RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY

8%
OF ALL TUMOURS OF THE THORACIC CAVITY ARE RARE EPITHELIAL TUMOURS

INCIDENCE

3 590
ESTIMATED NEW CASES
ITALY, 2015

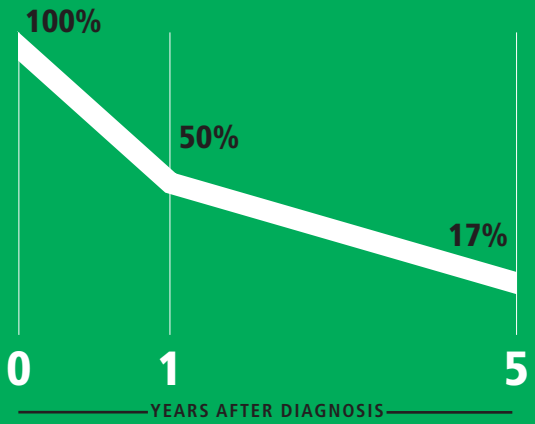
113	EPITHELIAL TUMOURS OF TRACHEA
1 699	RARE EPITHELIAL TUMOURS OF LUNG
232	EPITHELIAL TUMOURS OF THYMUS
1 546	MESOTHELIOMA OF PLEURA AND PERICARDIUM

95 %	OF RARE EPITHELIAL TUMOURS OUT OF ALL TUMOURS IN EACH SITE
4	
97	
74	

PREVALENCE

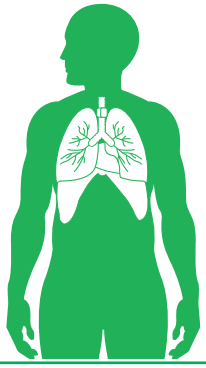
9 933
ESTIMATED PREVALENT CASES
ITALY, 2010

