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DIAGNOSIS AND SURGICAL TREATMENT OF MELANOMA: A MINI REVIEW

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Melanoma is a rare but the deadliest form of skin cancer. In the early stages, melanoma can be treated successfully by surgery and survival rates are high. However, in patients with metastases, survival rates drop significantly. Therefore, early and accurate diagnosis, prompt referral and proper management are crucial for ensuring the best prognosis. Also, multidisciplinary approach is necessary.

The diagnosis of melanoma is usually made by dermoscopic examination of suspected pigmented lesions. Misdiagnosis of melanoma is one of the most common reasons for initiating lawsuits for wrong treatment, when it comes to pathologists and dermatologists, immediately after breast cancer.

Regarding the treatment of metastatic melanoma, in the last 10 years several new drugs have been developed that have significantly improved the prognosis of patients suffering from this disease. However, a majority of patients do not show a lasting response to these treatments. Thus, new biomarkers and drug targets are needed to improve the accuracy of melanoma diagnosis and treatment.

This article discusses the current state of melanoma diagnosis and treatment based on the generally accepted consensus in this area and current national guidelines for treatment recommendations. The parts that remained open in the treatment algorithm (i.e. insufficiently clearly defined) are also mentioned.

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Key words: *melanoma, diagnosis, treatment, surgery, dermoscopy*

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Introduction

Cutaneous melanoma is a malignant tumor of the melanocytes, cells that are localized in the basal layer of the epidermis and produce the pigment melanin which is responsible for skin color (1).

Despite the fact that the incidence of many types of tumors is decreasing at the beginning of the 21st century, melanoma still remains a potentially fatal malignancy which incidence continues to increase. Currently, this malignant tumor is regarded as the fifth most common cancer in men and the sixth most common cancer in women in the United States. Furthermore, it has been estimated that 1 in 63 Americans will develop melanoma during their lifetime. On the other hand, the incidences of cutaneous melanoma vary greatly between European countries and are highest in Switzerland and the Scandinavian countries (2). However, the highest incidence and mortality rates from this cancer in the world have been noted in Australia and New Zealand (3).

Different incidence patterns of melanoma can be explained by variations in racial skin phenotype, as well as differences in sun exposure. In addition, as opposed to other solid tumors, melanoma mostly affects young and middle-aged individuals (4). Furthermore, patients with previous history of melanoma have an approximately 7% chance of developing a second primary melanoma. To date, it has been shown that exposure to UV radiation represents the predominant environmental risk factor for melanoma. Moreover, chronic sun exposure (especially in an intermittent pattern) and baseline history of severe sunburns are both suspected as causative (5, 6). In most patients, melanoma arises as a new lesion in the skin, while in less than 30% of cases this cancer occurs as a result of malignant transformation of pre-existing melanocytic nevi. Nevertheless, previous studies have shown that the number of common nevi and the presence of atypical nevi (irregular edges, uneven color, diameter

greater than 5 mm) represent important independent risk factors for melanoma. Finally, a positive family history has been documented in about 5-15% of patients, suggesting that genetic predisposition may contribute significantly to disease development and progression (7).

Melanoma treatment has always been a major challenge in plastic surgery. Although the basic concepts are well known, advances in basic research, as well as numerous clinical studies, are changing traditional treatment paradigms.

Diagnosis

The prognosis in patients with melanoma is closely related to the depth of the tumor, which in turn increases with time. Consequently, timely recognition and diagnosis, as well as prompt treatment, are crucial given the fact that five-year survival in the early stages of the disease exceeds 80% (IA-IIA) (2, 5). In comparison with other malignant tumors, cutaneous melanoma is, due to its localization, easily accessible to physicians for examination and therefore can be early detected by non-invasive approaches such as inspection of the patient's skin, dermoscopy and reflectance confocal microscopy (2). Routine clinical examination of suspected pigmented lesions usually includes the "ABCDE rule" which should indicate the presence of A: asymmetry, B: irregular borders, C: color variations, D: diameter > 6 mm, and E: elevated surface (Figure 1).

