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CASE SERIES

PERSONALISED ONE STEP MELANOMA SURGERY AND THE OUTDATED/CURRENT GUIDELINES FOR SURGICAL TREATMENT OF CUTANEOUS MELANOMA: FACTS AND CONTROVERSIES

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Abstract. *One step melanoma surgery (OSMS) is an innovative, personalized approach to the surgical treatment of cutaneous melanoma, which not only follows the total resection fields recommended by AJCC and EJC, but also has a significant advantage over these guidelines; namely, conduction of the procedure within a single surgical session. Guidelines for personalized surgical treatment of cutaneous melanoma can be used at any stage of the disease. The ideal purposes/goals of these newly introduced guidelines are to reduce the number of locoregional and distant recurrences and to stop the advancement of melanomas in a subsequent stage. In contrast to the histology, which under AJCC/EJC guidelines determines the extent of the subsequent or second surgical intervention, the leading starting points for personalized one step melanoma surgery are completely different and based on a complex final assessment, including: 1) clinical and dermatoscopic characteristics in favor of cutaneous melanoma, 2) preoperative ultrasound determination of tumor thickness, and, if possible, 3) the conduction of confocal microscopy. Another important and innovative proposal of the newly created OSMS guidelines is the requirement of absolute reciprocity between the preoperatively measured and subsequent histopathologically established surgical margins. The lack of such reciprocity under previously established guidelines (AJCC/EJC) till the present moment seriously calls into question the reliability of the data shared in the medical field concerning the size of resection fields. Three patients with suspected melanocytic lesions are presented and the applicability, advantages, and disadvantages of the personalized one step melanoma surgery versus two step melanoma surgery (AJCC/EJC) are discussed.*

Key words: *one step melanoma surgery, guidelines, melanoma, innovation, field of surgical security, histological boundaries*

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INTRODUCTION

Guidelines for the treatment of melanoma in particular, but also a number of other diseases, are of great importance for any clinician. However, they should not be considered mandatory [1]. The guidelines are, in reality, recommendations, and can be modified as long as this leads to justifiable benefits for patients or certain groups of patients [1]. The power of personalized medicine relies entirely on the individual approach it provides to the patients and the medical ethics of each therapist [2]. Though this personalized approach is not always guideline-dependent, in practice it is often more sparing and desirable by the patients themselves [3].

This publication emphasizes the advantages of personalized one step melanoma surgery (OSMS) when compared to the recommendations for treatment of melanoma by the AJCC.

The "guideline paradox" consists of the following circumstances: 1) Differences in recommendations on an international level – so-called variability in terms of certain parameters, 2) lack of flexibility in terms of innovation (e.g., reduction in the number of surgical sessions), and 3) lack of reciprocity between important interrelated parameters, which, if corrected, could be a further guarantee of better end results (e.g., fewer recurrences).

CASE REPORT 1

A 66-year-old patient visited the clinic for 3 pigmented lesions located in the upper back (Fig. 1a, 2a, 3a), that had been present for about 5 years. During the 3 months prior to presentation at our clinic, the patient noticed a change in the color, size and shape of the lesions. The patient had long-term arterial hypertension, controlled with bisoprolol 5 mg 1 tablet/day, amlodipine 5 mg 3 x 1 tablet/day, lisinopril/hydrochlorothiazide 20 mg/12.5 mg 2 x 1 tablet/day, and moxonidine 0.2 mg x 1 tablet/day. Type 2 diabetes mellitus was treated with gliclazide 60 mg 2 x 1 tablet/day and linagliptine 5 mg x 1 tablet/day. The dermatological examination revealed 3 pigmented lesions – one clinically and dermatoscopically suspicious for thin melanoma, located in the upper part of the right scapula, slightly lateral to the midline and two more, suspicious for melanoma in situ/dysplastic nevi located along the medial edge of the left scapula (Fig. 1a, 2a, 3a). Visible asymmetry, blurred borders and uneven pigmentation, as well as slight elevation for lesion 1 were clinically established (Fig. 1a, 2a, 3a). In lesions 2 and 3 asymmetry was not observed and the boundaries were relatively well defined, but uneven pigmentation, without elevation, was observed (Fig. 1a, 2a, 3a). Numerous solar lentigines, acquired nevi, cherry angiomas and seborrheic keratoses were seen on the surrounding skin (Fig. 1a, 2a, 3a). The performed laboratory tests were without abnormalities.

