Dermatol Ther (Heidelb) (2022) 12:1157–1165
https://doi.org/10.1007/s13555-022-00715-z

ORIGINAL RESEARCH

Malignant Melanoma: Direct Costs by Clinical and Pathological Profile

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Received: January 16, 2022 / Accepted: March 23, 2022 / Published online: April 15, 2022

ABSTRACT

Introduction: A number of studies have examined the impact of tumor stage on direct health care costs of patients with melanoma. This study aimed to investigate the association between the direct costs for melanoma and the patients' clinical and histological characteristics.

Methods: The present analysis included 1368 patients diagnosed with melanoma in 2017 in the Veneto Region (northeast Italy) and recorded in a regional population-based melanoma registry. The costs were assessed taking monthly and total direct costs into account. Log-linear multivariable analysis was used to identify the clinical and histological cost drivers, focusing on monthly and total direct costs per patient incurred during the first 2 years after a patient's diagnosis.

Results: On multivariable analysis, besides the stage of melanoma, also the presence of mitoses (> 2) was associated with higher monthly direct costs [odds ratio (OR) 1.55, 95% confidence interval (CI) 1.15–2.08, $p = 0.004$] in respect to cases with 0–2 mitoses. Vertical growth was associated with higher costs compared with radial growth (OR 1.28, 95% CI 1.00–1.64, $p = 0.055$). Moreover, the association between the absence of tumor-infiltrating lymphocytes (TILs) and higher monthly direct costs reached statistical significance (OR 1.31, 95% CI 1.05–1.64, $p = 0.017$). There were no differences in monthly direct costs by patients' sex or age, ulceration, or tumor site.

Conclusion: This study showed that not only tumor stage but also other clinical and histopathologic characteristics have an impact on the direct monthly and total costs of treating melanoma. Further studies on the cost-

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effectiveness of the various options for managing this disease should take these variables into account, as well as tumor stage, as cost drivers.

Keywords: Health economics; Melanoma; Healthcare services research; Direct costs

Key Summary Points

A number of studies investigated direct costs of melanoma by stage of tumor, but no published studies have examined the impact of clinical and histological characteristics (other than tumor stage) of patients with melanoma on the overall costs of their care.

This study showed that not only tumor stage but also other clinical and histopathologic characteristics (including mitotic rate, type of growth , and presence of TILs) have an impact on the direct monthly and total costs of treating melanoma.

Further studies on the cost-effectiveness of the various options for managing this disease should take these variables into account, as well as tumor stage, as cost drivers.

INTRODUCTION

Cutaneous malignant melanoma (CMM) incidence worldwide has increased steadily over the last decades, making it a growing public health problem. In Italy, the annual age-adjusted average incidence of CMM is 20.4 per 100,000 males, and 16.5 per 100,000 females, and it is rising [1]. While thin melanomas are the main contributors to the growing incidence rate, thicker lesions are also on the rise, and treatment of the latter is often more complex and costly. Depending on the stage of disease, treatment for melanoma can range from simple excision and sentinel lymph node biopsy to immunotherapy [2, 3]. Policy-makers therefore need to face the difficult task of guaranteeing all patients access to the most effective therapies while simultaneously ensuring the sustainability of healthcare systems as a whole. The use of diagnostic and therapeutic patient care pathways has enabled the development of a standardized approach not only to help specialists make more efficient decisions regarding their patients' management, but also in an endeavor to ensure a more rational allocation of resources.

In Italy, the treatment algorithm adopted follows the recommendations of the Italian Medical Oncological Association and the National Comprehensive Cancer Network. The Italian health system is nationalized, so economic assessments of the costs of melanoma conducted in the USA do not apply [4]. A previous Italian study found that the annual cost of patient care ranged from 149 euros for patients with in situ melanoma to 66,950 euros for those with stage IV disease [5].

So far, no published studies have examined the impact of clinical and histological characteristics (other than tumor stage) of patients with melanoma on the costs of their care. Using a regional registry of incident cases of melanoma at population level, this study aimed to investigate the associations between the direct costs of health care for cases of melanoma, total and per month until 2 years after the disease was diagnosed, and other clinical–histological characteristics of patients with melanoma, beyond stage at diagnosis.

METHODS

Context

The Italian National Health System is a public system financed mainly by general taxation, and organized essentially on a regional basis [6]. Its policies are grounded on fundamental values of universality, free access, freedom of choice, pluralism in provision, and equity. Regional authorities plan and organize healthcare facilities and activities in accordance with a national health plan designed to ensure an

equitable provision of comprehensive care throughout the country.

Veneto is a region in northeastern Italy. It has a resident population of 5 million with a mean age of 54.4 years. The per capita gross domestic product (GDP) in 2021 was estimated at 33,800 euros; 29.3% of the population 30–-34 years old have a university degree; and the unemployment rate is 5.8% [7].

