Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2024 Mar 20; 12(2):Ahead of Print
https://doi.org/10.3889/oamjms.2024.11805
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Oncology*

Real-world Observational Multi-center Study: Retrospective Analysis of Diagnostic and Treatment Patterns for Stage III–IV Melanoma in Ukraine from 2018 to 2020

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Edited by: Mirko Spiroski
Citation: Kukushkina M, Ryspayeva D, Lisovska N, Kryvonos Y, Skrypko V, Sokur I, Tarasenko T, Burma I, Gotko Y, Salo N, Poellinge B, Zreikat H. Real-world Observational Multi-center Study: Retrospective Analysis of Diagnostic and Treatment Patterns for Stage III–IV Melanoma in Ukraine from 2018 to 2020. Open Access Maced J Med Sci. 2024 Mar 20; 12(2):Ahead of Print https://doi.org/10.3889/oamjms.2024.11805
Keywords: Melanoma; Diagnostic; Chemotherapy; Immunotherapy; Targeted therapy
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Received: 02-Oct-2023
Revised: 20-Dec-2023
Accepted: 30-Jan-2024
Ahead of Print: 20-Mar-2024

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Despite open-access sources with information about cancer patients (National Cancer Registry of Ukraine), there are considerable gaps about actual diagnostic methods and specific treatment patterns or any details on how different regimens are applied for melanoma treatment in Ukraine.

OBJECTIVES: This non-interventional, multicenter, retrospective medical chart review study aims to describe real-world therapeutic strategies and characterize the profile of patients with melanoma Stage III–IV in real-life clinical practice in Ukraine.

METHODS: Anonymized data were collected from medical records of 747 patients in 9 oncology centers in Ukraine - four private and five public. The data variables were retrieved, captured in electronic case report forms, and analyzed with descriptive statistical methods.

INCLUSION CRITERIA: Subjects were not enrolled unless they met all the following criteria: (1) Age >18 years at the time of being diagnosed with III–IV stage melanoma. (2) Morphologically (including cytology) confirmed diagnosis of III–IV stage melanoma. Sufficient available medical records for data abstraction to meet the objectives of the study, that is, the patient has been under the medical care of the participating site for the entirety of the patient observation period or the patient's detailed historical data on their disease course, and clinical management are otherwise available at the participating site consent has been granted by the Institutional Review Board/Ethical Committee of the study site.

EXCLUSION CRITERIA: Subjects were not enrolled if they met any of the following criteria: (1) The patient has received treatment with anticancer systemic therapy for reasons other than melanoma. (2) Primary cancer other than melanoma. (3) The patient is participating (or was participating) in any investigational program/clinical trial with interventions outside of routine clinical practice. All the statistical tests were two sided and performed at a 0.05 significance level. p-values were rounded to three decimal places. $p < 0.001$ were reported as <0.001 in tables.

RESULTS: Most melanoma cases (95.05%) were diagnosed histologically, although information about the primary tumor's characteristics and treatment are heterogeneous. Most individuals (51.05%) diagnosed with Stage III undergo surgical treatment without additional therapy. Chemotherapy constitutes the primary form of systemic therapy for Stages III and IV, accounting for 33.3% and 45.65%, respectively.

CONCLUSION: It is crucial to tackle the problems associated with diagnosing and treating melanoma in Ukraine. This involves creating a unified registry for melanoma patients, establishing uniform methods for staging and re-staging, and standardizing medical records. Nevertheless, the most critical issue is the absence of access to modern therapy, which should be addressed at the state level.

Introduction

Melanoma incidence has been increasing globally over the past decades [1]. Specifically, in 2020, skin melanoma ranked as the 17th most prevalent cancer worldwide, accounting for 325,000 newly diagnosed cases [2], [3].

According to the National Cancer Registry of Ukraine, the estimated number of new melanoma cases in 2020 was 2,422, constituting 2.14% of all newly diagnosed cases (excluding non-melanoma skin cancer). In addition, there were 844 deaths attributed to melanoma, accounting for 1.5% of all cancer-related deaths. The incidence rate of cutaneous melanoma ranks 11th among men (2.7%) and 10th among women (2.8%) in the nosological structure of malignant neoplasms in 5-year cohorts of Ukrainian patients (2017–2021).