Surgical intervention was performed under local anesthesia, and all three lesions were removed in one session according to the OSMS guidelines by means of single elliptical excisions with 1 cm margins in all directions (Figs. 1b-d, 2b-d, 3b-d). Surgical wounds were closed with single interrupted sutures (Fig. 1e, f, 2e, f, 3e, f). Histopathological evaluation of lesion 1



Fig. 1. Case 1: 1a – clinical view of the lesions – lesions 2 and 3 are suspicious for dysplastic nevi, and lesion 1 for thin melanoma, 1b, c, d – surgical removal of lesion 2 by elliptical excision with surgical margins of 1 cm (OSMS) in all directions, 1e, f – closing of the surgical wound with single interrupted sutures

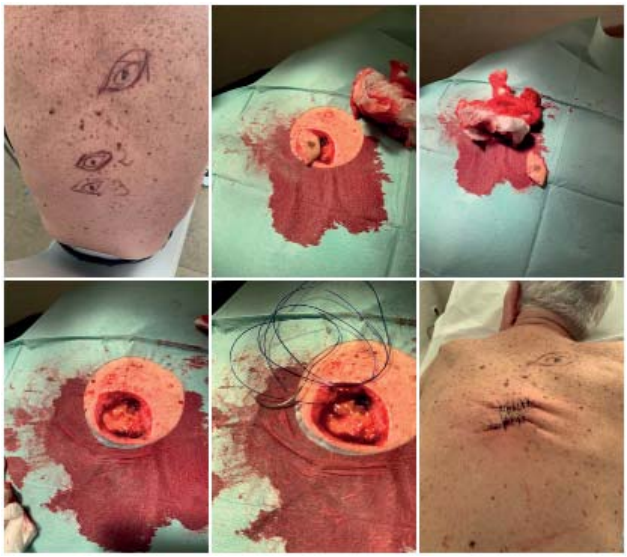


Fig. 2. Case 1: 2a – clinical view of the lesions – lesions 2 and 3 are suspicious for dysplastic nevi, and lesion 1 for thin melanoma, 2b, c, d – surgical removal of lesion 3 by elliptical excision with surgical margins of 1 cm (OSMS) in all directions, 2e, f – closing of the surgical wound with single interrupted sutures

showed a superficially invasive malignant melanoma, T1a N0M0, Clark level II, Breslow thickness 0.8 mm. No ulceration or spontaneous regression was noted; there was a moderate lymphocytic stromal response. Resection margins were clear. The other two lesions were identified as dysplastic nevi.



Fig. 3. Case 1: 3a – clinical view of the lesions – lesions 2 and 3 are suspicious for dysplastic nevi, and lesion 1 for thin melanoma, 3b, c, d, e – surgical removal of lesion 1 by elliptical excision with surgical margins of 1 cm (OSMS) in all directions, 3f – closing of the surgical wound with single interrupted sutures

CASE REPORT 2

The second case is that of a 53-year-old patient who presented with a single pigmented lesion (Fig. 4a) with a duration of about 2 years. In recent months the patient noticed a change in its size and color. Dermatological examination showed a slightly raised, evenly pigmented lesion with a saturated black color and size 2 x 1 cm on the lower lateral portion of the right scapular area (Fig. 4a). The boundaries of the lesion were well defined, but significant asymmetry was observed (Fig. 4a). Newly discovered hyperglycemia and hyperuricemia were demonstrated by laboratory tests. Glucose level was 7.07 mmol/l, and uric acid level was 466 µmol/l. Imaging tests (chest radiography, abdominal ultrasound and lymph node ultrasound) were normal, and tumor markers – S100 and LDH – showed no abnormalities. Surgical treatment was carried out under local anesthesia according to the OSMS guidelines for the treatment of melanoma with a field of operative safety of 1 cm in all directions (Fig. 4b, c, d, e). The operative wound was closed with single interrupted sutures (Fig. 4f). Histological examination showed a dysplastic compound melanocyte nevus, which in places showed evidence of incipient melanoma in situ, with clear resection margins.