To guarantee all residents equitable, uniform, and effective cancer care, the Veneto Regional Authority established a Veneto Oncology Network (*Rete Oncologica Veneta*) in 2013. Among other things, it is responsible for adapting the national guidelines for cancer care to the local context and establishing diagnostic and therapeutic patient care pathways that aim to achieve the best patient outcome, while ensuring the healthcare system's sustainability, and reducing inequalities and unwarranted variability in patient management. It thus developed an up-to-date clinical pathway for the diagnosis and treatment of melanoma that is shared by all melanoma centers in the Veneto Region [8].

In 2017, the Veneto Tumor Registry set up a high-resolution registry of melanoma cases in collaboration with the Veneto Oncology Network. In accordance with the guidelines of the International Agency for Research on Cancer (IARC) and the Italian Association of Tumor Registries (AIRTUM), the essential information collected on each case includes: the patient's date of birth, gender, and municipality of residence at the time of their diagnosis; data on the disease's incidence; topographical and morphological codes according to the International Classification of Diseases for Oncology (ICD-O-3); the grounds for the diagnosis; the patient's status (alive or dead); and follow-up data. In the specific case of CMM, further details were added to this basic information to obtain a high-resolution registry by retrospectively collecting details on the clinical features and stage of tumors at the time of their diagnosis [9].

Data and Variables

The present analysis was conducted with a population-based perspective including all 1368 patients diagnosed with melanoma in the Veneto Region in 2017. For each patient, the high-resolution melanoma registry contained a set of tumor characteristics including: TNM stage at diagnosis (as defined in the 7th edition of AJCC manual), growth phase (radial or vertical), presence of ulceration (yes/no), and tumor-infiltrating lymphocytes (TILs; yes/no), number of mitoses (categorized as 0–2, > 2) [10], tumor site (lower limbs, upper limbs, head, hands/feet, trunk). Patients were grouped by age as follows: < 40, 40–49, 50–59, 60–69, 70–79, and $80 +$ years.

Costs were assessed from the perspective of the Italian national health system, taking only direct costs into account. Each patient was linked via an anonymous unique identification code to all administrative data regarding their hospital admissions, day hospital service usage, drug prescriptions, admission to the emergency room, medical devices used at home, ambulatory services, and hospice admissions. In particular, by extracting relevant diagnostic or treatment procedures (those defined in the melanoma pathways [8]), it was possible to estimate the melanoma-specific direct costs per person. These data were used to calculate the total and monthly direct melanoma-related costs per patient for procedures and treatments incurred in the 2 years after their diagnosis. All costs are in euros.

Statistical Analyses

Absolute frequencies and percentages were used for the descriptive analysis. Costs are indicated as means and medians. Owing to the skewed distribution of the cost variables, 95% confidence intervals were estimated using the percentile bootstrap method, resampling 10,000 times. Differences in costs by patient groups were assessed with the Mann–Whitney or Kruskal–Wallis nonparametric tests, depending on the number of groups for each variable. Log-linear multivariable analysis was used to identify the clinical and histological cost drivers, focusing on the mean direct costs incurred per month during the first 2 years after a patient's diagnosis. In fact, to manage the skewed

Table 1 Melanoma-specific costs (mean and median) by histopathological characteristic

	N (%)	Melanoma-specific cost in €, mean (median) [95% CI]	*p* value
All patients	1368 (100.0%)	3820 (413) [3195–4445]	–
Sex			
Male	726 (53.1%)	4389 (473) [3476–5301]	0.006*
Female	642 (46.9%)	3175 (367) [2334–4016]	
Ulceration			
Yes	251 (18.3%)	9112 (1217) [6721–11504]	< 0.001
No	1023 (74.8%)	1851 (358) [1463–2239]	
Missing	94 (6.9%)	12826 (511) [7556–18096]	
Tumor-infiltrating lymphocytes			
Yes	862 (63.0%)	3044 (405) [2368–3720]	0.017
No	315 (23.0%)	4126 (467) [2874–5379]	
Missing	191 (14.0%)	6932 (367) [4350–9514]	
Age (year)			
< 40	133 (9.7%)	2915 (301) [1347–4483]	< 0.001
40–49	250 (18.3%)	3892 (373) [2198–5587]	
50–59	263 (19.2%)	3019 (501) [1884–4154]	
60–69	249 (18.2%)	3276 (454) [2080–4472]	
70–79	292 (21.3%)	5977 (495) [4240–7713]	
80+	181 (13.2%)	2840 (208) [1351–4330]	
Stage at diagnosis (AJCC 7th edition)			
I	854 (62.4%)	889 (329) [686–1092]	< 0.001
II	215 (15.7%)	3710 (759) [2315–5105]	
III	141 (10.3%)	13,792 (5905) [10,364–17,219]	
IV	63 (4.6%)	33,890 (5188) [23,436–44,343]	
Missing	95 (6.9%)	542 (212) [364–721]	
Mitoses			
0–2	860 (62.9%)	1446 (329) [1053–1839]	< 0.001
> 2	345 (25.2%)	7950 (1124) [6174–9726]	
Missing	163 (11.9%)	8174 (426) [5121–11230]	
Growth type			

