

RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA

0.2%
OF TUMOURS OF THE SKIN AND OF THE MUCOSA ARE RARE

INCIDENCE

532

ESTIMATED NEW CASES
ITALY, 2015

108 MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS)
424 ADNEXAL CARCINOMA OF SKIN

0.04

% OF RARE TUMOURS OUT OF ALL TUMOURS IN EACH SITE

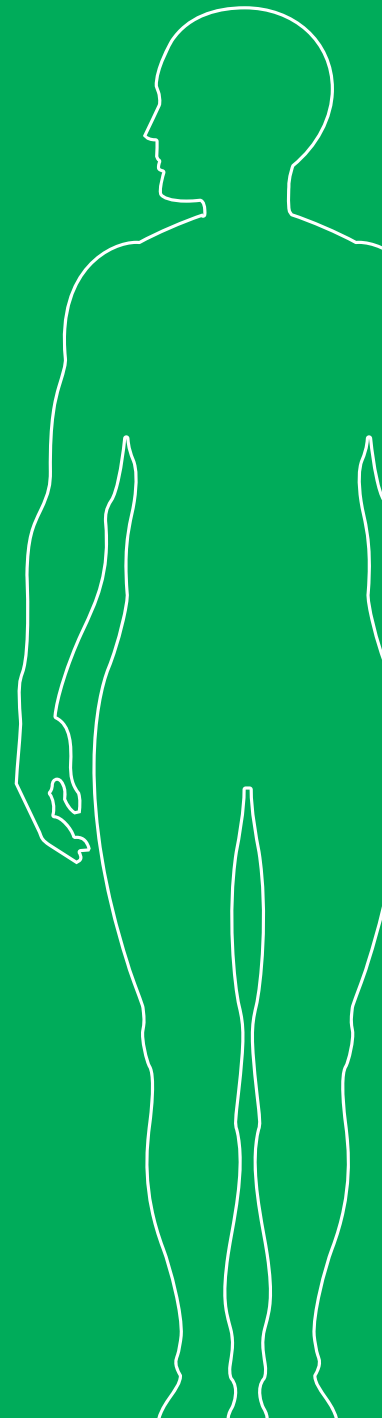
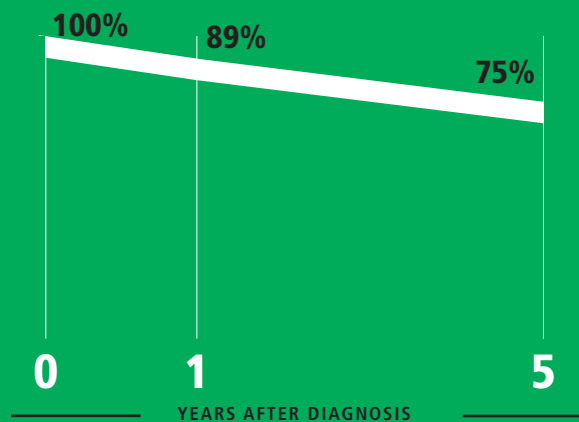
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PREVALENCE

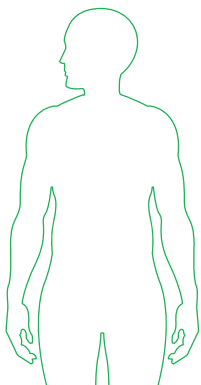
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ESTIMATED PREVALENT CASES
ITALY, 2010