In the year 2020, the National Cancer Registry recorded 28,058 cases of melanoma, indicating a

prevalence of 81.00/100,000 individuals and a crude incidence rate of 6.8/100,000. Specifically, 6.9% and 5.3% of new melanoma cases were classified as III and IV stage, respectively. A substantial portion of melanoma cases, 90.0%, received specialized treatment. Of these cases, 68.6% of patients exclusively underwent surgical treatment, while only 18.3% received systemic treatment [4].

Regrettably, the National Cancer Registry lacks specific data on treatment patterns, coverage, or the distribution of treatment types based on disease stage, particularly concerning melanoma.

Multiple treatment options for Stage III–IV melanoma are available, including anti-programmed death ligand-1 inhibitors and BRAF/MEK inhibitors for patients with BRAF-mutated tumors [5], [6], [7]. However, there is a challenge in ensuring that patients have sufficient access to these varied treatment modalities, including the recommended innovative treatment as per the current guidelines. Anti-PD1 antibodies, namely pembrolizumab and nivolumab, are officially approved for first-line therapy in 25 out of 30 countries, accounting for 83%. Full reimbursement is documented in 14 out of 30 countries, representing 47%. Chemotherapy (dacarbazine) is not used as a first- and second-line treatment in Western Europe. However, in 31% of Eastern European countries, dacarbazine is the solely available treatment for 50–90% of patients [8].

This observational study aims to gain insights into the actual practices concerning the treatment of patients diagnosed with metastatic melanoma at Stages III and IV throughout Ukraine. In addition, the study seeks to discern the factors influencing the treatment choices of these patients.

Materials and Methods

Study design and patient selection

This was an observational, non-interventional, multicenter study involving the retrospective review of medical charts, relying on secondary data collection. The study aimed to delineate real-world therapeutic strategies and profile patients with melanoma Stage III–IV in actual clinical practice in Ukraine. Data were retrieved from the medical records of 747 patients, spanning nine oncology centers, including both public and private institutions.

All eligible patients in this study were diagnosed with melanoma at Stages III–IV between January 2018 and December 2020. To be included, patients had to meet the following criteria:

1. Age >18 years at the time of being diagnosed with III–IV stage melanoma
2. Morphologically (including cytology) confirmed diagnosis of III–IV stage melanoma
3. Sufficient available medical records for data abstraction to meet the objectives of the study, that is, the patient has been under the medical care of the participating site for the entirety of the patient observation period or the patient's detailed historical data on their disease course, and clinical management is otherwise available at the participating site.

No informed consent form (ICF) was collected during the study. Instead, approval was obtained from the Institutional Review Board to collect medical data in anonymized/depersonalized form in the absence of the ICF (study site template). The study protocol underwent review and approval by the Ethical Committees of all nine centers, adhering to the ethical guidelines of the 1975 Declaration of Helsinki. Ethical data collection strictly followed the provisions outlined in the Law of Ukraine "On Personal Data Protection."

Exclusion criteria encompassed patients who had received anticancer systemic therapy for reasons unrelated to melanoma, those with primary cancer other than melanoma, or individuals involved in any investigational program or clinical trial with interventions beyond routine clinical practice at the time of potential data collection.

Procedures

The data variables were retrieved and anonymously captured in electronic case report forms. The duration of the chart abstraction period was 8 months.

In pursuit of the study objectives, the following data were collected:

- Sociodemographic and anthropometric variables at baseline (such as date of birth, sex, and race)
- Patient's characteristics at baseline (including family history of melanoma and diagnostic methods)
- Clinical and pathological features of melanoma
- Laboratory and molecular testing data (including lactate dehydrogenase [LDH] and genetic tests)
- Types of treatment administered, encompassing surgical procedures and therapeutic categories.

Statistical analysis

The data were analyzed using descriptive statistical methods. Categorical variables were presented as absolute and relative frequencies. For continuous variables, descriptive statistics, including the number of patients with available observations,

the number of missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum (min), and maximum (max), were tabulated. The normality of the distribution of continuous variables was examined using the Shapiro–Wilk test.

Time-to-event analyzes were performed using the Kaplan–Meier method and multivariable logistic regression analysis. Univariable and multivariable logistic regression analyzes were conducted to assess the association of demographic and clinical characteristics with the choice of treatment regimens or no treatment.

All statistical tests were two sided and conducted at a significance level of 0.05. The statistical analysis was carried out using the software package SPSS 26. Figures were generated using graph programs such as SAS® and/or Microsoft Excel, as well as GraphPad Prism (10.1.0).