SURVIVAL



SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY



INCIDENCE

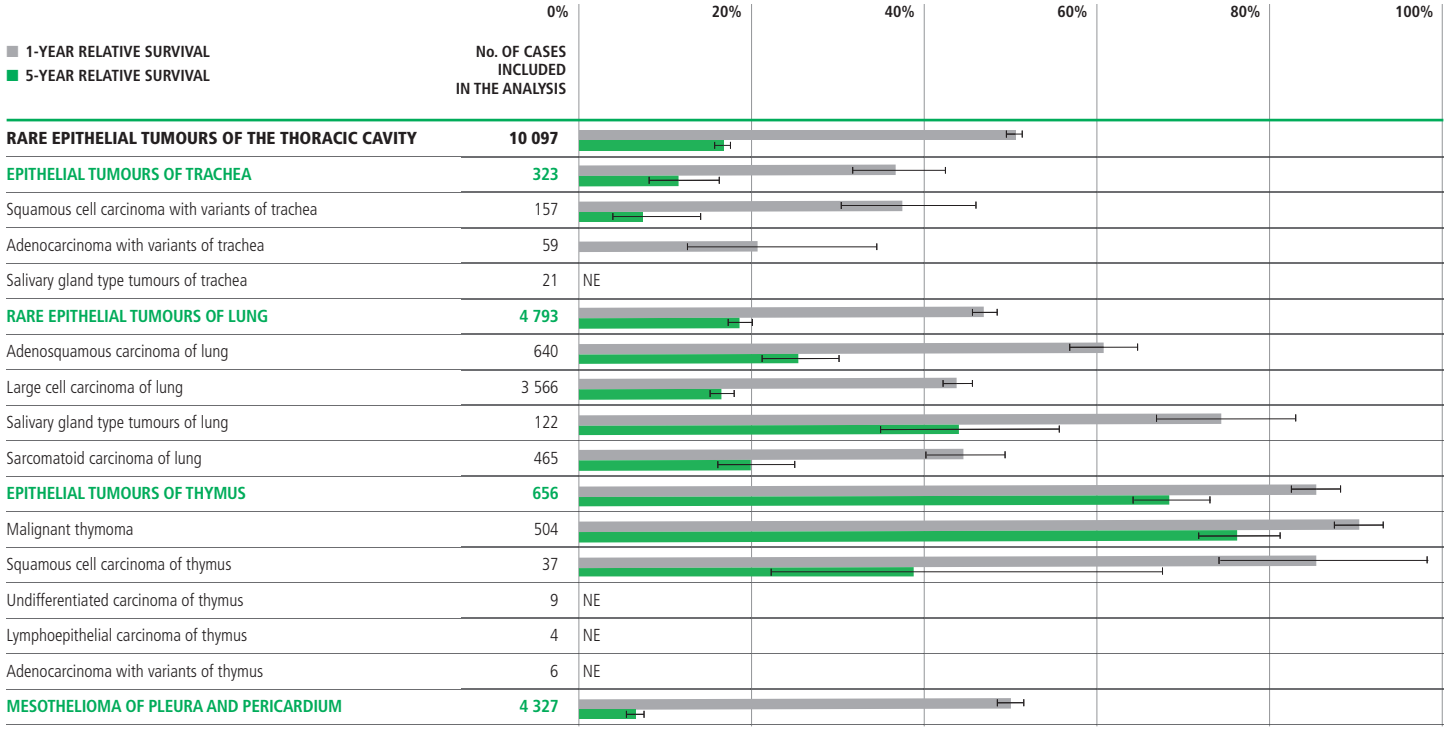
RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY. Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	AIRTUM POOL (period of diagnosis 2000-2010)														ITALY
					SEX				AGE						
					MALE		FEMALE		0-54 yrs		55-64 yrs		65+ yrs		
	RATE	95% CI	OBSERVED CASES (No.)	RARE CANCERS BY SITE (%)	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	ESTIMATED NEW CASES 2015
RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY	**5.42**	**5.33-5.52**	**12 027**	**8%**	**8.57**	**8.39-8.74**	**2.48**	**2.39-2.57**	**0.87**	**0.82-0.92**	**10.14**	**9.77-10.53**	**18.08**	**17.69-18.49**	**3 590**
EPITHELIAL TUMOURS OF TRACHEA	0.17	0.15-0.19	374	95%	0.27	0.24-0.30	0.07	0.06-0.09	0.03	0.02-0.04	0.33	0.27-0.41	0.55	0.48-0.62	113
Squamous cell carcinoma with variants of trachea	0.08	0.07-0.09	175		0.14	0.11-0.16	0.03	0.02-0.04	0.01	0.01-0.02	0.16	0.12-0.22	0.26	0.21-0.31	53
Adenocarcinoma with variants of trachea	0.03	0.02-0.04	64		0.05	0.04-0.06	0.01	0.01-0.02	<0.01	0.00-0.01	0.08	0.05-0.12	0.08	0.06-0.11	19
Salivary gland type tumours of trachea	0.01	0.01-0.02	26		0.01	0.01-0.02	0.01	0.01-0.02	<0.01	0.00-0.01	0.02	0.01-0.04	0.03	0.02-0.05	8
RARE EPITHELIAL TUMOURS OF LUNG	2.58	2.51-2.65	5 722	4%	4.37	4.24-4.49	0.91	0.85-0.96	0.40	0.36-0.43	4.97	4.71-5.25	8.57	8.30-8.85	1 699
