# Completeness of Data on Malignant Melanoma Skin Sites and Morphology in the Croatian National Cancer Registry 2000-2014: An Overview of Recent Progress

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**ABSTRACT** Mortality rates and five-year relative survival for malignant melanoma (MM) of the skin in Croatia are poor compared with most European countries. Epidemiological data recorded at the National Cancer Registry (CNCR) are used for informing various decision-makers and researchers, as well as for comparisons with other countries. We analyzed CNCR data on MM skin and morphology for 2000-2007 and 2008-2014 and compared them with European 2000-2007 data. We further stratified skin site analyses in Croatia by sex, different age groups, and sources of reports. We found 52% of case with "non-specified sites" in Croatia in 2000-2007; however, that proportion decreased to 36% in 2008-2014, with 29% of registered MM cases occurring on the trunk, 22% on the limbs, and 13% on the head and neck. The proportion of "non-specified sites" cases in reports originating from university hospitals decreased by 25% and by 9.2% in those from general hospitals. The proportion of "not otherwise specified" among histologically verified cases decreased from 96% in 2000-2007 to 84% in 2008-2014. Our results reveal a substantial proportion of inadequately reported cases, in particular when compared to data at the European level, where in 2000-2007 only 7.7% of cases were from "non-specified sites" and 19% were of non-specified morphology. Irrespective of recent progress, the proportion of unspecified cases still hampers insight into site distribution by subgroups. A further increase in the overall completeness of MM data within CNCR is needed to enable research-informed improvement of melanoma control in the country. Our findings call for engagement of all stakeholders in optimization of the national melanoma registration processes and using models such as RegisTree© to facilitate these initiatives.

**KEY WORDS**: malignant melanoma, Croatia, registry, data

## INTRODUCTION

Mortality and five-year survival for malignant melanoma of the skin (MM) in Croatia are poor compared with those in most European countries, but recent mortality trends indicate some progress when compared with other countries in Central and South-Eastern Europe (1-3). Age-standardized incidence rates (W) in Croatia were 8.75/100,000 in men, and 9.25/100,000 in women in 2012 (2). Irrespective of recent trends, Croatia had the sixth highest mortality rate in Europe for both men (2.95/100,000) and women (1.91/100,000) in 2012 (2,3). MM caused an estimated loss of 4297.04 Disability Adjusted Life Years (DALYs) (4), and accounted for 0.51% of all Years of Life Lost (YLLs) in Croatia in 2013 (4).

However, the relevance of MM societal burden is greater in the younger population, since it accounted for an estimated 1.16% of all YLL in the age group 15-49 (4). There is neither an official strategy nor action plan for dealing with the melanoma burden at the national level, but the epidemiological data recorded at the National Cancer Registry (CNCR) are used for informing various decision-makers and researchers, as well as for comparisons with other countries.

Results of a *EUROpe against cancer: Optimisation of the Use of Registries for Scientific Excellence in research* (EUROCOURSE) project have shown that, at the European level, cancer registry data were most actively used in several overlapping cancer research areas, including Public Health, Quality of Care, Survivorship, and Prognosis (5). According to the results of the latest *EUROpean Cancer REgistry Based Study on Survival and Care of Cancer Patients* (EUROCARE) study, five-year relative survival for MM diagnosed between 2000 and 2007 was 83.2% at European level, but 70.6% in Croatia, with only Bulgaria, Latvia, Lithuania, and Poland having lower survival (1). The EUROCARE-5 study also compared quality of data on MM, along with proportions of MM

cases of different localizations and morphological subtypes among different European regions (1). MM risk factors differ by skin site and histological type, suggesting different etiologic pathways of melanoma development by skin site (6). Proportions of MM of different localizations and morphological subtypes varied among different European regions, and so did relative survival by MM skin site and morphological subtype (1).

The aim of this study was to compare CNCR data on MM skin sites and morphology with the European level results of the EUROCARE-5 study, both within the EUROCARE-5 study period and in recent years, further disaggregate them by sex and different age groups, as well as sources of reports. We discuss the implications of the findings on melanoma surveillance and control in Croatia at the national and regional level, as well as the need for continuous and improved monitoring given the recent major treatment developments.