Fig. 4. Case 2: 4a – clinical view of the lesion suspicious for dysplastic nevus or melanoma in situ, 4b, c, d, e – surgical removal of the lesion by elliptical excision with surgical margins of 1 cm (OSMS) in all directions, 4f – closing of the surgical wound with single interrupted sutures

CASE REPORT 3

The third case is that of a 47-year-old woman with dysplastic nevus syndrome. The patient had clinical evidence of superficial spreading melanoma in the right abdominal area, and had undergone surgical removal by elliptical excision about 2 weeks prior to presentation at our clinic (Fig. 5a), but with unclear surgical margins. A resection margin of 1 cm in all directions was assumed from the size of the observed suture lines. Histologically established Breslow tumor thickness was 1 mm. The patient presented at the clinic with a request for dermatological examination and determination of a further diagnostic and therapeutic approach. There was no information on concomitant diseases or medications. About 2 weeks previously, she had herpes glutealis on the right side. At the patient's request, immediately after the melanoma operation, a PET scan was performed, which showed enlarged lymph nodes in the right inguinal area with a recommendation for follow-up. Physical examination showed a scar from the previous excision of melanoma in the lower right part of the abdomen (Fig. 5a) and several additional lesions on the back, suspected as dysplastic nevi or, possibly, melanoma in situ (Fig. 5b, c, d). Morphologically, the lesions were asymmetric, with unclear boundaries and non-uniform pigmentation (Fig. 5b, c, d). The color varied from light to dark brown and slight elevation was observed (Fig. 5b, c, d). Laboratory tests and examination of tumor markers S100 and LDH were performed, with no evidence of pathological changes. Under local anesthesia, reexcision of the previous melanoma was performed with a field of surgical safety of 1 cm in all directions (Fig.

6a, b, c). Surgical treatment of other lesions was performed according to the AJCC-recommended guidelines with a surgical safety margin of 0.2/0.3 cm in all directions (Fig. 6d, e, Fig. 7a, b, d, e, Fig. 8a-c). Surgical wounds were closed with single interrupted sutures (Fig. 6f, Fig. 7c, f, Fig. 8d). The removed lesions were sent for histological examination, which for 3 of the lesions showed data for lentigious melanocytic nevi with a mild degree of architectural and cytological atypia. In one of the lesions, the histological picture corresponded to melanoma in situ with a recommendation for re-excision. The reexcision showed clear resection lines with no evidence of residual tumor tissue.



Fig. 5. Case 3: 5a, b, c, d – clinical appearance of the lesions: a – scar from previous excision of melanoma with probable surgical margins of 1 cm in all directions, b, c, d – lesions suspicious for dysplastic nevi or melanoma in situ



Fig. 6. Case 3: 6a, b, c – re-excision of previous melanoma with surgical margins of 1 cm in all directions (according to AJCC), 6d, e, f – surgical removal of lesion two, suspicious for dysplastic nevus or melanoma in situ by elliptical excision with surgical margins of 0.5 cm (AJCC) in all directions

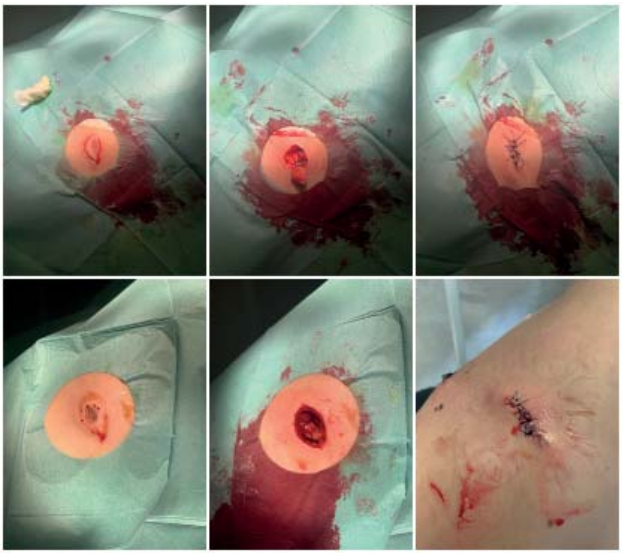


Fig. 7. Case 3: 7a, b, c – surgical removal of lesion three, suspicious for dysplastic nevus or melanoma in situ by elliptical excision with surgical margins of 0.5 cm (AJCC) in all directions, 7d, e, f – surgical removal of lesion four, suspicious for dysplastic nevus or melanoma in situ by elliptical excision with 0.5 cm surgical margins (AJCC) in all directions