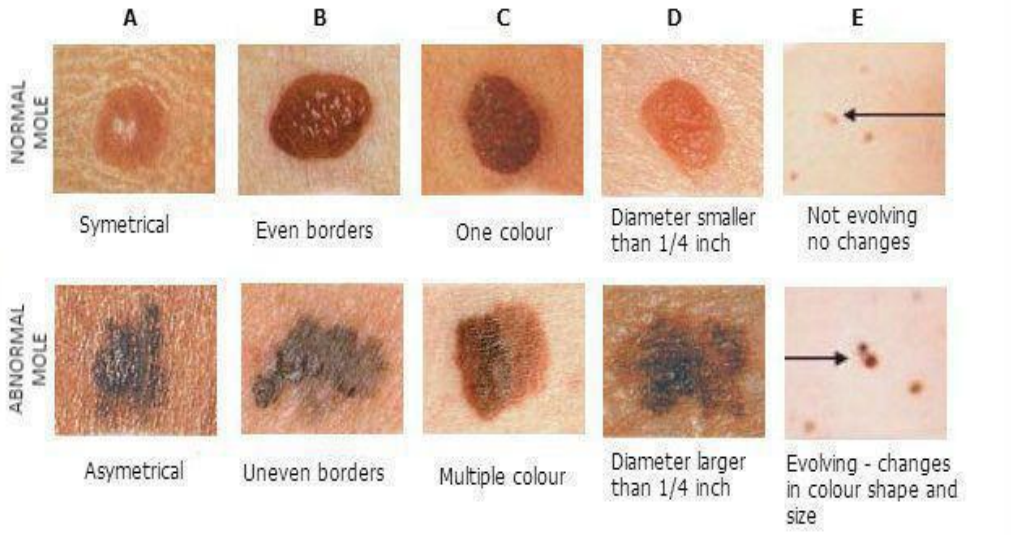

Figure 1. "ABCDE rule" for clinical examination of suspected mole lesions

However, a clinical diagnosis based on naked eye inspection is accurate in approximately 80% of cases if determined by dermatologists, while this rate is significantly lower (about 30%) in non-dermatological specialists (1). Therefore, in order to improve diagnostic efficacy and limit the number of false negative cases, skin surface microscope or a dermoscope can be used for better visualization of the lesion including subsurface features such as deeper pigment and microstructures of the epidermis, dermo-epidermal junction, papillary dermis and vascular structures (1, 8, 9). Although dermoscopy has been shown to be more sensitive and specific in classifying skin lesions than clinical examination with the naked eye alone, it remains limited by significant inter-physician variability and diagnostic accuracy is highly dependent on user experience. Even more, in the hands of untrained practitioners, this diagnostic method may result in poorer performance compared to routine clinical examination and there is a danger of increased excisions, over-referral or false reassurance (8, 10). On the other hand, an artificial intelligence algorithm categorizing photographs of pigmented lesions has been recently developed and it has been shown that it is capable of classifying melanoma with a level of competence comparable to that of dermatologists. However, further evaluation in a real-world, clinical setting is necessary in order to validate this potential diagnostic modality across the full distribution and spectrum of lesions encountered in typical practice (11, 12). Finally, although it is far from perfect, pathohistological analysis of suspected pigmented lesions after excisional biopsy still remains the gold standard for melanoma diagnosis (13, 14). For certain types of lesions there is large inter- and intra-observer variability among community-based pathologist whether a given lesion is benign or malignant.

Surgical treatment

Surgery remains the most appropriate treatment option and gives the best chances for curing patients with local melanoma, as well as disease

control in those with regional spread. Numerous randomized studies have provided better insight into the course of the disease and established certain recommendations for surgical treatment of primary melanoma.

Current, generally accepted algorithm for the surgical treatment of melanoma and "*conditio sine qua non*", begins with a biopsy of skin lesions that are clinically and dermoscopically suspicious of melanoma in order to establish a definitive pathohistological diagnosis (15). Compared to other sampling techniques such as "shave", "punch" and incisional biopsy that can lead to misjudgement of the depth of tumor invasion and, subsequently, inadequate initial surgical treatment, excisional biopsy (with a 1-3 mm surgical margins of clinically unaltered skin) remains the gold standard in diagnosis. The use of magnification, strong light, and, if available, Wood's light or confocal microscope during preoperative marking of the lesion significantly improves the precision level of excisional biopsy in defining detectable tumor margins (16).

In pathohistologically verified primary melanoma of the skin, it is necessary to perform a broad local excision with appropriate margins as recommended by national guidelines. The optimal time interval for performing the final surgical treatment is up to 4 weeks after excisional biopsy, and the recommended width of the re-excision from the middle of the postbiopsy scar depends on the thickness of the tumor according to Breslow (15):

- *in situ* melanoma - resection margins 0.5 cm,
- ≤ 2 mm - resection margins 1 cm,
- 2 mm - resection margins 2 cm.

Reducing safety margins is acceptable for melanoma "*in situ*" which is localized in the facial area, as well as for maintaining function in acral melanoma (the "slow Mohs" technique can be performed), although prospective randomized trials are lacking. In the case of acral lentiginous melanoma, "functional" amputation is indicated, while in subungual melanoma amputation can be avoided only if melanoma is diagnosed "*in situ*" or stage IA (15).