Adenosquamous carcinoma of lung	0.41	0.38-0.44	909		0.66	0.61-0.71	0.18	0.15-0.20	0.06	0.05-0.08	0.76	0.66-0.87	1.39	1.28-1.50	268
Large cell carcinoma of lung	1.84	1.78-1.89	4 071		3.18	3.07-3.29	0.58	0.54-0.62	0.26	0.23-0.28	3.53	3.31-3.76	6.20	5.97-6.43	1 213
Salivary gland type tumours of lung	0.06	0.05-0.07	140		0.09	0.07-0.11	0.04	0.03-0.05	0.03	0.02-0.04	0.12	0.09-0.17	0.15	0.11-0.19	41
Sarcomatoid carcinoma of lung	0.27	0.25-0.29	602		0.44	0.40-0.48	0.11	0.09-0.13	0.05	0.04-0.06	0.56	0.48-0.66	0.85	0.76-0.94	177
EPITHELIAL TUMOURS OF THYMUS	0.36	0.34-0.39	804	97%	0.41	0.38-0.45	0.32	0.28-0.35	0.18	0.16-0.20	0.73	0.64-0.84	0.75	0.67-0.84	232
Malignant thymoma	0.28	0.25-0.30	612		0.31	0.28-0.35	0.24	0.21-0.27	0.15	0.13-0.17	0.56	0.47-0.65	0.54	0.47-0.61	175
Squamous cell carcinoma of thymus	0.02	0.02-0.03	46		0.02	0.02-0.03	0.02	0.01-0.03	<0.01	0.00-0.01	0.06	0.04-0.10	0.05	0.03-0.08	13
Undifferentiated carcinoma of thymus	<0.01	0.00-0.01	9		NE	–	NE	–	NE	–	NE	–	NE	–	2
Lymphoepithelial carcinoma of thymus	<0.01	0.00-0.01	6		NE	–	NE	–	NE	–	NE	–	NE	–	2
Adenocarcinoma with variants of thymus	<0.01	0.00-0.01	7		NE	–	NE	–	NE	–	NE	–	NE	–	2
MESOTHELIOMA OF PLEURA AND PERICARDIUM	2.31	2.25-2.38	5 127	74%	3.51	3.40-3.63	1.19	1.12-1.25	0.27	0.24-0.29	4.10	3.86-4.35	8.21	7.94-8.48	1 546