Results

747 patients were included in the study; 380 of them were in Stage III and 367 in Stage IV. The distribution consisted of 385 men and 362 women.

The overall population had a mean age of 55.2 ± 14.1 years (median 56.3, 95% confidence interval 54.12–56.2). Most patients, 711 (95.2%), were of European descent.

As of the study initiation date, 247 patients were still alive, while 155 patients had died; information regarding 345 was unavailable. Melanoma was identified as the primary cause of death for 103/155 patients (66.5%); the cause of death for other patients is unknown.

Within the study, ten patients (1.3%) reported a family history of melanoma in first-degree relatives. Many patients either lacked a family history (n = 406, 54.4%) or had unknown family history information (n = 331, 44.3%). Twelve patients (1.6%) had multiple primary melanomas.

Patients and tumor characteristics are presented in Tables 1 and 2.

According to medical records, nearly 65% of doctors used the 7th Edition of the American Joint Committee on Cancer (AJCC) for staging melanoma, while others used the 8th Edition of AJCC.

Diagnosis of melanoma was confirmed by histology in 725 patients (97.1%), cytology in six patients (0.8%), and other patients by both methods.

It should be noted that there is no unified protocol for histological reports of melanoma in Ukraine. The obtained data indicate that the most used characteristics described in the pathology report were the histological subtype of melanoma, Breslow's thickness, status of ulceration, and Clark's level. The mean Breslow's thickness of the primary tumor was 3.3 mm for Stage III and 3.7 mm for Stage IV; in the total population, it was 3.5 mm, and more than one-third of patients had ulceration. The mitotic index of primary melanoma was reported only for 34 (4.6%) patients.

Table 1: Clinical characteristics of patients

Characteristics	All patients n (%)	Stage III n (%)	Stage IV n (%)
Number of patients, (%)	747 (100.0)	380 (51.0)	367 (49.0)
Male	385 (100.0)	185 (48.1)	200 (51.9)
Female	362 (100.0)	195 (53.9)	167 (46.1)
Mean age (years)	55.2 ± 14.1	56.5	53.8
Median age (years)	56.3	58.0	55.3
95% CI	54.2–56.2	55.0–58.0	52.3–55.3
The anatomical site of the primary tumor (s)			
Trunk	316 (42.1)	153 (40.2)	163 (44.4)
Lower extremity	162 (21.8)	104 (27.4)	58 (15.8)
Head and neck	108 (14.5)	55 (14.5)	53 (14.4)
Upper extremity	88 (11.8)	47 (12.4)	41 (11.2)
Other	57 (7.6)	18 (4.7)	39 (10.6)
Data unavailable	16 (2.1)	3 (0.8)	13 (3.5)

Sentinel lymph node (SLN) biopsy as one of the diagnostic instruments was performed only in 55/747 patients (7.3%). Dramatically, 34 of 55 (61.8%) patients had occult metastases in SLNs.

Among patients with Stage IV, brain metastases were found in 83/367 patients (22.6%). LDH for Stage IV was performed only for 30/367 patients (8.2%), and in 19/30 cases (63.3%), it was elevated.

The total rate of molecular genetic testing (BRAF, KIT, NRAS) was low and performed in

