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Health and Economic Burden of Skin Melanoma in Croatia – Cost-of-illness Study

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ABSTRACT Melanoma incidence is increasing, especially in the younger population. The aim of this study was to investigate the cost of this disease in the Croatian population and to identify costs through types of care and types of costs. The secondary goal was to estimate the prevalence of certain types of melanoma (as well as staging distribution) and to connect each stage and its prevalence in Croatia to related costs. A cost-of-illness analysis was performed, mainly including direct costs (monitoring, drugs, primary health care services, hospitalizations, and diagnostics). The calculations were based on data collected from Sestre milosrdnice University Hospital Center in Zagreb and from Cancer Registry Data. The number of patients with melanoma was calculated using the Markov model for melanoma staging and 5-year survival. The estimated total prevalence of melanoma in 2011 in Croatia was 2,180. The total cost of melanoma was estimated to 1,063,488 EUR, with 46% used for hospitalization and chemotherapy, 10% for dermatoscopy, and the remaining 17% being monitoring costs. The average cost per patient was estimated to range between 98 and 4,333 EUR depending on the stage of the disease. The cost of melanoma in the adult population in Croatia in a one-year timeframe accounted for as much as 0.04% of the total Croatian national health care budget for 2011. Study findings indicate the need for a clear strategy to achieve regular screening in order to detect the disease at an early stage.

KEY WORDS: skin cancer, melanoma, prevalence, burden, cost

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INTRODUCTION

Melanoma is one of the most aggressive skin tumors arising from pigment cells melanocytes. Melanoma is less common than basal cell and squamous cell skin carcinoma but is far more aggressive. Men are more often diagnosed later with more advanced tumors and worse cutaneous melanoma specific outcomes, correlated to more advanced stages of disease at diagnosis (1).

Diagnostics of cutaneous melanoma include clinical examination of the suspected tumor (the so called ABCDEFG rule), physical examination for signs of lymph node disease, and detailed examination of the lesion using high-resolution optical dermatoscopes or epiluminescent microscopes (2). Average age at time of diagnosis of melanoma is 50 years (3) and the sex distribution is equal, although incidence in men rises after 45 years of age.

Prolonged survival of melanoma patients in Western countries is attributed to early melanoma diagnosis (4), unlike Croatia where melanoma is still diagnosed in advanced stages resulting in a more aggressive tumor with high risk of metastasis and median survival of 6-9 months (5). The Croatian coast has around 2,600 sun hours every year, which may result in intensive periodical sun ultraviolet (UV) exposure, one of the most important risk factors for developing melanoma (6).

Melanoma incidence rates are rapidly increasing in Mediterranean countries. Because advanced melanoma is still largely incurable, early detection and identification of factors associated with the development and progression of the disease are of great importance. Screening for melanoma is not yet common in Mediterranean countries. The magnitude of risk associated with the combination of dysplastic nevi, and/or light eyes, light skin, and low propensity for tanning indicates the need for preventive education on melanoma in these populations (7). Many case-control studies indicated that a high number of nevi and the presence of atypical nevi are the strongest predictor of melanoma risk; this has also been recently confirmed in Mediterranean populations. However, little is known about how prevention programs based on specialized periodical examination of at-risk individuals impact melanoma diagnosis (8).

Staging of melanoma is performed through the American Joint Committee on Cancer (AJCC) with TNM (tumor-node-metastasis) staging classification based on the extent of primary tumor growth, regional lymph node involvement, and distant metastasis; it accounts for tumor thickness, level of invasion, and ulceration (9). Risk factors for the development of skin cancer may be both genetic and environmental. Solar UV exposure is the most important environmental risk factor for developing cutaneous melanoma, especially during the first 20 years of life (10).