SURVIVAL



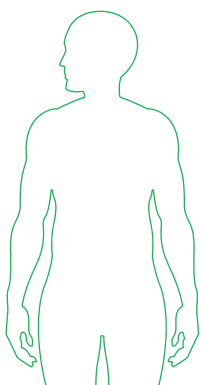
INCIDENCE



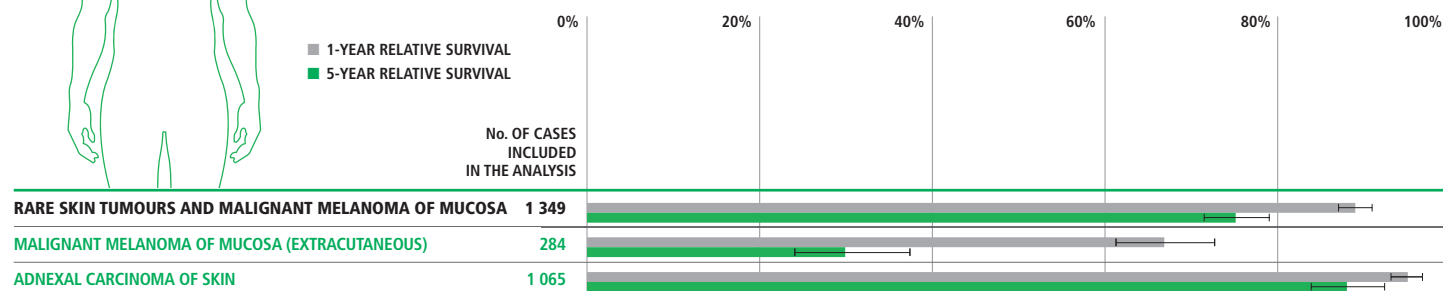
RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA. Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	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	
RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA	0.77	0.73-0.80	1 699	0.2%	0.83	0.78-0.89	0.70	0.66-0.75	0.13	0.11-0.15	0.93	0.82-1.05	2.86	2.70-3.02	532
MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS)	0.16	0.14-0.18	356	0.04%	0.12	0.10-0.15	0.19	0.17-0.22	0.04	0.03-0.05	0.25	0.19-0.31	0.54	0.47-0.61	108
ADNEXAL CARCINOMA OF SKIN	0.61	0.57-0.64	1 343	3.4%	0.71	0.66-0.76	0.51	0.47-0.55	0.09	0.08-0.11	0.68	0.59-0.79	2.32	2.18-2.47	424

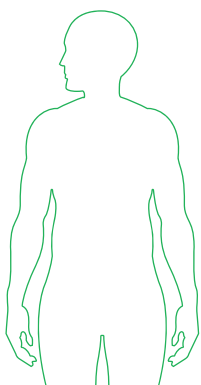
SURVIVAL



RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA. One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



PREVALENCE



RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA. 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		ESTIMATED PREVALENT CASES 2010
	≤ 2 YEARS		2-5 YEARS		≤ 15 YEARS		PROPORTION	95% CI	
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI			
RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA	1.40	1.16-1.67	1.70	1.44-2.00	5.66	5.17-6.18	7.50	6.83-8.17	4 403
MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS)	0.25	0.16-0.38	0.16	0.09-0.27	0.61	0.46-0.80	0.87	0.63-1.11	524
ADNEXAL CARCINOMA OF SKIN	1.15	0.93-1.40	1.54	1.29-1.82	5.05	4.59-5.55	6.63	6.00-7.25	3 879

This group includes two tumour types which are rare and understudied:

- malignant melanoma of the mucosa;
- skin adnexal tumours.

Because of their rarity, even the basic descriptive epidemiology of these tumour types is sparse, restricted to specific anatomic sites and confined to case reports or clinical series.

WHAT DO WE KNOW ABOUT THESE CANCERS?

Primary mucosal melanomas arise from melanocytes located in mucosal membranes. Although a majority of mucosal melanomas originate from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva, and vagina, they can arise in almost any part of mucosal membranes. In particular, primary oral melanomas may arise from nevi and pigmented areas such as amalgam tattoos, or post-inflammatory pigmentations due to tobacco usage or drugs aberrant reactions.¹ Most mucosal melanomas occur in occult sites, which together with the lack of early and specific signs contribute to late diagnosis and poor prognosis. Because of their rareness the knowledge about their pathogenesis and risk factors is insufficient, and moreover there are no well-established protocols for staging and treatment. Surgery is the mainstay of treatment, with trends toward more conservative treatment since radical surgery has not proven an advantage for survival. Radiotherapy can provide better local control in some locations, but did not show improvement in survival. There is no effective systemic therapy for these aggressive tumours. Compared with cutaneous and ocular melanoma, mucosal melanomas have the lowest percentage of five-year survival. Recently revealed molecular changes underlying mucosal melanomas offer new hope for development of more effective systemic therapy for mucosal melanomas.²

Skin adnexal tumours (SATs) are a large and diverse group of benign and malignant neoplasms, which exhibit morphological differentiation towards one of the different types of adnexal epithelium present in normal skin: apocrine-ecrine differentiation (tumours of the sweat glands, mammary and extramammary Paget's disease); follicular (tumours of hairs); and sebaceous (tumours of Zeis glands and meibomian glands of the eyelid). The histogenesis of adnexal tumours is still uncertain; however, the possibility of origin from a pluripotent stem cell is suggestive.³⁻⁶