## PATIENTS AND METHODS

CNCR was founded in 1959, as one of the oldest national registries in Europe, has contributed data to

**Table 1** Skin melanoma case reports according to skin-sites and morphology: EUROCARE-5 results for Europe 2000-2007 compared with Croatian data for 2000-2007 and for 2008-2014.

| Skin-site[1] | ICD-10 Code | | Europe 2000-2007[2] | Croatia 2000-2007 | Croatia 2008-2014 |
|---|---|---|---|---|---|
| Head and neck | C43.0-C43.4 | N | 37,245 | 512 | 503 |
| | | % | 15.4 | 13.6 | 12.9 |
| Trunk | C43.5 | N | 78,675 | 750 | 1118 |
| | | % | 32.6 | 20.0 | 28.6 |
| Limbs | C43.6 – C43.7 | N | 106,939 | 526 | 873 |
| | | % | 44.3 | 14.0 | 22.4 |
| Not specified sites | C43.8 - C43.9 | N | 18,626 | 1966 | 1411 |
| | | % | 7.7 | 52.4 | 36.1 |
| All cases | C43.0 – C43.9 | N | 241,485 | 3754 | 3905 |
| **Morphology[1]** | **Morphology Code** | | | | |
| Nodular melanoma | 8721 | N | 14,721 | 76 | 210 |
| | | % | 14.9 | 2.1 | 5.6 |
| Lentigo maligna | 8742 | N | 5932 | 0 | 8 |
| | | % | 6.0 | 0.0 | 0.2 |
| Superficial spreading | 8743 | N | 51,783 | 27 | 288 |
| | | % | 52.3 | 0.7 | 7.7 |
| Other specified sites[3] | - | N | 7571 | 44 | 96 |
| | | % | 7.6 | 1.2 | 2.6 |
| Not otherwise specified | 8720 | N | 19,061 | 3505 | 3136 |
| | | % | 19.2 | 96.0 | 84.1 |
| All cases | | N | 99,068 | 3652[4] | 3730[4] |

ICD=International Classification of Diseases
[1] Aggregated in line with EUROCARE-5 report on melanoma (1).
[2] EUROCARE-5 data, based on contributions from 86 cancer registries for skin-sites and from 51/86 cancer registries 'with adequate information on morphology' (arbitrarily defined as <30% not otherwise specified (NOS), code 8720 (1).
[3] Includes codes 8722-3, 8730, 8740-1, 8744-6, 8761, 8770-4 and 8780.
[4] Excludes autopsy and death certificate–only cases, n=102 (2000-2007), n=175 (2008-2014).

Cancer Incidence in Five Continents, volumes VII-X (7), and has recently participated in international cancer survival studies, EUROCARE-5 and CONCORD-2 (8,9). We obtained incidence data on MM (ICD-10 C43*) for the 2000-2014 period from CNCR and stratified them in two time periods: 2000-2007 and 2008-2014. CNCR collects data from various sources, both from the public and private sector, coded according to ICD-10 classification for topography and ICD-O-3 classification for morphology. This includes notifications received from health professionals working at hospital wards, outpatient clinics, and general practitioners as well as official cause of death statistics. The registry also receives pathological reports from hospital pathology departments. The notifications are first sent to the local County Public Health institute, whose staff, after the first phase of quality control, forwards the data to CNCR. The diagnosis of melanoma is accepted by the cancer registry only if the basis of diagnosis was histological or cytological confirmation that provides morphological diagnosis.

We compared our results with the results for Europe 2000-2007 from the EUROCARE-5 study, which was based on data contributions from 86 European cancer registries (1). Based on the C43 code extension, we stratified the data in four skin site groups as the ones used in the EUROCARE-5 report on melanoma, namely "head and neck" (C43.0-C43.4), "trunk" (C43.5), "limbs" (C43.6-C43.7), and "non-specified sites" (C43.8-C43.9). We calculated the proportions in each group in the total number of reported cases.

We also stratified the cases by morphological types, using morphological codes, namely "nodular melanoma" (8721), "lentigo maligna" (8742), "superficial spreading melanoma" (8743), "other specified sites" (including codes 8722-3, 8730, 8740-1, 8744-6, 8761, 8770-4, and 8780), and "not otherwise specified" (NOS, 8720). We further stratified the data on skin sites by sex, age (≤59 years and 60+ years), and by both sex and age (≤59 years and 60+ years) and calculated the proportions of each skin site in the total number of cases in each of the eight subgroups. Additionally, we stratified the sources of the reports in three groups: "university hospitals" (including university hospital centers and university hospitals), general hospitals, and "other sources", and then analyzed proportions of "non-specified sites" reports (C43.8-C43.9) for both time periods.