Table 2: Tumor characteristic

Characteristics	All patients n (%)	III stage n (%)	IV stage n (%)
Histologic subtype of melanoma			
Nodular	240 (32.1)	148 (39)	92 (25.0)
Superficial spreading	89 (12.0)	48 (12.6)	41 (11.2)
Acral lentiginous	6 (0.8)	5 (1.3)	1 (0.3)
Lentigo maligna melanoma	3 (0.4)	0 (0.0)	3 (0.8)
Other	168 (22.5)	90 (23.7)	78 (21.3)
Data unavailable	241 (32.3)	89 (23.4)	152 (41.4)
Breslow's thickness			
<1 mm	30 (4.0)	18 (4.7)	12 (3.3)
1–2 mm	47 (6.3)	28 (7.4)	19 (5.2)
2–4 mm	153 (20.5)	94 (25.0)	59 (16.0)
≥4 mm	240 (32.1)	138 (36.2)	102 (27.9)
Data unavailable	277 (37.1)	102 (26.7)	175 (47.7)
Ulceration			
Present	259 (34.7)	144 (37.9)	115 (31.3)
Absent	177 (23.7)	103 (27.1)	74 (20.1)
Data unavailable	311 (41.6)	133 (35.0)	178 (48.5)
The Clark level of invasion			
1	1 (0.1)	0 (0.0)	1 (0.3)
2	23 (3.0)	15 (4.0)	8 (2.2)
3	147 (19.7)	81 (21.3)	66 (17.9)
4	207 (27.7)	122 (32.1)	85 (23.4)
5	69 (9.2)	43 (11.3)	26 (7.0)
Data unavailable	300 (40.2)	119 (31.3)	181 (49.3)
Regional lymph node metastases			
Present	535 (71.6)	329 (86.6)	206 (56.1)
Absent	73 (9.8)	23 (6.1)	50 (13.6)
Data unavailable	139 (18.6)	28 (7.3)	111 (30.3)
Satellite	36 (4.8)	24 (6.3)	12 (3.3)
Transit metastases	52 (7.0)	38 (10.0)	14 (3.8)
Brain metastases			
Present	83 (11.1)	-	83 (22.6)
LDH			
>upper norm range	19 (2.5)	-	19 (5.2)
<upper norm range	11 (1.5)	-	11 (3.0)
Unknown	717 (96.0)	-	337 (91.8)

LDH: Lactate dehydrogenase.

158/747 (21.2%) patients: in 56/380 (14.7%) for Stage III and 102/367 (27.8%) for Stage IV (Table 3).

Table 3: Molecular genetic tests

Type of mutations	All patients n (%)	III stage n (%)	IV stage n (%)
BRAF	147 (19.7)	53 (14.0)	94 (25.5)
KIT	9 (1.2)	3 (0.7)	6 (1.6)
NRAS	2 (0.3)	0 (0)	2 (0.5)

Treatment modalities were analyzed regarding the tumor stage. Among 380 patients with Stage III, 194 (51.1%) had surgical treatment, 182 (47.9%) had surgery and adjuvant therapy; only 4 (1.0%) patients had unresectable regional metastases and received systemic treatment alone. 65 (17.7%) patients with distant metastases had surgical treatment too.

For resectable melanoma Stage III after surgical treatment, 182 (47.9%) patients received adjuvant therapy: 58 (31.9%) α2b-interferon, 56 (30.7%) pembrolizumab, and 53 (29.1%) chemotherapy. Target therapy with BRAF- and MEK-inhibitors in the adjuvant setting was used in 14 (7.7%) patients and other therapy in 1 patient (0.5%) only.

The consequences of systemic treatment for Stage IV melanoma are summarized in Figure 1. Chemotherapy was used over 40% in the 1st, 2nd, and 3rd lines, followed by anti-PD1 pembrolizumab, the only registered immune check inhibitor in Ukraine. Administration of targeted therapy increased from 1st to 3rd line of systemic treatment from 9.6% to 30%, respectively. α2b-interferon was used in 1st and 2nd lines. Dacarbazine was the most frequently administrated chemotherapeutical drug, followed by paclitaxel, carboplatin, and lomustine.

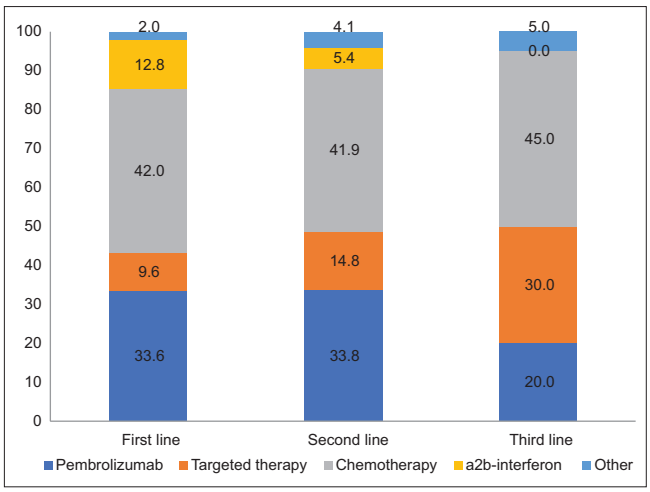

Figure 1: Systemic therapy for melanoma Stage IV

Discussion

Recent treatment modalities have significantly improved the prognosis of advanced melanoma: particularly, antiPD-1 therapy and combined immunotherapy in the first line increased 5-year overall survival to 43–44% and 52%, respectively, for Stage IV melanoma [9]. Real-world data facilitate a deep understanding of new agent implementation in clinical practice [10], [11], [12].