Table 1 continued

	N (%)	Melanoma-specific cost in €, mean (median) [95% CI]	*p* value
Radial	270 (19.7%)	940 (268) [559–1321]	< 0.001
Vertical	804 (58.8%)	3891 (475) [3091–4692]	
Missing	294 (21.5%)	6387 (460) [4485–8289]	
Tumor site			
Lower limbs	248 (18.1%)	2067 (365) [1294–2839]	0.028
Upper limbs	172 (12.6%)	1658 (446) [973–2343]	
Head	151 (11.0%)	3031 (396) [1552–4509]	
Hands/feet	63 (4.6%)	2721 (447) [1044–4397]	
Trunk	680 (49.7%)	3967 (412) [3049–4884]	
Missing	54 (3.9%)	22,873 (2211) [13,414–32,331]	

*Mann–Whitney test; for all others, Kruskal–Wallis test

distribution of the costs, the model was estimated on their logarithmic transformation of costs. The mean direct costs per patient per month were calculated from the sum of the total costs incurred over 2 years after a patient's diagnosis and the months the patient was alive, to account for early deaths. The independent variables considered were: sex, age group, tumor stage, growth phase, ulceration, TILs, and tumor site.

The R 3.6.2 statistical package was used for record linkage and all statistical analyses.

Ethics

The data analysis was performed on anonymous aggregated data with no chance of individuals being identifiable. Ethical approval for the study was obtained from the Veneto Oncological Institute's ethics committee (no. 52/2016).

RESULTS

Table 1 presents the mean and median direct costs of health care for melanoma during the first 2 years after their diagnosis, by patients' sociodemographic and clinical variables. Statistically significant differences in the median costs are also reported. A total of 1368 patients were considered, and 726 (53%) of them were male. The mean and median costs per patient during the first 2 years after their diagnosis averaged respectively 3820 and 413 euros across the entire sample.

On multivariable analysis of the monthly melanoma-specific direct costs in the first 2 years after their diagnosis, tumor stages II, III, and IV were associated with higher costs than stage I (respectively: 1.84, 95% CI 1.27–2.67, $p = 0.001$; 9.03, 95% CI 6.13–13.30, $p < 0.001$; 7.52, 95% CI 3.89–14.54, $p < 0.001$) (Table 2, bold indicates statistically significance threshold at 0.05). The presence of > 2 (1.55, 95% CI 1.15–2.08, $p = 0.004$) mitoses was also associated with higher monthly direct costs than in cases with 0–2 mitoses. Vertical growth was associated with higher costs compared with radial growth (1.28, 95% CI 1.00–1.64, $p = 0.055$). The association between the presence of TILs and higher monthly direct costs reached statistical significance (1.31, 95% CI 1.05–1.64, $p = 0.017$). The impact of age on costs was only significant when the extreme groups (< 40 and 80 + year-olds) were compared, although a rising trend was apparent for

Table 2 Log-linear regression analysis of the association between monthly direct costs of melanoma in the first 2 years after diagnosis and sex, age, tumor stage at diagnosis, mitoses, ulceration, growth phase, TILs, and tumor site (variables with missing values)

		Exp (coefficient)	95% CI	*p* value
Sex (reference: female)	Male	1.09	(0.90–1.31)	0.390
Age (reference: < 40 years)	40–49	1.11	(0.78–1.58)	0.565
	50–59	1.36	(0.96–1.94)	0.084
	60–69	1.17	(0.82–1.67)	0.393
	70–79	1.19	(0.84–1.70)	0.327
	80+	0.42	(0.29–0.63)	< **0.001**
Stage at diagnosis (reference: I)	II	1.84	(1.27–2.67)	**0.001**
	III	9.03	(6.13–13.30)	< **0.001**
	IV	7.52	(3.89–14.54)	< **0.001**
	Missing	0.47	(0.26–0.86)	**0.014**
Mitoses (reference: 0–2)	> 2	1.55	(1.15–2.08)	**0.004**
	Missing	1.91	(1.13–3.24)	**0.016**
Ulceration (reference: no)	Yes	1.04	(0.76–1.43)	0.788
	Missing	0.84	(0.46–1.51)	0.557
Tumor-infiltrating lymphocytes (TILs) (reference: yes)	No	1.31	(1.05–1.64)	**0.017**
	Missing	1.10	(0.76–1.59)	0.601
Growth type (reference: radial)	Vertical	1.28	(1.00–1.64)	0.055
	Missing	1.17	(0.85–1.60)	0.334
Tumor site (reference: lower limbs)	Upper limbs	1.06	(0.76–1.49)	0.711
	Head	1.14	(0.80–1.62)	0.468
	Hands/feet	1.12	(0.70–1.81)	0.628
	Trunk	1.21	(0.94–1.56)	0.136
	Missing	1.00	(0.49–2.03)	0.999