Melanoma accounts for less than 5% of skin cancers (11). In the last four decades, a continuous growth of melanoma incidence has been reported throughout the world (12), with the highest incidence in Australia (13,14). In Croatia from the year 1968 to 1995, melanoma has increased by 309% and melanoma mortality by 310% (15). The annual global incidence of melanoma in 2008 was estimated to be 197,000 (16) with a lifetime probability of 0.3% for both sexes. The incidence of melanoma is highest among fair-skinned populations (17) and increases with age, particularly in men (18). Data show that cases of malignant melanoma have increased by a larger amount than many other major cancers and that the incidence has more than doubled since the early 1970s (19). In 2008 in Croatia there were 286 new cases and 118 yearly deaths in men and 275 new cases and 79 deaths in women. Melanoma represented 2.6% of male cancer incidence and 1.1% of cancer deaths in men and 2.9% of female cancer incidence and 1.4% of cancer deaths in women (15). For those diagnosed with stage IIIC melanoma, 5-year survival is 40%, whereas 5-year survival is less than 20% in stage IV metastatic melanoma (20).

Until recently, only dacarbazine (an alkylating agent that links together specific sections of DNA, which prevents cell division and results in cell death) has been approved as standard treatment for metastatic melanoma in Croatia, despite its modest efficacy and lack of data for survival benefit (21). Several novel therapies have been approved for the treatment of metastatic melanoma, representing a major therapeutic advance in treatment. The availability of ipilimumab, pembrolizumab, nivolumab, vemurafenib, dabrafenib and trametinib (22, 23) represents a major therapeutic advance in the treatment of patients with metastatic melanoma.

Due to incidence and mortality rise as well as the rising trend of melanoma diagnosed in the young adult population, the issues concerning the cost of this disease are to be addressed and should serve as a decision-making tool for the financers and providers of health care. Cost-of-illness studies measure the economic burden of a disease to estimate the maximum amount of lives that might potentially be saved (or gained) if the disease is to be decreased (or even eradicated) (24). In concordance with other costing studies, costs in our study were structured depending on the type of cost and the staging where the costs occurred.

The aim of this study was to estimate the prevalence of certain type of melanoma (as well as staging distribution) and to connect each staging and its prevalence in Croatia with related costs.

MATERIALS AND METHODS

Data collection

For incidence data, we have used the data of diagnosed and treated patients at the Department of

Acta Dermatovenerol Croat
2017;25(1):1-7

Dermatology and Venereology Sestre milosrdnice, University Hospital Center in Zagreb, which was matched with the Oncology Department as well as with Croatian Cancer Registry data. Patient distribution was staged according to AJCC staging, and treatment variables were structured according to a valid treatment algorithm for treating melanoma in Croatia (25,26).

The Markov model was developed for prevalence data, with local incidence data from the Croatian Cancer Registry data for the 2007-2011 period. Model inputs were incidence data 2007-2011 by staging distribution and 5-year survival data. Furthermore, the frequency of diagnostics and treatments were analyzed according to guidelines and validated by three independent clinical experts. The sources of data include: a) patient hospital charts; b) the Croatian Cancer Registry, which provides national data on incidence and mortality; c) databases published by the NHIF (National Health Insurance Fund) on the number of hospitalizations per diagnosis; d) cost was based on prices published in the National Gazette; f) utilization of medications was cross-referenced with data from the Agency for Medicinal Products and Medical Devices and with clinical expert opinion. The process of data collection and analysis is shown in Figure 1.

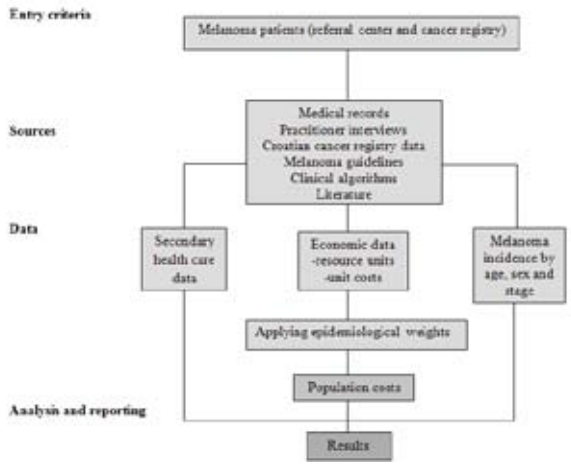

Figure 1. The protocol of data collection and analysis.

