

Clinical Study on the Increased Incidence of Nodular Melanoma Cases Compared to Superficial Melanoma

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ABSTRACT: Our study group was comprised of 67 patients with melanoma, admitted and operated in our clinic between 2010-2018. Only the patients with melanoma localized on the head, torso and upper limb were selected for our study. We attempted to establish a link between the clinical appearance, presence or absence of ulceration, presence or absence of regional lymphadenopathy or distant metastases, surgical technique, histopathological type, Clark level and Breslow depth, disease stage (TNM), adjuvant therapies and survival rates at 1, 3, 5 and 10 years.

KEYWORDS: Melanoma, ulceration, surgical technique, Clark level, Breslow thickness, lymphadenopathy.

Introduction

Malignant melanoma (MM) is a skin tumor derived from melanocytes, which undergo a malignant transformation generating alteration of the systems that control and regulate cell division. This disturbance causes the appearance of modified daughter cells, which multiply continuously and anarchically [1].

The main risk factors associated with MM are family history and genetic predisposition, exposure to ultraviolet radiation (UV) and excessive steroid hormones.

A previous history of MM increases the risk of developing another tumor by 5-15%.

In individuals with multiple MM, about 50% develop a second primary tumor in the same region, and 50% develop the second tumor in the first year after the initial diagnosis, which requires long-term medical supervision for the patients.

The monitorization of cutaneous melanoma should be based on early detection of transformed nevi, as well as dysplastic nevi with malignant transformation potential, early detection, and diagnosis of any new lesion.

This means that the patient should contact the general practitioner, dermatologist, or plastic surgeon to establish paraclinical investigations such as computed dermatoscopy, blood tests, computerized tomography (CT) or magnetic resonance

imaging (MRI), needed for the diagnosis of MM.

An important investigation, before any surgery and first intention is the computerized dermatoscopy performed by the dermatologist with modern devices, such as Fotofinder or Molemax, which map the nevi on the body and identify suspect lesions.

The study aimed to evaluate the survival rates for the operated patients, in relation to the subtypes of melanoma and their subsequent healing in the post-surgical period. We chose cutaneous melanoma as the object of study because of the increasing incidence reported worldwide. The highest incidence was reported in the 40-60 age group.

Materials and Methods

After obtaining informed consent, we selected 67 patients operated for melanoma over a 9-year period (2010-2018) at the Plastic Surgery Department of the Emergency County Hospital of Craiova, whom were confirmed both histologically and immunohistochemically. We assessed the evolution of postoperative wounds, tracked possible local complications.

The histopathological subtypes that were diagnosed:

- melanoma with superficial spreading (MSS)
- nodular melanoma (NM)
- achromic melanoma (AM)

I. Surgery

The oncologic safety margins were selected by:

- performing a dermatoscopy with thermography to determine the horizontal distance from the melanoma to the area where the thermography indicated normal temperatures [2].

- performing an ultrasound with elastography, to measure the horizontal distance from the melanoma where edema can be observed in the soft tissues: $H=0.54 \times (T+U)$

H-horizontal distance from the melanoma to the incision (cm);

T-horizontal distance from the melanoma to the area where the thermography indicates the normal temperature (cm);

U-horizontal distance from melanoma to the area where ultrasonography indicates lack of edema (cm).

0.54-coefficient of veracity

The basic principle is focused on the reflexogenic morphology of the ultrasonographic waves that appear in the peritumoral tissues, the ultrasound being performed from the healthy tissues towards the tumor, thus establishing the distance from the tumor edge and the dermal edema. Ultrasound offered the possibility to visualize the pathological changes in depth, but which were not included in the formula.

We considered the presence or absence of loco-regional lymphadenopathy detected clinically, by ultrasound or CT. Lymphadenectomy was performed in these cases.

Based on these considerations, the following procedures were performed:

- excision and direct suture in 10 cases
- excision+plastic surgery with split thickness skin graft in 12 cases
- excision+plastic surgery with split thickness skin graft and lymphadenectomy in 20 cases
- excision+flap+lymphadenectomy in 19 cases
- excision+flap in 6 cases

To differentiate the operated cases, we envisioned a classification of severity according to the performed intervention, to make a prognosis of survival after surgery: I) excision without skin grafting and lymphadenectomy and II) excision with skin grafting, flaps and lymphadenectomy.

Local anesthesia was used for tumors between 0.5-1cm and thickness <2cm, and general anesthesia was used for the rest.

II. Histopathological analysis

The excised tumor was placed in a container with 10% formaldehyde and paraffin sections were stained with hematoxylin-eosin.

