	<b>11.36-12.00</b>	<b>3 725</b>	
<b>TUMOURS OF THE CNS</b>	<b>5.67</b>	<b>5.57-5.77</b>	<b>12 566</b>	<b>NA</b>	<b>6.70</b>	<b>6.54-6.85</b>	<b>4.70</b>	<b>4.58-4.83</b>	<b>2.86</b>	<b>2.77-2.94</b>	<b>11.58</b>	<b>11.18-11.99</b>	<b>11.62</b>	<b>11.30-11.94</b>	<b>3 588</b>	
Astrocytic tumours of the CNS	4.92	4.83-5.01	10 904		5.89	5.74-6.03	4.01	3.90-4.13	2.24	2.17-2.32	10.42	10.04-10.81	10.67	10.37-10.98	3 125	
Oligodendroglial tumours of the CNS	0.38	0.35-0.40	836		0.43	0.40-0.48	0.32	0.29-0.36	0.33	0.30-0.36	0.64	0.55-0.74	0.39	0.33-0.45	231	
Ependymal tumours of the CNS	0.23	0.21-0.25	504		0.24	0.21-0.27	0.21	0.19-0.24	0.23	0.21-0.26	0.29	0.23-0.36	0.18	0.14-0.22	139	
Neuronal and mixed neuronal-glioma tumours	NAV	NAV	NAV		NAV	-	NAV	-	NAV	-	NAV	-	NAV	-	NAV	
Choroid plexus carcinoma of the CNS	<0.01	0.00-0.01	13		NE	-	NE	-	NE	-	NE	-	NE	-	4	
Malignant meningiomas	0.13	0.12-0.15	299		0.12	0.10-0.14	0.15	0.13-0.17	0.05	0.04-0.06	0.22	0.17-0.29	0.37	0.32-0.43	86	
<b>EMBRYONAL TUMOURS OF THE CNS</b>	<b>0.23</b>	<b>0.21-0.25</b>	<b>505</b>	<b>NA</b>	<b>0.30</b>	<b>0.26-0.33</b>	<b>0.16</b>	<b>0.14-0.19</b>	<b>0.31</b>	<b>0.28-0.34</b>	<b>0.06</b>	<b>0.03-0.10</b>	<b>0.05</b>	<b>0.03-0.08</b>	<b>137</b>	

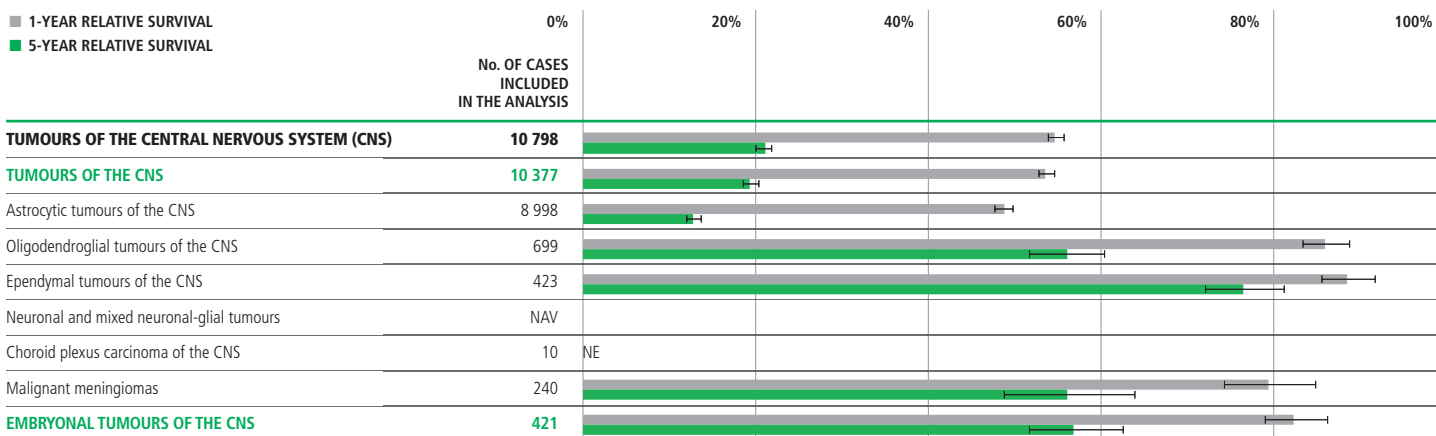
NE: not estimable because 15 or less incident cases were observed