Adjusted R^2 = 0.25

patients aged 40–60 years. Finally, there were no statistically significant differences in monthly direct costs by patients' sex, ulceration, or tumor site. Similar results were found on multivariable analysis of the total direct costs over 2 years after diagnosis (data not shown).

DISCUSSION

This study identified that the presence of ulceration as well as more than two mitoses and vertical growth were significantly associated with higher monthly costs even after adjusting for stage at diagnosis.

It is intriguing that, although our analysis was adjusted for tumor stage, the presence of

mitoses significantly influenced the monthly and total direct costs of melanoma. The mitotic index was omitted from the 8th edition of the American Joint Committee on Cancer TNM system for prognostic purposes, but it appears to have a crucial role in predicting survival and costs—as we had previously found using an artificial intelligence-based model [11]. This may be partly due to the relevance attributed to mitoses in the earlier NCCN guidelines, which called for a more aggressive treatment, with consequently higher costs.

In our study, vertical growth proved effective as a cost predictor. Being a negative prognostic factor, vertical growth could induce physicians to opt for more aggressive treatments, whereas horizontally growing neoplasms are biologically indolent (in the absence of regression) and lack in metastatic capacity [12].

The strengths of our study lie in: its design (a population-based, not center-specific study), which lends the data greater external validity; a great statistical power of the sample; and relatively low missing data rates.

Limitations

The limitations of this study concern the focus only on direct costs: being based on real-world data obtained from administrative hospital flows, it does not include (potentially significant) indirect costs. While the present study examined costs over 2 years after diagnosis, a longer follow-up might give us a better idea of whether the overall costs of illness were associated with the melanoma patients' clinical–histological characteristics. On the other hand, a previous study assessing the cost distribution by year after diagnosis found that, for various malignant conditions, the costs peak in the first year after diagnosis, and then tend to decline [13]. Finally, it is worth noting that some information is missing from our database regarding histopathological variables for some patients. If missing data were associated with both costs and anatomopathological groups, our findings regarding the association between costs and groups might be biased. Further studies are needed to analyze the differences in costs after recent changes to the CMM treatment paradigm and the introduction of immunotherapies.

CONCLUSIONS

This study showed that not only tumor stage but also other clinical and pathologic features have an impact on the direct monthly and total costs of treating melanoma. Further studies on the cost-effectiveness of the various options for managing this disease should take these variables into account, as well as tumor stage, as cost drivers.

ACKNOWLEDGEMENTS

Funding. Funding for this study and for the journal's Rapid Service Fee was provided by CARIPARO, Fondazione Cassa di Risparmio di Padova e Rovigo. The company had no role in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the paper for publication.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author contributions. Alessandra Buja conceived the study. Vincenzo Baldo and Alessandra Buja developed the methods. Romina Spina, Manuel Zorzi, Paolo del Fiore and Saveria Tropea collected the data. Chiara De Toni and Claudia Cozzolino performed the analyses. Giuseppe de Luca, Massimo Rugge, Antonella Vecchiato, Alessandra Buja an Manuel Zorzi wrote the draft. Massimo Rugge, Simone Mocellin, Carlo and Riccardo Rossi supervised the project and approved the final draft. All authors read and approved the final manuscript.

Disclosures. Alessandra Buja, Massimo Rugge, Giuseppe De Luca, Manuel Zorzi, Chiara De Toni, Claudia Cozzolino, Antonella Vecchiato, Paolo Del Fiore, Saveria Tropea, Romina Spina, Vincenzo Baldo, Carlo Riccardo Rossi and Simone Mocellin have no competing interests of any sort to disclose.

Compliance with Ethics Guidelines. The data analysis was performed on anonymous aggregated data with no chance of individuals being identifiable. Ethical approval for the study was obtained from the Veneto Oncological Institute's Ethics Committee (no. 52/2016).

Data Availability. The data supporting the findings of this study are held by the Veneto Epidemiological Registry and were used under license for the present work, but they are not publicly available. These data are nonetheless available from Manuel Zorzi on reasonable request and subject to permission being obtained from the Veneto Epidemiological Registry (Veneto Regional Authority).

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