Immunohistochemistry was also performed and showed high expression of HMB45 and S100 in tumor areas, as well as high Ki-67 indexes in 60 cases.

Following the surgical excisions, patients were monitored for months or years, both in the outpatient clinic and at the oncologist, to determine life expectancy and quality of life.

Regarding the composition of the proposed subgroups, we used the following criteria:

- presence of the tumor (ABCDE rule)
- presence of modified lymph nodes
- presence of distant metastases
- standard imaging and laboratory investigations
- pathological examination based on American Joint Committee on Cancer (AJCC/UICC recommendations, NCCN Guidelines Version 2.2021 Cutaneous Melanoma)

The histological markers investigated were:

- Histological subtype of MM present
- Breslow depth
- Clark level
- Mitotic rate
- Presence of ulceration
- Lymphatic permeability

All surgical procedures were preceded by primary tumor biopsy, MM diagnosis and choice of type of surgery.

Prior to the surgical excision, the safety margins for the tumors were established, depending on the size and macroscopic appearance of the tumor, its anatomical location, the presence of satellite adenopathy or metastases.

Results

We compared the distribution by sex (male/female) and environment of origin (rural/urban) and did not identify statistically significant differences between the two series-34 female to 33 male, and 34 urban to 33 rural.

A percentage of 65% of the tumors were *de novo* MM, developed on healthy skin, and 35% developed on preexisting nevi.

A significant increase in the number of cases of NM, compared to MSS was identified. In addition, 5 cases of AM, a less commonly developed subtype of melanoma, were identified (Figure 1, Table 1).

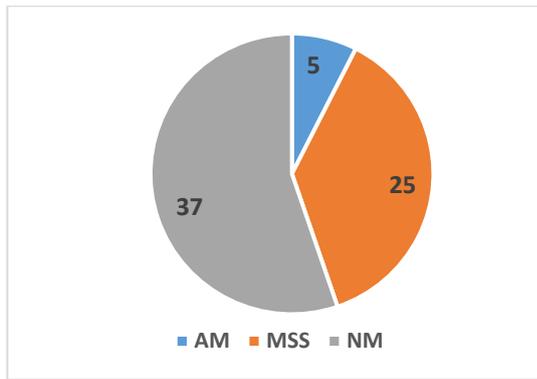


Figure 1. Subtypes of melanoma.

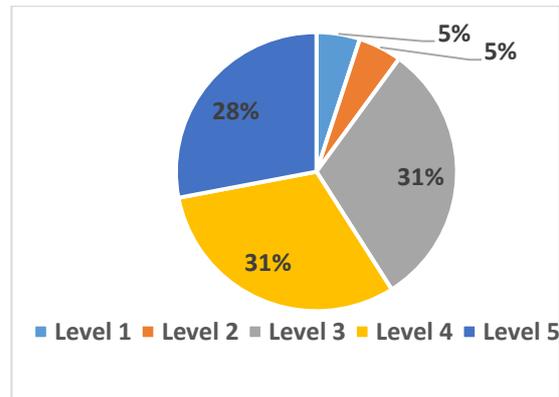


Figure 2. Clark level.

Table 1. Type and topography of MM.

Topography	MSS	NM	AM	No. of cases
Head	2	12	1	15 (22.38%)
Torso	10	17	4	31 (46.26 %)
Upper limb	3	1	0	4 (5.9%)
Lower limb	10	7	0	17 (25.37%)
TOTAL	25	37	5	67

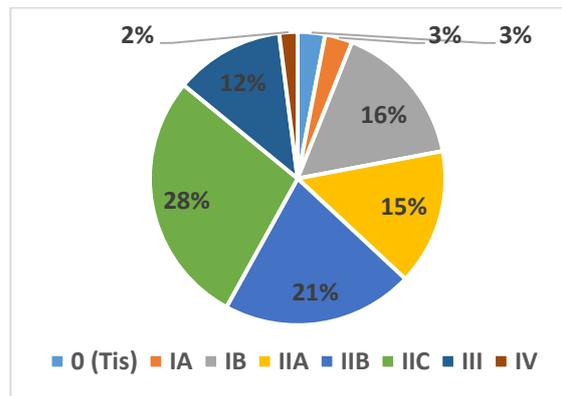


Figure 3. TNM Staging.

We analyzed the staging data according to the eighth edition of the AJCC, although we conducted a retrospective study.

Only 2 patients (3%) were diagnosed in stage 0 (melanoma in situ), 10 patients (15%) presented in stage I with tumor thickness <1mm.