NAV: not available

NA: not applicable

# SURVIVAL

**TUMOURS OF THE CENTRAL NERVOUS SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



NE: not estimable because 30 or less incident cases were observed

NAV: not available

# PREVALENCE

**TUMOURS OF THE CENTRAL NERVOUS SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration ( $\leq 2$ , 2-5,  $\leq 15$  years) prior to prevalence date (1<sup>st</sup> January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

	AIRTUM POOL								ITALY	
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE			ESTIMATED PREVALENT CASES 2010
	$\leq 2$ YEARS		2-5 YEARS		$\leq 15$ YEARS		PROPORTION	95% CI		
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI				
<b>TUMOURS OF THE CENTRAL NERVOUS SYSTEM (CNS)</b>	<b>7.19</b>	<b>6.64-7.78</b>	<b>4.28</b>	<b>3.86-4.74</b>	<b>19.14</b>	<b>18.23-20.08</b>	<b>45.66</b>	<b>42.34-48.98</b>	<b>26 610</b>	
<b>TUMOURS OF THE CNS</b>	<b>6.93</b>	<b>6.39-7.50</b>	<b>3.93</b>	<b>3.53-4.37</b>	<b>17.61</b>	<b>16.74-18.51</b>	<b>39.70</b>	<b>36.84-42.63</b>	<b>23 121</b>	
Astrocytic tumours of the CNS	5.46	4.98-5.97	2.22	1.92-2.55	11.47	10.77-12.21	28.98	26.30-31.66	16 882	
Oligodendroglial tumours of the CNS	0.91	0.72-1.13	0.72	0.56-0.93	2.82	2.47-3.19	3.45	3.01-3.89	1 973	
Ependymal tumours of the CNS	0.39	0.27-0.55	0.61	0.46-0.80	2.45	2.13-2.80	6.09	5.14-7.05	3 565	
Neuronal and mixed neuronal-glioma tumours	NAV	-	NAV	-	NAV	-	NAV	-	NAV	
Choroid plexus carcinoma of the CNS	NE	-	0.03	0.01-0.10	0.03	0.01-0.10	0.25	0.00-0.57	145	
Malignant meningiomas	0.17	0.10-0.28	0.35	0.23-0.50	0.85	0.67-1.07	1.21	0.93-1.49	701	
<b>EMBRYONAL TUMOURS OF THE CNS</b>	<b>0.26</b>	<b>0.17-0.40</b>	<b>0.35</b>	<b>0.24-0.50</b>	<b>1.53</b>	<b>1.28-1.81</b>	<b>5.93</b>	<b>4.29-7.56</b>	<b>3 489</b>	

NE: not estimable in observed prevalence if no cases were observed within  $\leq 2$ , 2-5,  $\leq 15$  years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

NAV: not available

Primary central nervous system tumours (CNS) are of ecto- and mesodermal origin and arise from the brain, cranial nerves, meninges, pituitary, pineal and vascular elements. The standard definition of CNS tumours is that of the 2007 WHO classification,<sup>1</sup> which is based on histological characteristics and lists approximately 100 subtypes of CNS malignancies in seven categories with different molecular biology, clinical behaviour, and, presumably, aetiology. Statistics on CNS tumours are estimated by grouping all malignancies arising in all CNS anatomic sites (ICD-10 topography codes C70-C72). However, rare tumours are more appropriately defined as a combination of topographical and morphological characteristics, according to the International Classification of Diseases for Oncology (ICD-O).

Thus, based on an adaptation of the WHO classification and further work by RARECAREnet:<sup>2</sup>

CNS tumours have been divided into:

- tumours of the CNS (major histological groups (astrocytic tumours, oligodendroglial tumours, ependymal tumours, neuronal and mixed neuronal-glial tumours, choroid plexus carcinoma, malignant meningiomas);
- embryonal tumours (including pineoblastoma).

