THE FUTURE OF PERSONALIZED MEDICINE: ONE STEP MELANOMA SURGERY

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Abstract. *The divergent, personalized approach in the surgical treatment of cutaneous melanoma is the one in which the treatment of the neoplasm differs from that proposed within the generally accepted standards or guidelines. According to their presumption, guidelines are not obligatory for the treatment of a certain type of disease and cannot replace the judgment of the clinician. Which to a large extent determines the freedom (or possible one) of the clinician's action regarding the „personalization“ in the choice of a new, divergent therapy. It is interesting, for example, that the occurrence of locoregional recurrences in patients with melanoma after guideline therapy insures clinicians against both criticism of treatment choice and the end results. However, the lack of recurrences after innovative/personalized surgical treatment of cutaneous melanoma is accompanied for unknown reasons by a serious dose of unwarranted criticism. The fact is that a personalized surgical approach in the treatment of skin melanomas and the recommended by AJCC guidelines approach lead to exactly the same end results and that should not be ignored. The difference lies in the fact that this end result can be achieved by one step melanoma surgery (OSMS), for example, which is carried out in a single surgical session. Several advantages of OSMS can be noted: 1) it provides high efficiency in a short time, even in the initial stage of the disease, 2) it is cost-effective, and 3) according to initial clinical observations we have a much lower to no propensity for locoregional relapses.*

Key words: skin melanoma, AJCC, OSMS, tumor thickness, surgical approach

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INTRODUCTION

Melanoma is a malignant tumor most commonly affecting the skin, the incidence of which is increasing worldwide [1]. Although in most cases tumors are detected at an early stage of their development, mortality in patients with cutaneous melanoma remains relatively stable [2]. This requires a rethinking of the current therapeutic strategy in order to reduce relapses after therapy and patient mor-

talidity in general. Surgery remains the main method in the early treatment of primary melanoma [3]. Surgical treatment of melanoma refers to certain rules, which include primary excision of melanoma with a surgical safety margin of 0.5 cm in all directions, subsequent histological examination of the removed lesion and determination of Breslow tumor thickness [4]. Based on the already stated tumor thickness, the need for repeated surgical excision is determined, which is accompanied by or without removal of the so-called

draining lymph node [4]. The innovative approach in the treatment of cutaneous melanoma aims to reduce the number of surgical sessions and to minimize the subsequent mental trauma for the patients themselves [5, 6]. Another important aspect that is observed is the economic parameters or the financial point of view, which for about 300,000 melanoma patients per year could be of colossal proportions [7]. We present 2 cases of patients with melanocytic lesions, discussing the applicability of the standard and customized, divergent surgical approach depending on: 1) the clinical morphology of the primary lesion, 2) the dermatoscopic finding and 3) the presence or absence of specific ultrasound equipment for preoperative measurement of tumor thickness.

CASE REPORT 1

We present a 47-year-old patient with a lesion in the area of the head about 6 months old (Figs. 1a, 1b, 1c), discovered accidentally after a visit to a hairdresser and its subsequent mechanical irritation and

bleeding, two or three weeks before entering the hospital. The patient denied taking medication, as well as the presence of concomitant diseases. The patient was admitted to the clinic in order to determine the subsequent diagnostic and therapeutic approach. During the dermatological examination we observed a solitary, blue-colored, tumor formation measuring 5 by 5 mm in the scalp area (Figs. 1a, 1b, 1c). In the differential-diagnostic aspect, Blue nevus, nodular melanoma, nodular melanoma based on blue nevus, melanoma metastasis, glomangioma or angiokeratoma were considered.

Surgical removal of the tumor formation was performed under local anesthesia with a surgical safety field of 0.5 cm according to AJCC (Figs. 1d, 1e, 1f), and the resulting surgical defect was closed by single, interrupted sutures. Histopathological verification showed evidence of a Blue nevus. Immunohistochemical examination showed the following expression: S-100; Melan A; HMB-45: positive reaction. Postoperative treatment included active monitoring.