## RESULTS

We found 3754 reported melanoma cases in Croatia in the 2000-2007 period, and 3905 in the 2008-2014 period (Table 1). The proportion of cases reported among "non-specified sites" decreased from 52% to 36% between the two periods. The proportion of melanomas localized on the trunk and limbs increased, whereas the proportion of head and neck melanomas decreased between the two periods in Croatia, as shown in Table 1. Compared with Croatian data, data collected in the EUROCARE-5 study had lower proportion of "non-specified sites" cases (7.7%), higher proportions of limb melanomas and trunk
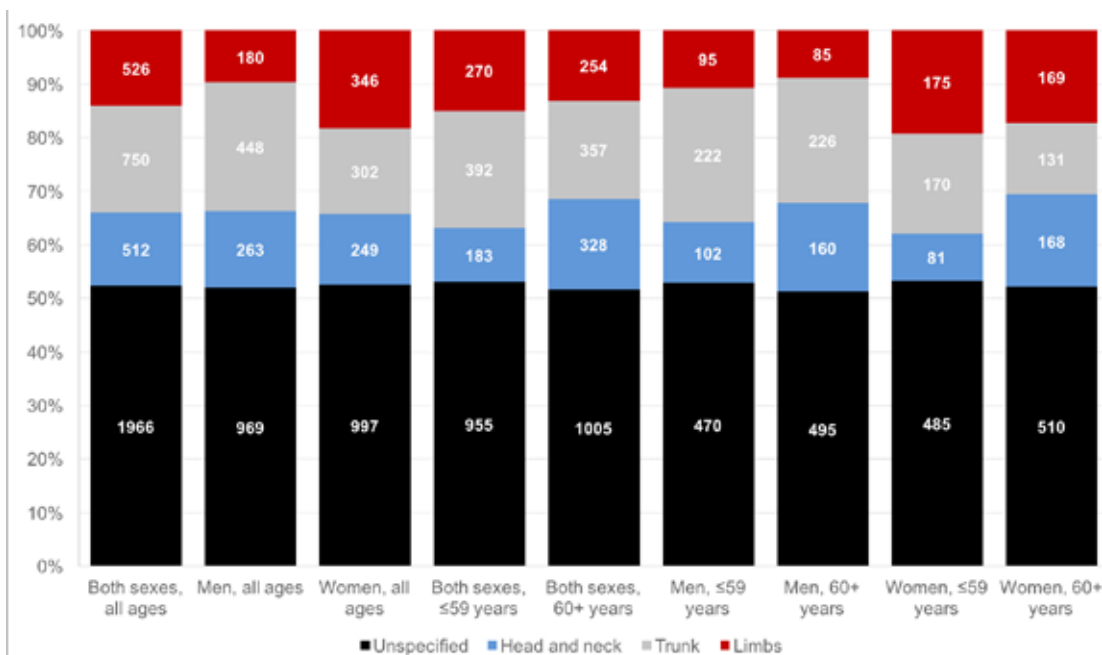