Stage II was the most representative, with 26 patients (38%) diagnosed, 22 patients (33%) were diagnosed with stage III melanoma and 7 patients (10%) in metastatic disease (stage IV).

Due to the limitation of the sentinel lymph node, the lymph node involvement (N) was mostly established clinically and through CT and echography.

Clark level and Breslow thickness play an important role in the diagnosis of melanoma.

These systems assess the depth of the tumor and are used as a prognostic factor. Clark level was pathologically determined on the excisional sample.

There was no significant difference between Clark III and IV levels and these were the main determinations at 30%, between patients and 33% respectively.

Only 4% of patients had Clark I level, 18 patients (27%) were diagnosed with level V (Figure 2, 3).

The study group was divided into three subgroups (AM, MSS, NM) to curate statistical data, clinical diagnosis, the results of paraclinical investigations, surgical techniques used, the results of histopathological and immunohistochemical (Figures 4-12).

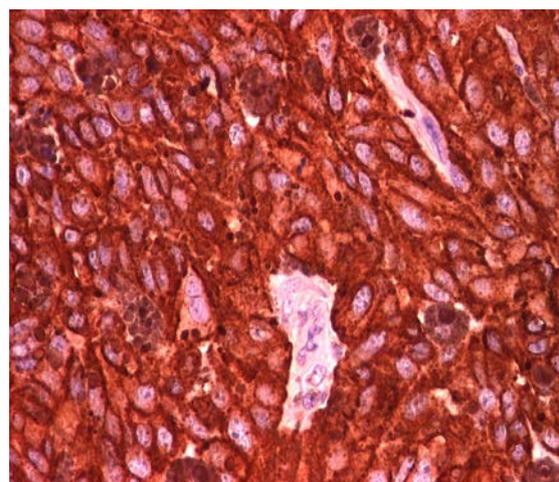


Figure 4. HMB45 positive in cell membranes, 100x

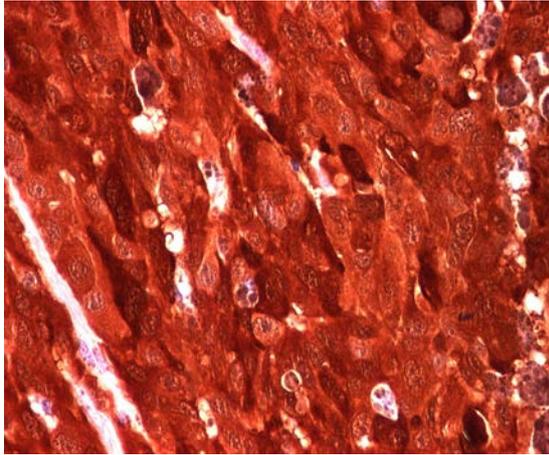


Figure 5. S100 positive in tumoral cells, 100x

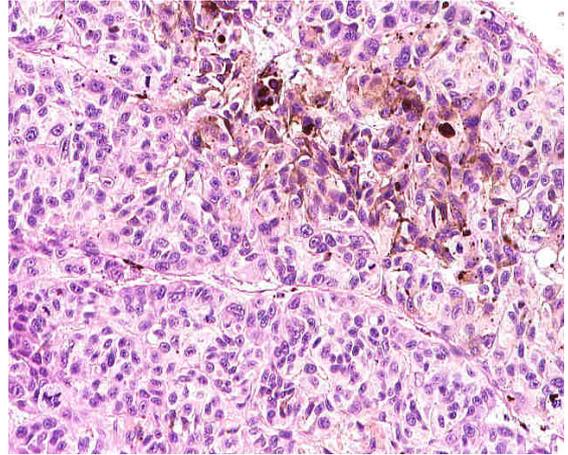


Figure 8. NM, Hematoxylin and eosin staining, 100x.



Figure 6. Patient from figure 5, post excision.

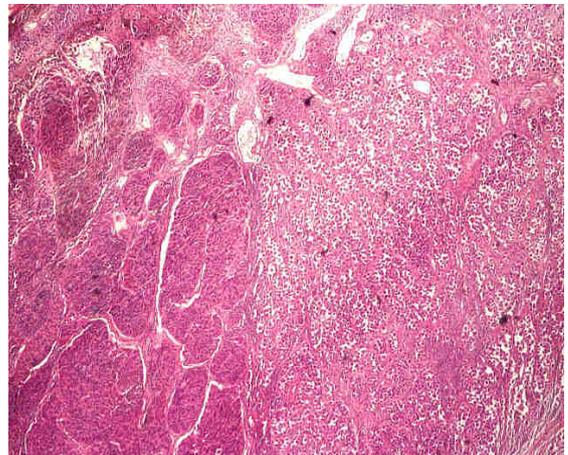


Figure 9. NM, Hematoxylin and eosin staining, 20x.