Fig. 1. a, b, c: show solitary, blue-colored, tumor formation measuring 5 by 5 mm in the scalp area

d, e show: Intraoperative view: elliptical excision of the Blue nevus, located in the scalp area

f shows: The closure of surgical defect by single, discontinuous sutures

Figs. 2 a, 2 b, 2 c show: a slightly raised, dark brown pigmented lesion with a well-defined but irregular edge located in the scalp area

CASE REPORT 2

A 45-year-old man with a lesion on the scalp, dating from about 6 years, which had grown rapidly over

the last nine months, changed its color, and became itching (Figs. 2a, 2b, 2c). From the anamnesis, the patient did not report concomitant diseases and medication. There was evidence of painful sunburns on the body and face in the past. During the dermatological examination we observed a slightly raised, dark-brown pigmented lesion with a well-defined but irregular edge located in the scalp area (Figs. 2a, 2b, 2c). From the collected anamnestic and available clinical data, we concluded that it is probably malignant melanoma. Laboratory tests were performed that showed no deviations from normal paraclinical values, with the exception of creatinine level – 119 μmol (ref. range up to 110 μmol). No metastases were found from the CT of the neck/head, single lymph nodes up to 8 mm in size in the middle and upper cervical third (insignificant) were visualized bilaterally along the vascular-nervous bundle. Ultrasound diagnosis and radiography of the lungs and abdomen showed no pathological changes. Surgical removal of the tumor formation was performed under local anesthesia with a surgical field of 1 cm (Figs. 3a, 3b, 3c), and subsequently the surgical defect was closed by single, interrupted sutures (Fig. 4). The histopathological examination revealed the diagnosis superficial spreading melanoma (SSM), T1bN0M0, stage IA, Clark II, with a Breslow thickness of 1 mm, without ulceration and spontaneous regeneration, with low mitotic activity and well-defined lymphocytic stromal reaction, without perineural invasion and clean resection fields.

Fig. 3 a shows: Preoperative measurement of the surgical security field, according to the guideline for one-step melanoma surgery; **b, c** show: Intraoperative view: elliptical excision of the melanoma, located in the scalp area; **d** shows: The closure of surgical defect by single, discontinuous sutures

Fig. 4. The removal of surgical sutures and the perfect postoperative cicatrix

DISCUSSION

Malignant melanoma is a disease, the diagnosis and treatment of which put clinicians to a serious test of the mind and raise the question of whether they tend to be flexible and innovative [3].

The current guidelines for the treatment of primary cutaneous melanoma in situ (MIS) according to AJCC (Table 1), based on Breslow thickness, include resection of 0.5 to 1 cm for in situ melanoma; a 1.0 cm operative field is also the recommended resection area for melanoma up to 1.0 mm and between 1 and 2 mm [4]. According to the recommendations (Table 1), this area is 1 cm for melanomas with a thickness between 1.01-2.00 mm; two centimeters is also the recommended area for the treatment of melanomas with a thickness of 2.01-4 mm [4]. In melanomas thicker than 4 mm, resection of more than 2 cm in all directions is not recommended [4]. If we follow the current recommendations of the AJCC, the treatment of melanoma should begin with resection with a margin of operative safety of 0.5 cm in all directions, followed by postoperative measurement of tumor thickness and mandatory planning of re-excision as soon as possible [4]. Tumor thickness in cutaneous melanomas is in fact the main indicator determining the plan of action, the choice of surgical boundaries, re-excision, additional determination of a draining lymph node and possible lymph dissection [8,9]. One step melanoma surgery offers a new innovative approach, which is undoubtedly one of the innovations in medicine of our time [10, 11]. The innovation is applicable to almost all patients with clear clinical and dermatoscopic criteria for dysplastic nevi, thin cutaneous melanomas or melanoma in situ lesions, even without the need for preoperative ultrasound measurement of tumor thickness [12]. It is believed

that preoperative ultrasound diagnostics with a good resolution of 20 MHz to a very large extent correctly identifies thin melanomas and this allows to choose the most appropriate surgical boundaries and possibly to save the need for further re-excision [13]. The recommendations for OSMS (Table 2) state that in all lesions that are clinically and dermatoscopically indicative of cutaneous melanoma or in situ melanoma, preoperative ultrasound may not be mandatory [12].

Table 1. AJCC recommendations for surgical margins: always two surgical sessions

Breslow thickness	Recommended surgical margins
Melanoma in situ	0.5 cm (primary excision with 0,5 cm in all directions, followed by secondary excision 0.2/0.5 cm additionally)
< 1 mm	0.5 cm primary excision (followed by secondary excision with 0,5 cm in all directions)
1.00 mm	0.5 cm primary excision (followed by secondary excision with 0,5 cm with SLND)
2-4 mm	0.5 cm primary excision (followed by secondary excision with 1,5 cm in all directions/with SLND)
> 4 mm	0.5 cm primary excision (followed by secondary excision with 1,5 cm in all directions/ without SLND if nodes not enlarged)