Following local excision, sentinel lymph node biopsy (SLNB) is the next step performed in patients with clinically and ultrasound-undetectable lymph nodes. This diagnostic standard in many patients with invasive melanoma and subsequent (elective) lymph node dissection remains controversial due to the conflicting results of several large clinical studies. According to current recommendations, SLNB is recommended for all patients with moderate melanoma (1.0 to 4.0 mm) (17) and for 0.75 to 1 mm thick high-risk lesions (ulceration and/or high mitotic index on pathohistological findings) (18).

SLNB with subsequent lymph node dissection may increase cure rates for patients with advanced melanoma. However, many patients who have died from melanoma have been shown to have negative SLNB. Also, lymph node dissection itself was not superior in terms of survival from clinical and radiological monitoring of lymph nodes in patients with nodal micrometastases identified by SLNB. It is expected that modern molecular diagnostics will have a more significant impact on the identification of specific risk groups of patients with SLNB in the future. If lymph node metastases are clinically evident or confirmed by ultrasound or computed tomography (CT) scan, radical dissection of the regional lymphatic basin is considered as standard therapy (15).

Melanomas diagnosed during pregnancy can be treated by preoperative lymphoscintigraphy and extensive local excision under local anesthesia, with SLNB under general anesthesia which is delayed until parturition (19).

In patients who have local recurrences (up to 2 cm from the primary tumor), in transit metastases (lesions localized more than 2 cm from the primary tumor to the regional lymphatic basin) or satellitosis that are surgically accessible, radical excision including clinically healthy, protective skin edges should be performed (15).

A deeper understanding of the molecular pathogenesis of melanoma in the last ten years has led to a significant shift in the treatment of patients with metastatic disease. As a result, diagnostic tests, risk assessment, and melanoma treatment are changing faster than ever. In addition to surgery, based on the results of large international studies, "target" treatments and immunotherapy have been introduced, which restored hope to this group of patients with a poor prognosis to fight and cope with a serious illness.

Conclusion

In the era of systemic treatments that have improved the prognosis for patients with advanced disease, surgery combined with early and accurate diagnosis remains the cornerstone of effective treatment of malignant melanoma. Also, given the fact that in many countries patients with suspicious skin lesions first consult a primary care physician, it is of great significance to develop training programs that will facilitate the uptake and use of dermoscopy in primary care. Finally, early prevention of melanoma through educating young people, using sunscreen, wearing protective clothing, limiting sun exposure, as well as identifying high-risk populations, such as those with a potential familial predisposition or gene mutation, is essential to reduce melanoma incidence rates.

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DIJAGNOZA I HIRURŠKO LEČENJE MELANOMA – KRATKI PREGLED

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Melanom je redak, ali najsmrtonosniji oblik karcinoma kože. U ranim fazama, melanom se može uspešno lečiti hirurški i stope preživljavanje su visoke. Međutim, kod bolesnika sa prisustvom metastaza, stopa preživljavanja značajno opada. Stoga su rana i ispravna dijagnoza, pravovremeno upućivanje i pravilno lečenje ključni za obezbeđivanje najbolje moguće prognoze bolesnika. Takođe, multidisciplanirni pristup veoma je važan.

Dijagnoza melanoma uglavnom se postavlja dermoskopskim pregledom suspektnih, pigmentnih lezija. Pogrešna dijagnoza melanoma jedan je od najčešćih razloga pokretanja tužbi za pogresno lečenje, kada su patolozi i dermatolozi u pitanju, odmah posle raka dojke.

Što se tiče lečenja metastatskog melanoma, u poslednjih 10 godina razvijeno je nekoliko novih lekova, koji su značajno poboljšali prognozu bolesnika koji boluju od ove bolesti. Međutim, većina bolesnika ne pokazuje trajni odgovor na ove tretmane. Stoga su potrebni novi biomarkeri i nova ciljna mesta za delovanje lekova, kako bi se poboljšali tačnost dijagnoze i lečenje melanoma.

Ovaj članak govori o trenutnom stanju dijagnoze i lečenja melanoma kod nas i u svetu, na osnovu opšte prihvaćenog konsenzusa u ovoj oblasti i aktuelnih vodiča sa preporukama o lečenju. Takođe, pomenuti su i delovi koji su u algoritmu lečenja ostali otvoreni,tj. nedovoljno jasno definisani.

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Ključne reči: *melanom, dijagnoza, terapija, hirurgija, dermoskopija*