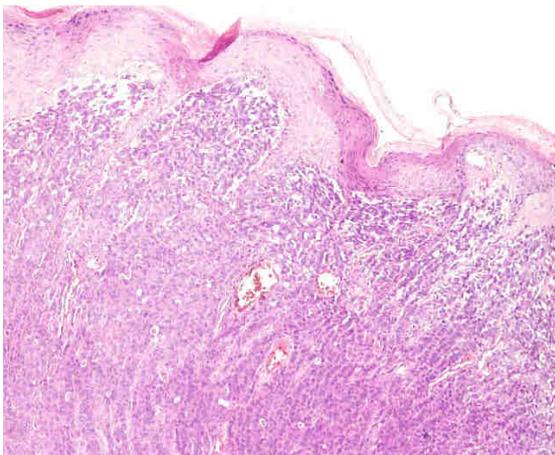


Figure 7. MSS, Hematoxylin and eosin staining, 20x.

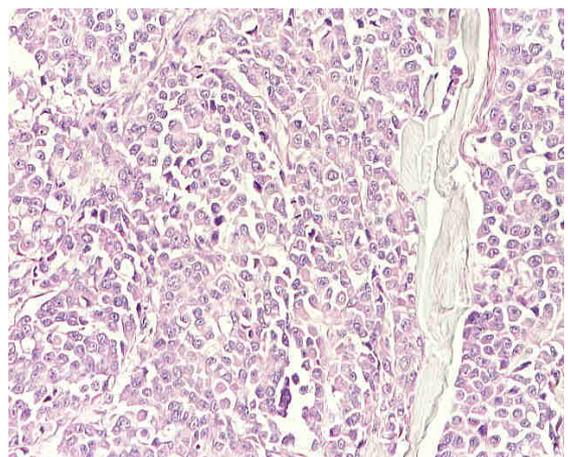


Figure 10. AM, Hematoxylin and eosin staining, 100x.

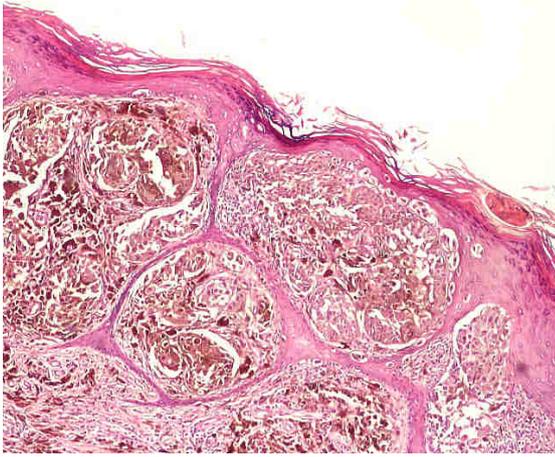


Figure 11. Melanoma in situ, Hematoxylin and eosin staining, 20x.

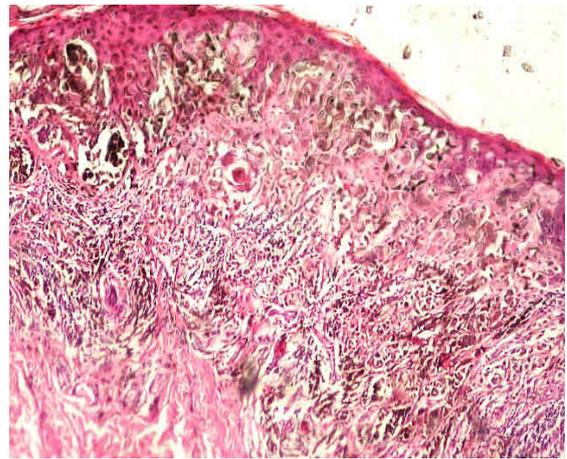


Figure 12. Dysplastic nevus and melanoma in situ, Hematoxylin and eosin staining, 20x.

As can be observed from the data, there is a higher incidence of NM on the torso and head, compared to the thoracic and pelvic limb, where other clinical subtypes of melanoma are more frequent.

Moreover, a much higher incidence of NM was observed (Figures 13-16).