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

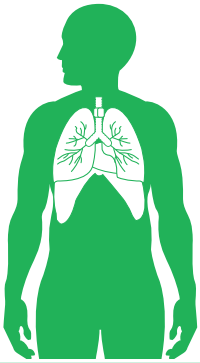
SURVIVAL

RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY. One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



	No. OF CASES INCLUDED IN THE ANALYSIS
RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY	**10 097**
EPITHELIAL TUMOURS OF TRACHEA	323
Squamous cell carcinoma with variants of trachea	157
Adenocarcinoma with variants of trachea	59
Salivary gland type tumours of trachea	21
RARE EPITHELIAL TUMOURS OF LUNG	4 793
Adenosquamous carcinoma of lung	640
Large cell carcinoma of lung	3 566
Salivary gland type tumours of lung	122
Sarcomatoid carcinoma of lung	465
EPITHELIAL TUMOURS OF THYMUS	656
Malignant thymoma	504
Squamous cell carcinoma of thymus	37
Undifferentiated carcinoma of thymus	9
Lymphoepithelial carcinoma of thymus	4
Adenocarcinoma with variants of thymus	6
MESOTHELIOMA OF PLEURA AND PERICARDIUM	4 327

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



PREVALENCE

RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY. Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

	AIRTUM POOL								ITALY
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE		
	≤2 YEARS		2-5 YEARS		≤15 YEARS				
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	ESTIMATED PREVALENT CASES 2010
RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY	**6.69**	**6.16-7.25**	**2.79**	**2.45-3.16**	**14.22**	**13.44-15.04**	**17.29**	**16.31-18.27**	**9 933**
EPITHELIAL TUMOURS OF TRACHEA	**0.15**	**0.08-0.26**	**0.09**	**0.04-0.18**	**0.34**	**0.23-0.49**	**0.42**	**0.27-0.57**	**240**
Squamous cell carcinoma with variants of trachea	0.07	0.03-0.15	0.03	0.01-0.10	0.14	0.07-0.24	0.15	0.06-0.23	80
Adenocarcinoma with variants of trachea	0.01	0.00-0.06	0.01	0.00-0.06	0.03	0.01-0.10	0.04	0.00-0.08	24
Salivary gland type tumours of trachea	0.05	0.01-0.12	0.02	0.00-0.08	0.13	0.06-0.23	0.20	0.08-0.32	120
RARE EPITHELIAL TUMOURS OF LUNG	**2.87**	**2.53-3.25**	**1.44**	**1.20-1.72**	**7.34**	**6.78-7.93**	**9.12**	**8.40-9.84**	**5 218**
Adenosquamous carcinoma of lung	0.40	0.28-0.56	0.21	0.12-0.33	0.94	0.75-1.17	1.12	0.88-1.37	635
Large cell carcinoma of lung	2.05	1.76-2.37	0.99	0.79-1.23	5.32	4.84-5.82	6.72	6.09-7.34	3 841
Salivary gland type tumours of lung	0.11	0.06-0.21	0.13	0.06-0.23	0.41	0.29-0.57	0.56	0.37-0.74	318
Sarcomatoid carcinoma of lung	0.31	0.20-0.45	0.11	0.06-0.21	0.67	0.51-0.86	0.73	0.54-0.91	425
EPITHELIAL TUMOURS OF THYMUS	**0.72**	**0.56-0.93**	**0.57**	**0.43-0.76**	**2.46**	**2.14-2.81**	**3.31**	**2.86-3.76**	**1 921**
Malignant thymoma	0.61	0.46-0.80	0.48	0.35-0.65	2.15	1.85-2.48	2.93	2.50-3.36	1 698
Squamous cell carcinoma of thymus	0.03	0.01-0.10	0.02	0.00-0.08	0.06	0.02-0.13	0.09	0.01-0.18	52
Undifferentiated carcinoma of thymus	NE	–	NE	–	0.01	0.00-0.06	0.01	0.00-0.03	6
Lymphoepithelial carcinoma of thymus	0.01	0.00-0.06	NE	–	0.02	0.00-0.08	0.03	0.00-0.08	21
Adenocarcinoma with variants of thymus	NE	–	NE	–	NE	–	NE	–	NE
MESOTHELIOMA OF PLEURA AND PERICARDIUM	**2.94**	**2.59-3.32**	**0.68**	**0.52-0.88**	**4.08**	**3.67-4.53**	**4.44**	**3.97-4.90**	**2 554**

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

Rare epithelial tumours represent 8% of all tumours of the thoracic cavity and include:

- **epithelial tumours of trachea** (squamous cell carcinoma, adenocarcinoma, and salivary gland type tumours);
- **rare epithelial tumours of lung** (adenosquamous carcinoma, large cell carcinoma, salivary gland type tumours, sarcomatoid carcinoma);
- **epithelial tumours of thymus** (malignant thymoma, squamous cell carcinoma, undifferentiated carcinoma, lymphoepithelial carcinoma, adenocarcinoma).

In this group we also describe

- **malignant pleural and pericardial mesothelioma**.

WHAT DO WE KNOW ABOUT THESE CANCERS?

Apart from mesothelioma, little information is available on patterns of incidence and survival for these tumours. This is largely because in the routine statistics these tumours are grouped together with other sites. **Tumours of the trachea** are grouped with lung and bronchus and tumours of the thymus are often grouped together with those of the heart, mediastinum, and pleura.[1] These tumour types have a different aetiology. Cancer of the trachea is associated with active and passive smoking, occupational exposure (to arsenic, asbestos, chromium, welding fumes) and environmental exposure (air pollution from traffic and industrial emissions).[2] Its usually insidious onset often leads to a delay in diagnosis, making these potentially treatable lesions difficult to treat and often fatal. Thus, early diagnosis is the most important factor affecting survival. Cigarette smoking is the most important risk factor of **lung cancer**, including its rare epithelial forms, together with occupational or environmental exposure to radon, asbestos, and heavy metals such as chromium, cadmium, and arsenic.[3] Adenosquamous carcinoma of the lung exhibits highly aggressive biological behaviour with early lymph node metastasis (46%) and its prognosis is worse than that of both squamous cell carcinoma and adenocarcinoma.[4] Large cell carcinomas often occur in the outer regions of the lungs and tend to grow rapidly and spread more quickly than some other forms of non-small cell lung cancer: they are more strongly associated with smoking than some other types of non-small cell lung cancers.