The results presented in this section refer exclusively to malignant tumours of the CNS. Epidemiological features of the carcinomas of the pituitary gland are described in the endocrine tumours grouping.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

The aetiology of CNS tumours is not well established; common risk factors for other cancers (e.g., diet, smoking, physical activity, alcohol) do not seem to play a significant role. A relationship with exposure to chemical carcinogens has been reported, but the only environmental factor unequivocally associated with an increased risk is therapeutic irradiation, especially in children; exposure to non-ionizing radiation by cellular phones is controversial.<sup>3</sup> Finally, an increased risk is also attributed to hereditary syndromes.<sup>4</sup>

According to the WHO grading scheme, CNS tumours can be stratified by degree of malignancy:

Grade I: lesions with low proliferative potential and the possibility of cure by surgical resection alone;

Grade II: infiltrative neoplasms with low proliferative activity, but tendency to recur and progress to a higher grade;

Grade III: lesions with histological evidence of malignancy;

Grade IV: cytologically malignant, mitotically active, necrosis-prone, fatal neoplasms with rapid evolution.

**Astrocytomas** include a heterogeneous group of histotypes. WHO grade I refers to low-grade astrocytomas, such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. WHO Grade II includes infiltrating neoplasms such as pilomyxoid, diffuse, protoplasmic astrocytoma, as well as oligoastrocytoma. Negative prognostic factors include age  $\geq 40$  years, astrocytoma histology, maximum diameter  $\geq 6$  cm, baseline neurologic deficits, residual mass after surgery  $> 1$  cm. WHO Grade III includes anaplastic astrocytoma, which is (with glioblastoma, see next) one of the most common primary malignant brain tumours in adults.<sup>4</sup> WHO Grade IV includes glioblastoma (the most lethal brain tumour), gliosarcoma, and giant cell glioblastoma.

**Oligodendroglial tumours** express different levels of clinical aggressiveness: this category includes oligodendroglioma (WHO Grade II) and anaplastic oligodendroglioma (WHO Grade III), both deriving from the oligodendrocytic cell line. Highly prevalent cytogenetic alterations, namely mutations of the isocitrate dehydrogenase-1 (IDH1) and chromosomal arm 1p and 19q codeletion, are predictors of more favourable prognosis of these tumours.<sup>6</sup>

**Ependymal tumours** are derived from ependymal glial cells and include different subtypes, with varying degree of differentiation and malignancy: WHO Grade I: subependymoma, myxopapillary ependymoma; WHO Grade II/III: ependymoma NOS; WHO Grade III/IV: anaplastic ependymoma.

**Neuronal and mixed neuronal-glial tumours** are very rare and characterised by a variable degree of neuronal differentiation, with neoplastic neuronal cells alone (e.g., gangliocytoma) or mixed to neoplastic glial cells.

**Primary choroid plexus carcinomas** are rare aggressive WHO grade III tumours which usually occur in children under 12 years of age and account for nearly 20% of all choroid plexus tumours.<sup>4,7</sup> Since the choroid plexus is the neuroepithelial tissue that produces cerebrospinal fluid, these tumours are mostly located in the lateral ventricle (mainly in children) and less frequently in the fourth ventricle (mainly in adults).

**Malignant meningiomas** are WHO Grade III with a low tendency to metastasise but a high rate of recurrence and progression.<sup>4,8</sup> Higher grade meningiomas are often associated with neurofibromatosis type 2 (NF2) mutation, loss of chromosome 22, and additional chromosomal aberrations.<sup>6</sup> Prior radiation therapy to head and neck can be a risk factor.

**Embryonal tumours** include several tumours of embryonal origin – typically occurring in infants and young children – characterised by high malignancy and therefore classified as WHO Grade IV: medulloblastoma (MB) and its variants: e.g., desmoplastic/nodular-, anaplastic-, large cell-MB; primitive neuroectodermal tumours (PNETs) and variants: e.g., neuroblastoma, ganglioneuroblastoma, neuroepithelioma, medulloepithelioma; atypical teratoid/rhabdoid tumours (ATRTs).