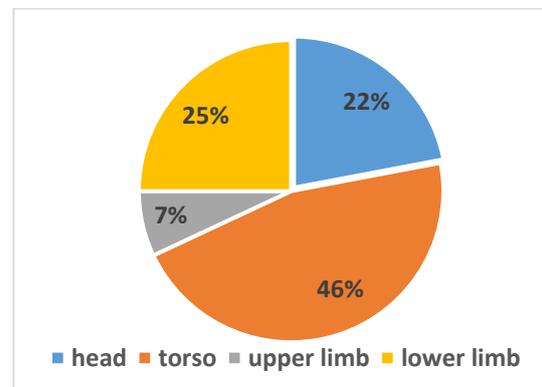


Figure 13. Distribution of cases by anatomical areas.



Figure 14. Male, 67-year-old patient with NM localized on the thorax, approximately 1 year prior to first presentation.



Figure 15. Female patient, 47-year-old, MSS left forearm, appeared 8 months prior to first presentation.



Figure 16. Male, 78-year-old, MSS, posterior thoracic region, appeared 15 months prior to first presentation.

Discussions

The NM subtype represents a large number of thick melanomas, representing up to 65% of all melanomas with a thickness of more than 2mm [3-6].

Previous studies [3,4,7] have shown that the average number of mitoses reported for NM: MSS was 2.5:1/mm² [7].

The distinctive characteristics of the two subtypes of melanoma could be caused by the different genetic pathways and of separate origins [8-10].

It can be hypothesized that the origin of NM in dermal stem cells and SM in epidermal stem cells [9] could explain the differences in evolution between the two subtypes of melanoma. The much faster growth rate of NM,

compared to MSS, should be considered a feature strongly associated with higher Breslow thickness scores and mitotic rate among NM lesions [11].

From our research, most cases of NM were ulcerated, with present adenopathy and rapid distant metastasis. A guarded prognosis of NM was closely related to a higher Breslow thickness, which was observed more probably because of the delayed diagnosis and faster growth rate, not necessarily due to the intrinsic malignancy of NM. Although MSS was found to have a better prognosis than NM, after the Breslow adjustment, no significant difference in survival rates was found [12].

The two most common histological subtypes of melanoma, NM and MSS, evolve according to a linear pattern of progression, because malignant melanocytes first spread radially and then invade vertically. However, recent clinical, pathological, and molecular data from other authors indicate that these two histological subtypes may evolve as distinct entities [13].

This is partly due to the current understanding of the linear model of melanoma progression, which implies that melanoma begins with the transformation of epidermal melanocytes that initially undergo radial growth (MSS) and subsequently the transition to vertical growth (NM). It is currently accepted that the rate of dermal invasion is the only aspect that separates NM and SSM subtypes. However, evidence has emerged challenging this linear pattern of progression and suggesting that these two subtypes are distinct entities [9].

Most epidemiological studies suggest that MSS is the most common histological subtype of malignant melanoma, but recent data does not appear to reflect current patterns observed [14-16].

Of the total cases examined in our clinic, 65% of NM occurred de novo and 35% on preexisting nevi, and MSS only appeared on preexisting nevi. The average age of onset of melanoma was 65 years. MSS was more common in the 50 to 60-year-old age group in both women and men (six cases), compared to NM (two cases) and AM (one case). Approximately 44% of the studied cases had a poor prognosis because of the presence of ulceration and intravascular invasion of transformed melanocytes in the venous and lymphatic capillaries.

Metastatic adenopathy has been ubiquitously present in NM, which had an extremely poor prognosis, with life expectancy under one year.

Cases of AM, because of its particular form, were diagnosed in advanced stages with metastatic lymph nodes, and had a poor life expectancy (under 1.5 years). Cases without local and regional adenopathy, without ulceration or bleeding had the best prognosis. The most aggressive forms of melanoma were found on the head and torso, with the fastest growth rates.

Prolonged sun exposure is, perhaps, the most important pathophysiological mechanism of melanoma genesis. Exposure that is associated with impaired skin function caused by the appearance of thymine dimers in the structure of DNA, with the emergence of genetic mutations that lead to the formation of abnormal melanocytes with increased mitosis rates compared to normal cells. The effects of radiation depress the immune system by affecting control of tumor cells.

Conclusions

Although older epidemiological studies suggest the predominance of the MSS subtype, this study confirms the latest statistics that suggest a significant increase in the incidence of nodular melanoma.

Most nodular melanomas appeared de novo and are not associated with pigmented nevi in 66% of cases.

The study highlights the need to implement a national screening program for skin tumors given the presentation of patients in advanced stages/high Clark levels, with a severely reduced life expectancy and unfavorable prognosis.

Public awareness, addressability to the general practitioners, avoiding prolonged exposure to the sun and tanning salons and increasing the use of creams with SPF must be encouraged.

Conflict of interests

None to declare.

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