Based on our retrospective analysis of routine clinical practice in Ukraine, our study has shown the challenges that arise during the implementation process. Although the data we have highlighted are valuable, we must acknowledge the potential limitations of real-world evidence, such as its retrospective nature and the limited number of patients included in our study. After researching, we identified some disadvantages of diagnosing and treating melanoma in Ukraine.

Medical charts in electronic and paper forms have been discussed due to the issues associated with accessing and saving paper medical charts. The lack of standardization of electronic medical records in Ukraine has resulted in varying structures of patient information across medical centers, leading to difficulties in accessing and applying actual medical information. As a result, many medical charts need more data. However, the progress in electronic medical document management has been promising. It helps doctors lead the patient, fill out the documentation, and prevent losing data.

An adequate staging procedure is crucial for clinical decisions and communication among physicians. In our study, we utilized both the previous and current editions of the AJCC staging systems, considering the period taken for analysis. However, we observed that there needs to be a unified approach to re-staging, leading to a gap between the actual stage of the disease and the records in medical documents. This discrepancy results in incorrect patient information.

Another issue concerns the diagnostic methods, precisely the histological diagnostic method. There are a few issues related to the histological diagnosis protocol. First, there is a need for a unified protocol for histological diagnosis, as various diagnostic procedures, which are often outdated, are still being used. Second, there is limited access to SLN biopsy, as this method is unavailable in state medical centers. Finally, molecular diagnostic tests are usually outside of a governmental program and must be done in private laboratories, which can be costly. Therefore, these tests are typically only available in private clinics, that reduces the accuracy of the diagnosis and its compliance with modern protocols. However, the recent registration of indocyanine green dye for SLN biopsy decrease the cost of the procedure. That removes dependence on the supply of radiopharmaceuticals, which is especially important in wartime.

The situation with drug treatment of melanoma is more complicated due to the lack of registration and availability of innovative drugs. A limited selection of oncological medicines is available in the Ukrainian

public procurement. In addition, the Ukrainian program for reimbursement does not cover any medications from the oncological group, except for chemotherapy. This means that there are no drugs available for target therapy and immune checkpoint inhibitors that are purchased by the state. Only a few medications recommended by international guidelines for treating melanoma are registered in Ukraine, including pembrolizumab, dabrafenib and trametinib, vemurafenib, and cobimetinib. Due to the high cost of oncology drugs, most patients cannot afford them [8]. This leads to the fact that 50% of patients with Stage III melanoma receive only surgical treatment without any further adjuvant therapy. At the same time, chemotherapy remains the primary systemic therapy for Stage III and IV melanoma.

In 2023, Ukrainian national recommendations were developed based on European recommendations to increase doctors' awareness and standardize medical care for melanoma patients and its control. As well inclusion of a group of molecular genetic methods (BRCA 1, BRCA 2, KRAS, NRAS, EGFR, BRAF, ALK, HER2, and others) in the list of medical guarantee programs in 2024 will facilitate patients' access to modern methods of diagnosis and the ability of doctors to select treatment more individually.

Conclusion

Significant features of diagnosis and treatment for Stages III–IV melanoma in Ukraine from 2018 to 2020 were identified. The most commonly used diagnostic methods are not up-to-date nor are the systemic therapies. More than 50% of patients with Stage III melanoma receive only surgery without further adjuvant therapy. Chemotherapy continues to be the primary method of systemic treatment for Stages III and IV melanoma patients due to the unavailability of modern drugs.

Addressing the issues identified in diagnosing and treating melanoma in Ukraine is essential. This includes the establishment of a single registry for melanoma patients, the development of consistent methods for staging and re-staging, and the standardization of medical records. However, the most pressing issue is the lack of access to modern therapy, which needs to be resolved at the state level.

Acknowledgments

We are grateful to medical centers that allowed and facilitated data collection of information in medical charts, sub-investigators, and study coordinators, who made a significant contribution to the gathering and processing of information, namely Serhii Dedkov, Alevtyna Nalimova, Andrii Molnar, Lesia Grabchak, Oleg Atamanyuk, and Olga Soloshenko.

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