Many autoimmune syndromes are associated with **thymic epithelial tumours** (TETs); myasthenia gravis is the most common one, followed by autoimmune pure red cell aplasia, hypogammaglobulinaemia, and paraneoplastic autoimmune syndromes.[5] According to the 2004 World Health Organization classification, TETs are divided into thymomas (Ts: A, A/B, B1, B2, B3 subtypes) and thymic carcinomas (TCs: C) depending on cancer cell shape, degree of atypia, and extent of intratumoural thymocytes.[6] Available data demonstrate a poor prognosis for lesions classified as B3 and C, intermediate prognosis for B2, and favourable outcomes for A, AB, and B1 tumours. Squamous, undifferentiated, and lymphoepithelial carcinomas are not included among TETs, but are included in the list of rare cancers proposed by RARECARE as separate entities.[1] All subtypes of **malignant mesothelioma** (MM) **of the pleura and pericardium** are rare. In Italy, population-based registration of MM is carried out by the AIRTUM general cancer registries and by the Italian National Mesothelioma Registry (ReNaM) (https://ricercascientifica.inail.it/renam/Index.asp). The main risk factor of pleural MM is asbestos exposure. Other risk factors implicated in the pathogenesis of MM are ionising radiation and exposure to Thorotrast 9. Family clusters linked to the polymorphism of the genes involved in the repair process of DNA11,12 seem to make patients more vulnerable, still in the presence of asbestos exposure.[7] Pericardial mesothelioma cases have been associated with chest radiation treatment.[8] Microscopic diagnosis, which today has standardised the immunohistochemical panel, recognises three main subtypes of MM: epithelioid (more than half of the cases of MM), sarcomatoid (a worse prognosis), and biphasic (both components).

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

All cancers of the trachea are rare and overall only 374 cases were observed in the AIRTUM database in 11 years (2000-2010). Squamous cell carcinoma is the most common histotype (47%), followed by adenocarcinoma. Salivary gland type tumours represent a particularly rare histological type (only 26 cases in the period 2000-2010) (incidence table, p. 52). All histotypes are more common in males than females and their incidence increases with age, peaking in the 75-84-year age group (data not shown). Approximately 110 Italians are estimated to be diagnosed with cancers of the trachea in 2015.

Rare epithelial tumours of the lung represent only 4% of all cancers of this site. Among the rare forms, large cell carcinoma is the most common (71%), followed by adenosquamous carcinoma (16%), sarcomatoid carcinoma (11%), and salivary gland type tumours (2%). As in the case of the more frequent forms, even rare epithelial tumours of the lung are more common in males and increase with age (see table p. 52). Often the morphology of these tumours is not well specified: the percentage of unspecified forms, though reduced in the last few years, is still very high (29% of cancers of the lung; 35% in people >65 years old; data not shown). This is important because it could lead to an underestimation of the incidence of the rare epithelial cancer described here. In 2015, 1,699 new cases were estimated (see table p. 52).

Thymus cancers are all rare. Malignant thymoma is the most common form (76%), followed by squamous cell carcinoma (6%). Undifferentiated carcinoma, lymphoepithelial carcinoma, and adenocarcinoma represent particularly rare histological types (only 9, 6, and 7 cases were observed in the period 2000-2010, respectively). Malignant thymoma is more frequent in males than females; incidence peaks in the 65-74-year age group (data not shown). Squamous cell carcinoma incidence is similar in males and females; it has the highest incidence rate in the 60-69-year age group (data not shown). Even in Europe these cancers are extremely rare. Approximately 230 Italians are estimated to be diagnosed with cancers of the thymus in 2015.

The incidence of **pleural and pericardial MM** is higher in males than in females and in the over 65 age group. In the period 2000-2010, 5,127 cases were observed in the AIRTUM dataset (see table p. 52). The occurrence of MM showed an increasing trend in recent decades; in Italy different models have predicted a peak in incidence between 2010 and 2020.[9] All cancers of the thoracic cavity have a slightly higher incidence in Italy than in Europe (RARECAREnet database, www.rarecarenet.eu), except large cell carcinoma and salivary gland type tumours of the lung.