**Figure 1.** Reported cases of skin melanoma and proportions according to skin-sites in Croatia, 2000-2007, for all ages, both sexes and for different subgroups.
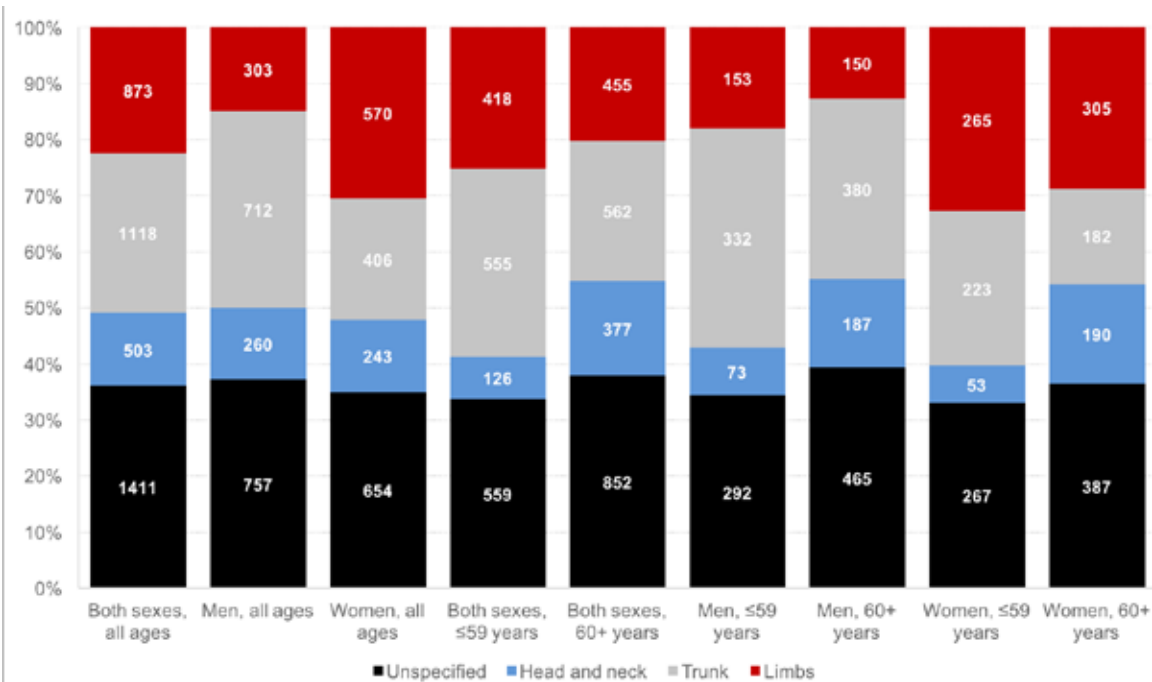
**Figure 2.** Reported cases of skin melanoma and proportions according to skin-sites in Croatia, 2008-2014, for all ages, both sexes and for different subgroups.

melanomas, and a similar proportion of head and neck melanomas reported during 2000-2007 (Table 1). Most cases among histologically verified MM reported in Croatia were coded as NOS, with a decrease from 96 % to 84% between the two periods (Table 1).

The number of reported cases recorded in 2000-2007 varied by different subgroups, as did proportions of head and neck, limb, and trunk melanomas, but the proportion of cases from "non-specified sites" was around 50% across all subgroups (Figure 1).

The proportion of "non-specified" sites was not as consistent across different subgroups during 2008-2014 (Figure 2).

Absolute numbers of cases and the proportion of cases reported from university hospitals decreased from 2466 cases, i.e. 65.7% of all reported cases in 2000-2007, to 2066 cases, i.e. 52.9% of all reported cases in 2008-2014 (Table 2). The absolute numbers of cases and the proportions of cases reported from general hospitals and other sources increased between the two periods (Table 2). The proportion of "non-specified sites" cases in reports originating from university hospitals decreased by 25% and by 9.2% in those from general hospitals, but it remained stable in those originating from other sources (Table 2).

**Table 2.** Cases of skin melanoma reported to Croatian National Cancer Registry in the periods 2000-2007 and 2008-2014, by report source.

| Period | Skin melanoma case reports according to ICD-10 codes | | Source | | | |
| | | | University hospitals[1] | General hospitals | Other sources | Overall |
|---|---|---|---|---|---|---|
| 2000-2007 | All cases, C43.0 – C43.9 | N | 2466 | 717 | 571 | 3754 |
| | Not specified sites, C43.8 - C43.9 | N | 1322 | 357 | 286 | 1966 |
| | | % | 53.6 | 49.7 | 50.1 | 52.4 |
| 2008-2014 | All cases, C43.0 – C43.9 | N | 2066 | 1023 | 816 | 3905 |
| | Not specified sites, C43.8 - C43.9 | N | 588 | 414 | 409 | 1411 |
| | | % | 28.5 | 40.5 | 50.1 | 36.1 |

ICD=International Classification of Diseases; C43.8= Malignant melanoma of overlapping sites of skin; C43.9= Malignant melanoma of skin, unspecified.
[1] Includes university hospital centers and university hospitals.

## DISCUSSION

The proportion of "non-specified sites" MM among the reported cases in Croatia is decreasing, as well as the ratio of cases with non-specified morphology. Irrespective of recent progress in these data quality indicators, which are most prominent in cases originating from university hospitals, our results reveal a substantial proportion of inadequately reported cases, in particular when compared with European-level data. This lack of high-quality data limits insight into nationwide site-distribution and morphological types, in particular by different age and sex subgroups.