Most SATs are benign, and local complete surgical excision is curative. However, diagnosing some of these tumours has important implications, as they might be markers for syndromes associated with internal malignancies, such as trichilemmomas in Cowden syndrome and sebaceous tumours in Muir-Torre syndrome.^{7,8} Benign lesions are typical of the young. A malignant counterpart of almost every SAT has been described. These tumours are rare, locally aggressive, and have the potential for nodal involvement and distant metastasis, with a poor clinical outcome. Therefore, establishing a diagnosis of malignancy in SAT is important for therapeutic and prognostic purposes. Because pathologists may not frequently encounter SATs, and owing to their different derivation and broad histogenesis, diagnosing these tumours may be challenging even to an experienced pathologist. SATs appear as single nodular lesions resembling dermal melanocytic nevi, epidermoid cysts, and basal cell carcinoma. Thus, their diagnosis relies on histological evaluation, including immunohistochemistry to support

differential diagnosis (podoplanin (D2-40) to distinguish basal cell carcinoma from trichoepithelioma, monoclonal antibody Ber-EP4 to reliably discriminate between microcystic adnexal carcinoma and basal cell carcinoma).⁸

In this study, we conducted the first comprehensive and largest analysis, to our knowledge, of incidence, prevalence and survival of these rare tumours in the Italian population. In the list of rare cancers proposed by RARECARE,⁹ extramammary Paget's disease is not included among SATs, as it is often an epiphenomenon of another invasive malignancy and because the actual invasiveness of the lesion is still debated. Mammary Paget's disease is included and described among the rare cancers of the breast.

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

All mucosal melanomas are rare and are so rare that only 350 cases were observed in Italy in 11 years. These tumours are slightly more common in females than males and are typical of older people (peak in the eighth decade of life). In the AIRTUM database, mucosal melanoma occurs most frequently in the female genital tract and in the head and neck, as previously reported in Europe¹ and the USA.¹⁰

All SATs are rare and 1,300 cases were observed in Italy in the period 2000-2010 in the AIRTUM database. SATs are more common in males than females and the incidence rate (IR) increases exponentially with age, with peak frequencies in the eighth decade of life. The most frequent SATs are those with apocrine and eccrine differentiation, followed by sebaceous tumours and adenoid cystic carcinoma with skin appendage carcinoma, NOS, accounting for 20%. These results are similar to those observed in the SEER database (period of diagnosis 2001-2006), which reports a high IR of apocrine and eccrine followed by sebaceous and, differently from the Italian results, microcystic adnexal carcinoma. Skin appendage carcinoma, NOS, is lower in the SEER database (about 10%).¹¹ Interesting is the absence of follicular tumours in both the AIRTUM and SEER databases.

Survival

Five-year relative (RS) of **mucosal melanomas** is 30%, most likely because of the late diagnosis and the lack of protocols for their treatment. Survival of SAT is good, as it is 95% after 1 year and 88% after 5 years from diagnosis. This is probably due to the fact that these tumours are mainly locally aggressive tumours. In the AIRTUM database there is no information on stage; however, according to the SEER database, 5-year RS is 99% in local SATs, 93% in SATs with regional involvement (which are 15% of all SATs) and 43% in SATs with distant metastases (which are very rare; 1.6% out of all SATs observed in the SEER database in the period 1992-2004). With regard to survival for the different differentiations, it seems that 5-year RS is slightly lower for tumours with sebaceous differentiation.¹¹

These results are in line with those observed in Europe in the RARECAREnet database (www.rarecarenet.eu). As expected, for both mucosal melanomas and SATs, the observed survival (not shown in table) is lower than the relative one because these tumours affect mainly old people.

Prevalence

Around 4,400 persons were estimated to be alive in 2010 with a past diagnosis of one of these rare cancers in Italy. The most prevalent cancers are SATs (88% of cases), coherently with the high incidence and survival of these tumours.

GENERAL REMARKS

SATs affect mainly old people, have high survival, are rarely metastatic at diagnosis, and surgery is the mainstay treatment. However, diagnosing these tumours may be challenging. Survival of mucosal melanoma is low because of lack of treatment protocols and delay in diagnosis.

A possible solution to address the challenges for diagnosis and treatment of these tumours is the identification of an expert centre, with a multidisciplinary team, able to support the therapeutic decision for locally advanced and metastatic SATs and mucosal melanoma. The expert centre should also be able to provide a second pathological opinion to ensure the appropriate diagnosis of SATs. For melanoma of the mucosa, revision of the pathological sample is important, but not as essential as for SATs.

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