Cost analysis

The analysis included direct medical costs which were: drug costs (mostly chemotherapy costs since other drug costs such as non-steroid anti-inflammatory drugs were marginal), cost of diagnostic procedures (such as ultrasound, magnetic resonance imaging (MR), computed tomography (CT)), hospitalization costs, outpatient procedures (surgery), costs of monitoring (secondary and primary health care), and patient and palliative support. Non-medical costs usually relate to costs that do not refer to medical procedures, products, or services (e.g. costs of transport), and were not included in the study due to lack of data and an estimated small share in total costs (costs that are paid by the national insurer). Additionally, intangible costs of pain and suffering as well as diminished quality of life were omitted, due to our inability to quantify them.

Estimation of the direct costs was performed using a bottom-up approach, and the cost of certain procedure or product was multiplied by the prevalence or frequency of item usage. This means that different therapy and diagnostic costs were summed up to obtain the average cost of the treatment of a certain stage of the disease. Total cost was calculated by multiplying the unit cost of particular items (procedure, drug, or other medical event) with average estimated item utilization frequency, in line with clinical guidelines, to get an average cost per disease stage. These data are multiplied with the costs of all of the stages along with prevalence (a multiplication variable) to add up to the total cost of melanoma. In this way, we used unit costs for specific chemotherapy types, diagnostics, surgery, radiotherapy, and hospitalization. Unit costs were calculated without discounting costs since the timeframe was short enough to avoid cost depreciation correlated with time. Costs of treatment in primary health care also included administration costs of prescribing, counseling, and home therapy (costs of field nurse where needed). By using the data from the Referral Centr of the Ministry of Health of the Republic of Croatia (RC), we estimated data at the national level. The logic behind this was that this referral center also takes patients nationwide, and the numbers were compared to national statistics on melanoma. In order to estimate cost and resources utilization as realistically as possible, the difference between clinical guidelines and actual practice was overcome with clinical opinions of different clinical experts. This study takes into account a budget holder`s perspective, meaning that only the costs that are paid by the national health insurance fund are taken into calculation.

Epidemiological data

A prevalence-based approach was used in a freeze-frame of one year`s clinical setting, regardless of the individual data of the disease onset. This approach is taken when all medical care and morbidity related costs are included within a study year. Thus, mortality and disability costs are taken into account only for patients for whom these events take place in the study year (27). Where the prevalence data was not present, it was calculated by multiplying the

incidence with overall survival, taking into account the different survival data per staging. The Croatian National Cancer Registry was founded in 1959 and processes data electronically since 1968. Data sources include: application forms for discharged patients and outpatient reports of malignant neoplasms, including copies of histological/cytological findings. The data on deaths are collected from the cancer mortality database of the Central Bureau of Statistics and the Croatian National Institute of Public Health, which is the only fully electronic data source (28).

RESULTS

In 2011 there were a total of 559 new cases of melanoma in Croatia; 234 patients were diagnosed in the RC (Table 1) which means that RC had more than 40% of all new melanoma cases in Croatia (29). Some patients with advanced disease went directly to a surgeon or oncologist and visited a dermatologist only for a control skin examination.

Every year there are more than 500 newly diagnosed cases of melanoma in Croatia. Cancer registry data show that the incidence is slightly higher in men than in women. Melanoma is classified into 4 categories in the registry: local disease, regional disease (melanoma with lymph node involvement), distant disease (metastatic melanoma), and unknown stage. Every year, more than 35% of cases are recorded as unknown stage, which could be the consequence of reporting through a paper medium and other factors impacting quality of data. Early stage melanomas are more often diagnosed in an outpatient setting and these cases, unfortunately, are basically not reported because they demand only re-excision and clinical follow-up, almost never reaching the hospitalization stage or treatment. This makes these cancers more likely than others to be underreported in the cancer registry.

Table 1. Number of melanoma patients in 2011 in Croatia, classified by American Joint Committee on Cancer (AJCC) staging

AJCC stage	Number of patients in referral center
0	12
1A	69
1B	36
2A	41
2B	16
2C	7
3A	17
3B	7
3C	13
4	16
Total	**234**

In some years, the total number of melanoma was higher than the sum of all 4 categories – the difference arises because some persons were registered only through death certificates (do not have any oncology-slip or record of malignant neoplasms) and do not fall into any of these categories. For example, in 2011 there were a total of 559 incidence cases, but when we add local, regional, distant, and unknown melanoma we have 534 melanoma cases (Figure 2). The difference (559-534=25) means that for 25 people the only record of malignant disease came from information about death. Considering death occurred within a year we believe that thes 25 cases represent a distant disease.