**Pineoblastomas** are also included among embryonal tumours, although separately classified by WHO as pineal tumours (Grade IV). In summary: MBs, PNETs, ATRTs, and pineoblastomas probably represent biologically distinct entities, so the classification of embryonal tumours, currently debated, may be susceptible to further revisions.<sup>4</sup>

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

All CNS tumours are rare and are more frequent in males than in females, with an M/F ratio ranging from 1.14 to 1.81, with the sole exception of malignant meningiomas (M/F: 0.81). The most frequent histotype is astrocytoma – which accounts for 83% of the total –, followed by oligodendroglial tumours (6.4%), ependymal and embryonal tumours (both at 3.9%), and malignant meningiomas (2.3%).

Incidence of all tumours tends to increase after age 40 years, with a peak in the 65-75-year age group; however, astrocytomas and embryonal tumours also occur in young children. In particular, embryonal neoplasms in the first 15 years of age account for nearly

50% of all embryonal neoplasms at all ages. Among these, medulloblastomas – located exclusively in the cerebellum – are the most common (70%), followed by primitive neuroectodermal tumours (PNETs, 20%). Pineoblastoma (a malignant pineal parenchymal tumour) is very rare and accounts for less than 3% of all rare CNS tumours.

The Italian estimates for each subtype are fully in line with the corresponding European incidence estimates based on the RARECAREnet database ([www.rarecaren.net](http://www.rarecaren.net)).

The proportion of NOS cancer cases in the AIRTUM database in the study period (2000-2010) is estimated at 37%, with a differential distribution across age, ranging from 20% in the 0-24-year age group to 52% in the over 65 age group. This raises the issue of a potential underestimation of true incidence, mostly in the elderly, but does not jeopardise the overall description of the frequency of CNS tumours here presented.

## Survival

One and 5-year relative survival (RS) of CNS tumours is 55% and 21%, respectively. However, these results are strongly affected by astrocytic tumours, which are both the most common among these tumours and those with the worst survival (49% and 13% at 1 and 5 years, respectively). There is a striking difference in relative survival between each of the other CNS tumours and astrocytomas; namely, 5-year RS is 76% for ependymal tumours and 56%-57% for all other histotypes.

The poor prognosis of astrocytomas is at least partially explained by the high proportion (64%) of WHO grade IV tumours in this group. On the contrary, ependymal tumours and oligodendrogliomas have a high proportion of WHO grade II tumours (82% and 71%, respectively); oligodendrogliomas have a higher proportion of WHO grade III tumours compared to ependymal tumours, which can contribute to explain the estimated difference in survival between these two histotypes.

Italian estimates are in line with the corresponding European survival estimates based on the RARECAREnet database for most of the subtypes, with the only exceptions of astrocytomas (in which 1-year survival is 48% in Italy vs. 41% in Europe) and – to a lesser extent – oligodendroglial tumours. This finding is consistent with other reports where geographical differences have been measured;<sup>2</sup> whether this can be attributed to different case-mix, timeliness of diagnosis, access to treatment (especially radiotherapy) or is rather the effect of differential case selection or classification should be further investigated.

## Prevalence

About 27,000 persons were alive in Italy in 2010 with a past diagnosis of CNS tumours; of these, about 3,500 had an embryonal tumour of CNS in their clinical history, while the others had been diagnosed with any of the tumours of the CNS (astrocytic, oligodendroglial, ependymal, neuronal and mixed neuronal-glial, choroid plexus carcinoma, malignant meningioma). Astrocytic tumours were the most common among prevalent CNS cancers, followed by ependymal and oligodendroglial tumours.

The prevalence estimates well reflect the different incidence and survival of these tumours. Interestingly, very long-term survivors, those who survived more than 15 years after diagnosis, were on average 56% among prevalent cases of the heterogeneous group of tumours of the CNS, and 74% among cases of embryonal tumours of the CNS. A possible explanation for the proportion of long-term survivors is the high frequency of low-grade tumours which have a good prognosis.<sup>2</sup> The estimates here presented are slightly lower than those previously published in the AIRTUM prevalence monograph, mainly because undefined tumours (such as ICD-O M8000 and M8001) are not included in our definition.

## REFERENCES

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