A scheme has been developed to facilitate better use of cancer registry data in different cancer research areas, in which cancer registries have been visualized as trees ("Cancer Registration Tree" – RegisTree©) (10). RegisTree© represents "transmission and refinery capacity (through their trunks and height – information) by a combination of fluids (through roots – data), energy from sunlight (through leaves – inspiration, ideas), and regular production of nuts and fruits (information)" (10). Our results illustrate some areas for improvement of the Croatian "Melanoma Registration Tree", including the input from "roots", i.e. completeness of data on skin sites, as well as the "fruits", i.e. countrywide insight into site-distribution by subgroups, but also how improvement of input coming from "roots" has led to improvement of "fruits" over time. Differences in proportions of different localization of MM cases among European regions point to the fact that, although data from other countries or regions can be useful in guiding public health research and prevention efforts in individual countries, local epidemiological data is needed for fully informed decisions on customization at the national level (1). Reliable Croatian national-level data on MM skin sites and morphology could add focus and additional value in designing prevention messages for public and healthcare professionals and contribute to more effective communication (11). Furthermore, Croatia has joined the EUROMELANOMA campaign in 2008 and has several other preventive activities underway, but the effect of these efforts can only be monitored and evaluated through adequate melanoma surveillance at the national level (11). Similarly, other melanoma research areas where CNCR data can be used have specific features in the Croatian setting (5). Along with lower survival and higher mortality rates, Croatia has comparatively lower resources available not only for prevention, but also for treatment of advanced melanoma, and so poor decisions on allocation of resources have a greater opportunity cost as compared with wealthier Western European countries (3,11,12). Inadequate resource allocation leads to missed opportunities for earlier diagnoses and timely surgical treatment for a greater proportio of MM patients in Croatia, and thus increases the pool of those with advanced disease in need of costly treatments. Considering the low resource capacity in Croatia, this probably translates to limited access to novel therapeutic possibilities for the patients who could receive the greatest benefit.

Awareness of the importance of the quality of reported mortality and incidence data, and the complementary value of population-based and institution-based registries in achieving horizontal synergy in melanoma research seems to be increasing among clinicians in Croatia and Central Europe (13-15). Potential input in the CNCR ("roots") comes from each phase of the journey of the patient with melanoma, from detection to cure or death (10). This includes general practitioners, dermatologists, surgeons, oncologists, pathologists, nuclear medicine specialists, and palliative care providers, who are commonly involved in different areas of melanoma research as well (10). To ensure that the future reporting does not overburden their busy schedules, but that the output of CNCR ("fruits") still meets their needs, all stakeholders should be engaged in reaching consensus on national optimization of the registration processes (5). For example, the increasing proportio of cases reported to CNCR from non-hospital sources (Table 2) suggests an increasing importance of CNCR melanoma data at the national level in the context of Breslow thickness. Data on Breslow thickness are currently occasionally (i.e. not routinely) reported from clinical registries in individual institutions, mostly university hospitals, as they are usually active in research and publish such data thanks to their scientific efforts (14,15). Considering our findings presented in Table 2, one could hypothesize that thinner melanomas get excised in non-university hospital or non-hospital settings, and thus nationwide melanoma thickness could be overestimated if based on data from hospital registries, in particular university hospital registries. Collection of Breslow thickness data in CNCR could thus be considered for gaining a more accurate and reliable perspective. This would also enable exploration of trends of Breslow thickness like in other countries (16). Furthermore, Crocetti *et al.* indicate the possibility of overdiagnosis as a limitation of melanoma survival analyses within the EUROCARE-5 study (1). One could speculate that comparatively lower melanoma survival in Croatia may in part be explained by a lesser extent of overdiagnosis than in Northern and Western European countries. However, exploring and answering this and other questions relevant for

different stakeholders in Croatia, such as the dynamics of melanoma societal burden, is currently not possible like it is in other countries with available comprehensive national data on Breslow thickness (17-19).

## CONCLUSION

Irrespective of recent progress, most prominent in reports originating from university hospitals, in comparison with EUROCARE-5 results the proportion of unspecified cases in CNCR is still comparatively high and hampers countrywide insight into site-distribution by subgroups. Due to practical reasons, the second period we analyzed (2008-2014) is one year shorter than the first one (2000-2007), which should be taken into consideration when interpreting our results. A further increase in overall completeness of MM data within CNCR is needed to enable research-informed improvement of melanoma control in Croatia. Our results call for future engagement of all stakeholders in the optimization of national melanoma registration processes and creating a well rooted melanoma "registry tree", enabling it to fully blossom, with future fruits meeting everyone's needs.

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