According to our model, the estimated prevalence of melanoma in Croatia for the year 2011 was 2,180. There were 1,595 patients with local disease, 452 with regional disease, and 133 patients with metastatic melanoma. The total cost of melanoma in Croatia is estimated at 1,063,488 EUR. As seen below, the metastatic form bears more than 50% of the financial burder while at the same time having the smallest patient number.

Similar results are found when the costs were calculated using AJCC staging. Costs were slightly higher due to more precise staging for localized and regional disease. As with crude staging, the highest share in costs was reported for stage 4, accounting for 54.19% of total costs (Table 2). Stages 1B, 2A, 2B, and 2C were placed in one category because these stages have almost the same cost per patient according to clinical algorithms, similar "pathways", diagnostics, and therapeutic procedures.

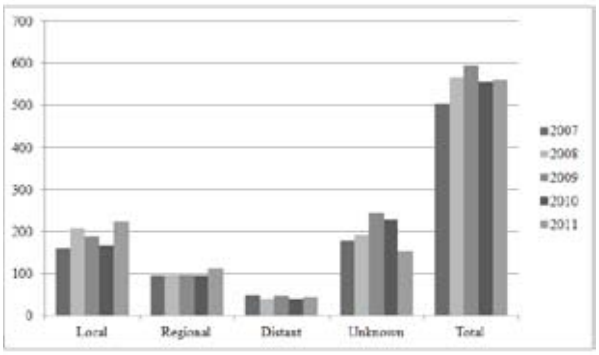

Figure 2. Cancer registry data for patients with melanoma by staging in Croatia in the 2007-2011 period,

Table 2. Cost per population by American Joint Committee on Cancer (AJCC) staging and by cancer registry data staging

Stage	No of patients	Total costs (EUR)	Share of costs	Stage	No of patients	Total costs (€)	Share in costs
0	96	10,439	0.98%	**Localized melanoma**	1,595	192,278	18.08%
1A	606	59,347	5.58%				
1B/2A-C	893	122,492	11.52%				
3A/3B	294	148,279	13.94%	**Regional disease**	452	294,919	27.73%
3C	158	146,64	13.79%				
4	133	576,291	54.19%	**Metastatic melanoma**	133	576,291	54.19%
Total	**2,180**	**1,063,488**	**100.00%**	**Total**	**2,180**	**1,063,488**	**100,00%**

Comparing average costs per single patient according to disease staging, stage 4 patients had the highest cost of 4,333 EUR. Patients in stage 0 or 1A had costs in ranging between 98 and 109 EUR, which is almost 44 times lower than patients with metastatic disease. This leads to the conclusion that the cost of treating one patient at an advanced stage of melanoma can cover the cost of treatment for many patients with melanoma detected at an early stage (Figure 3).

DISCUSSION AND CONCLUSIONS

Melanoma leads to substantial direct medical care costs. The cost of melanoma in Croatia in 2011 was estimated at 1,063,488 EUR. The highest share of this amount came from drugs and hospitalization. An interesting fact is that only 10% of total costs was for dermatoscopy, while 46% of the costs was related to hospitalization and medication (Figure 4). Aggregate treatment costs were at 17%, forming the total cost for the monitoring in the outpatient/office-based setting and specialist setting. Similar to other countries and cost studies, melanoma treatment costs varied by phase of care and stage at diagnosis. Costs per patient and total costs were highest by far for patients with metastatic melanoma. From April 2014, vemurafenib was reimbursed in Croatia for the treatment of patients with metastatic melanoma and positive BRAF V600 mutation. According to the drug price list, the monthly cost of vemurafenib per patient is 8,656 EUR. BRAF mutation is positive in approximately half of the patients with melanoma, and it is expected that 66 patients will be treated with vemurafenib annually due to tumor progression. The total annual cost of treatment for these patients would be 3,942,134 EUR. In this case the total cost of treating melanoma would be higher by almost five-times – 4,987,622 EUR and 90.6% of the share of the costs would be used for patients with stage 4 melanoma. The cost of one dermatoscopy in Croatia is 9.77 EUR. According to the cost in 2011, the difference in the cost of treatment of stages of 1 and 4 is 4,224 EUR, which means that 432 dermatoscopy exams could be done for the annual cost of treatment of one metastatic disease. When we look at the same scenario with vemurafenib, the difference in the cost of treatment of stages 1 and 4 is as high as 33,867 EUR, which means that 3,466 dermatoscopy exams could be done for the annual cost of treatment of one metastatic disease.