If the primary lesion has a tumor thickness of more than 1 mm and less than 2 mm, the operative field should be 1 cm combined with the simultaneous removal of the draining lymph node within one surgical session (Table 2) [5, 14]. In melanomas between 2 and 4 mm thickness, ultrasound can be used again, with the surgical safety field being 2 cm in all directions and the draining lymph node being removed in parallel (Table 2) [5, 14]. For tumor thicknesses greater than 4 mm, OSMS again offers adequate treatment within one surgical session (Table 2) [6]. When the locoregional lymph nodes are affected, the primary lesion is removed within one surgical session together with them, observing a field of operative safety of 2 cm in all directions (Table 2). If the lymph nodes are not clinically and ultrasound affected, it is not recommended to determine a draining lymph node (even in tumors over 4 mm thick) due to the likely presence of metastases [3, 5, 10].

Thus described, the innovative „One-step melanoma surgery“ method leads to a reduction in the number of surgical interventions from two to one, as well as to: the absolute lack of the possibility of violating the deadlines within which the secondary excision should be performed [3, 5].

Table 2. Personalized melanoma surgery & One step melanoma surgery (OSMS) recommendations for new surgical margins – one surgical session

Breslow thickness	Recommended surgical margins
Melanoma in situ	cm (clinical/dermatoscopic evaluation obligate/if possibility for echographical examination – from benefit)
< 1 mm	cm (clinical/dermatoscopic evaluation obligate/if possibility for echographical examination – from benefit if available!)
1.01-2.0 mm	1.0 cm (clinical/dermatoscopic evaluation obligate) (with SLND), (echographical tumour thickness measurement preoperatively)
2-4 mm	2 cm (clinical/dermatoscopic evaluation obligate) (with SLND) echographical tumour thickness measurement Preoperatively
> 4 mm	2.0 cm (clinical/dermatoscopic evaluation obligate) a) no enlarged lymph nodes – 2 cm resection is sufficient! b) in the presence of enlarged lymph nodes – to be removed together with the reexcision of the primary tumorous tissue! c) If lymphatic nodes involutive/benign (after AB therapy): no resection!

When there is ambiguity regarding a certain type of melanocyte lesions and the possibility that this type of lesion may be nodular melanoma (such as patient 1 described by us) with a thickness of more than 1 mm, the applicability of OSMS is questionable and it is desirable to perform surgical treatment by AJCC rules.

The reason is that in lesions with incompletely clear clinical and dermatoscopic criteria for nodular melanoma/metastasis or irritated blue nevus, for example, even if the predicted/measured tumor thickness is more than 1 mm, AJCC guidelines line with/ or give significantly more a high dose of certainty for the clinician regarding: 1) the possible danger of a more aggressive (in this case illogical) excision with a wider field of surgical safety of 1 or more centimeters, and 2) of a possible excision described in point 1 in combination with the additional conduction of a sentinel lymph node (again unreasonably aggressive therapy). Both mentioned variants turn out to be illogically determined not only from a professional, but also from a legal point of view, and the reason for this is: the lack of certainty regarding the dignity of the primary tumor lesion due to its difficult to interpret (clinical and dermatoscopic) morphology.

In the described second patient, the lesion was identified clinically and dermatoscopically as a thin melanoma with a possible tumor thickness of less than 1 mm and was approached individually, with a different from the AJCC surgical field, namely a total resection field of 1 cm in all directions, but within only one surgical session. This saves secondary surgical excision, which is recommended by the AJCC, but the total resection field is the same for both the AJCC and the OSMS recommendations [3, 5].

Clinical morphology and dermatoscopic findings are often the key in the selection of the field of surgical safety and the corresponding guidelines – AJCC/ OSMS [3, 5]. Preoperative ultrasound measurement of tumor thickness is not always mandatory and necessary when the lesion is indicative of thin melanoma, dysplastic nevus, or melanoma in situ [12]. The individual or personalized surgical approach in patients with melanoma should take into account not only the AJCC guidelines, but also those of the OSMS – namely, personalized surgical treatment [15]. The reduction in the number of surgical sessions within the new shared surgical treatment algorithms is probably also the reason for the reduced to completely absent tendency to locoregional recurrences in patients with cutaneous melanoma [3, 5, 12].

Another problem that somewhat determines the need for a more liberal model and at the same time a more aggressive model for surgical treatment of melanoma is the lack of a logical requirement for full compliance of clinically measured boundaries for surgical resection with histopathologically evaluated distances of resection edges from the tumor tissue in the histopathological preparations according to the AJCC recommendations [15].

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