Survival

Prognosis of patients diagnosed with an **epithelial tumour of the trachea** is poor, with less than half of the patients surviving the first year, and 12% alive 5 years after diagnosis. All histotypes share this poor prognosis, except salivary gland type tumours (survival figure, p. 52). In the AIRTUM database we do not have an appropriate number of cases of salivary gland tumours to estimate 5-year relative survival (RS); however, according to the European RARECAREnet database, it is 70%. Prognosis of patients with a tracheal malignancy is poor, however, surgical treatment can lead to good survival rates. Thus, the lower prognosis of these rare cancers is due to delay in diagnosis (due to its aspecific and asthma-mimicking symptoms), advanced stage at diagnosis, and limited experience among clinicians. Centralising the care and treatment of tracheal cancers could make surgery accessible to a larger number of patients, leading to better survival of these patients.[10] One-year and 5-year RS of **rare epithelial tumours of the lung** is 47% and 19%, respectively. Salivary gland type tumours have the highest 1- and 5-year RS (74% and 44%, respectively, see figure p. 52). For these rare forms, as well as for the most common cancers of the lung, no significant improvements in survival were reported over the last decades.[11] The worse prognosis of these cancers is mainly due to the more advanced stage at diagnosis and advanced age of the patients, which often condition radical surgery. For the early forms, if well treated, survival is significantly higher than the advanced forms.[12,13] However, there is considerable heterogeneity in the management of these patients, sometimes even in the same region.[14] Relative survival is rather good for patients diagnosed with an **epithelial tumour of the thymus**, with a 1- year RS of 85% and a 5-year RS of 68% (see figure p. 52). A combination of stage and histologic subtype should be considered in predicting survival. Types A, AB, and B1 have an excellent overall survival rate of between 90% and 95% at 10 years. Five-year RS for types B2, B3, and C is 75%, 70%, and 48%, respectively. Thymomas rarely metastasise, whereas TCs display a more aggressive phenotype, with distant metastases in liver, lymph nodes, and bones.[15] It is difficult to trace a standard treatment for thymomas. Although thymomas have a relatively good prognosis, they include a heterogeneous group of histologies, with different prognosis and for which there are no clear guidelines; so even for thymoma it would be appropriate to support a network that brings together experts to define common guidelines for better treatment. In France there is a national initiative named RYTHMIC, Réseau tumeurs THYmiques et Cancer (www.rythmic.org); in Italy, a network for thymic malignancies, TYME (TYmic MalignanciEs), was launched by the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, in 2014. One-year and 5-year RS of **pleural and pericardial MM** is 50% and 7%, respectively (see figure p. 52). Tools for early diagnosis and effective screening programs regarding MM are not available. Chest radiography and computer tomography (CT) were evaluated as ineffective in screening for MM in asbestos-exposed workers.[16,17] For pleural MM an optimal strategy is far from being standardised. Management of this disease requires a multidisciplinary team and it is recommended that patients who are considered candidates for a multimodal approach be included in a prospective trial at a specialised centre.

Among rare epithelial tumours of the thoracic cavity, squamous cell carcinoma of the thymus and mesothelioma of the pleura and pericardium show the most important differences between 1- year and 5-year RS (46 and 43 points, respectively).

Italian data and European RARECAREnet data are similar for all these tumours, except for pleural MM which has slightly higher survival in Italy than in Europe.

Prevalence

About 10,000 persons were estimated alive in 2010 with a diagnosis of rare epithelial tumours of the thoracic cavity in Italy. Most prevalent cases are patients with a previous diagnosis of large cell carcinomas of the lung, mainly because of the relatively high incidence of these tumours compared to the others. The distribution of prevalence by time since diagnosis is fairly similar for the different types of tumours, except for those with poor prognosis (large cell carcinoma and sarcomatoid carcinoma of lung and mesothelioma of pleura and pericardium), that show a higher proportion of prevalent cases in the two years just after diagnosis.

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