As was expected and found in similar studies, metastatic melanoma bears significant costs – the cost of treating one patient at an advanced stage of melanoma can cover the cost of treatment for many

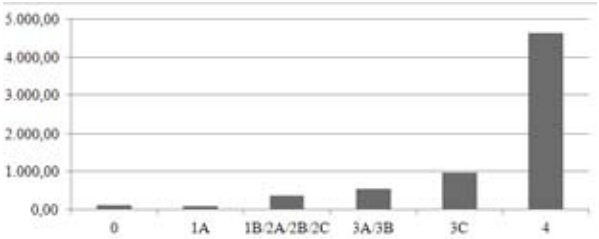

Figure 3. Average cost per patient in disease staging (EUR).

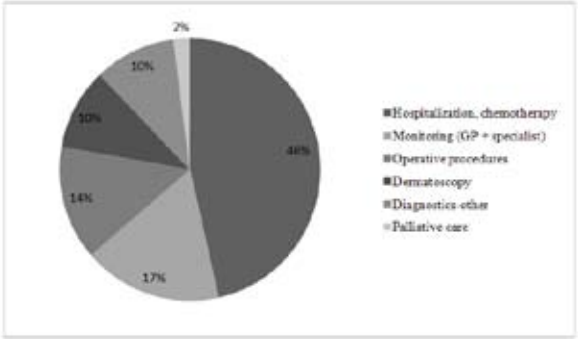

Figure 4. Cost structure.

patients with melanoma detected at an early stage. It is important to emphasize that the diagnosis of cutaneous melanoma at an early stage (stage 0, 1, and 2) saves lives, reduces treatment costs, and generates significant savings. The savings could be redirected towards programs of prevention and early detection of melanoma or could be invested in drugs for the treatment of advanced-stage patients. It is obvious that prevention is very important for the reduction of mortality and for financial reasons. Given the substantial cost of treating melanoma, public health actions should include primary prevention (education on the importance of reduction of exposure to UV radiation) and secondary prevention (early detection of melanoma).

Unlike in some western countries, melanoma screening is still not obligatory nationwide in Croatia. Despite many public campaigns in Croatia, melanoma still represents one of the major public health problems with a high burden and costs.

Although there is evidence that screening campaigns lead to a substantial yield of earlier and thinner melanomas, the precise effects of these programs in reducing melanoma mortality are still debatable (30).

The consequences of melanoma diagnosed at a late stage are usually related to the loss of productivity as a result of an individual's inability to work because of the disease complications. Such inability to work can be due to sick leave, early retirement, or premature death. There is also a psychological burden of being diagnosed with a life-threatening malignancy. All these can severely affect patient quality of life, burden their careers, and further compromise their health.

Many countries are well aware of the importance of photoprotective behavior because of the large number of patients with melanoma, such as Australia, and thus integrate principles of health economics in their guidelines on reducing the risk of melanoma for many years; however, this strategy is still not sufficiently represented in most countries (31,32).

We believe that cost-analysis of an illness may influence decision-makers in deciding and setting priorities, especially when screening decisions are to be made. Patient organizations and the society in general as well as health workers may find such studies useful in various ways as important stakeholders in shaping the policy landscape in the health care system.

Limitations of the study

The usual limitation of cost-of-illness study is the lack of support in deciding on how to allocate the health care resources. Additionally, it is hard to compare the results due to different methods as well as different health care financing in each country.

Early stage melanomas are more often diagnosed in an outpatient setting, and these cases, unfortunately, are often not reported because they only require re-excision and clinical follow-up, almost never reaching the hospitalization stage or treatment. This makes these cancers more likely than others to be underreported in a cancer registry.

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