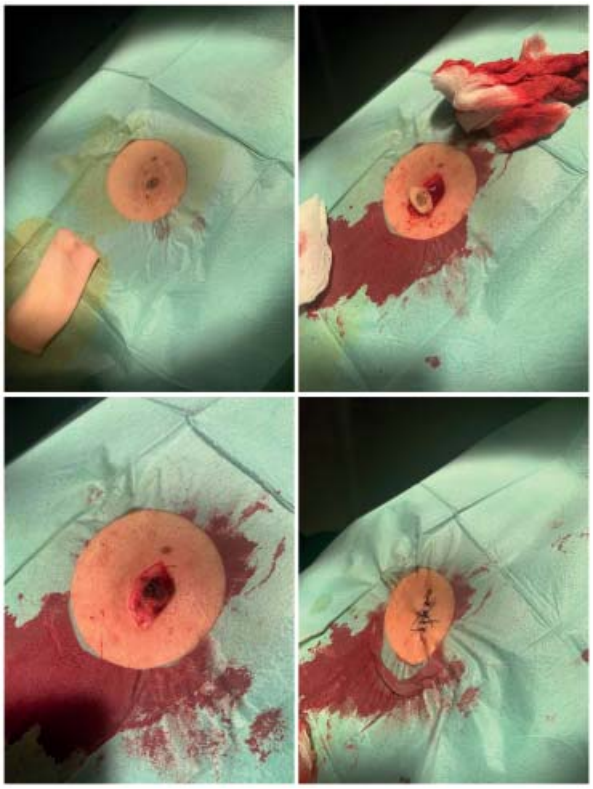


Fig. 8. Case 3: 8a, b, c, d – Surgical removal of lesion five, suspicious for dysplastic nevus or melanoma in situ by elliptical excision with 0.5 cm surgical margins (AJCC) in all directions

DISCUSSION

Whenever possible, the search for weaknesses in a certain area should be accompanied by the search for appropriate solutions. In the absence of receptivity to a particular hypothesis or a logical recommendation [1-4], "the issues, arising from a particular bizarre whim/recommendation" [5, 6] usually deepen. This is precisely true for the guidelines for melanoma and their changes or rare revisions [5, 6], which, slowly but surely, strive for "half-improvement" [6].

The main priority for innovative treatment should be the initial stages of melanoma or thin and medium thickness cutaneous melanomas. The reason for this is the generally poor prognosis of thick cutaneous melanomas, especially those with tumor thickness greater than 4 mm. An important guideline-related problem concerns the number of surgical sessions in the thin melanomas or melanoma in situ lesions, as well as in severely dysplastic nevi, which can often be very difficult to differentiate from one another [4, 5].

The search for logically conditioned reciprocity between clinically measured and subsequent histopathologically established resection margins around tumor tissue (even by international AJCC/EJC guidelines) has proved to be a difficult but clearly not impossible cause. The gradual, step by step finding of the right solutions, which aim to reduce the frequency of recurrences, should definitely be accompanied by a more frequent revision/improvements of these guidelines.

One serious weakness of certain guidelines, in the case of AJCC for surgical treatment of cutaneous melanoma, is the presence of a certain amount of variability in the surgical approach to melanoma as a whole [5, 6]. The first example of this is the variability in the size of the resection field in melanoma in situ, which can be between 0.5 and 1 cm/within two surgical sessions according to AJCC, while in EJC guidelines it is more clearly defined – with margins of operative security of 0.5 cm in all directions/again within two surgical sessions (Table 1, 2, 3). Another area of variability concerns intermediate thickness cutaneus melanomas class A, or those between 1 and 2 mm in tumor thickness, where according to the AJCC the field of surgical safety can vary between 1 and 2 cm [1] (Table 1, 2). Thus, according to the AJCC, the treatment of melanomas with a thickness of more than 1 mm,

Table 1. Surgical margin recommendations for primary cutaneous melanoma modified from AJCC, Swetter et al., 2019/2021 [5, 6]

Tumor thickness (Breslow)	Surgical margin*
In situ	0.5-1 cm† always 2 surgical sessions
≤ 1.0 mm	1 cm/always 2 surgical sessions
> 1.0 to 2.0 mm	1-2 cm/always 2 surgical sessions
> 2.0 mm	2 cm/ always 2 surgical sessions (if necessary)

*Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histologic margins as measured by the pathologist. Margins may be modified for functional considerations or anatomic location.
† Margins larger than 0.5 cm may be necessary for melanoma in situ, lentigo maligna type.

Table 2. Modified from Swetter et al. papers [5, 6]

Breslow thickness	Recommended surgical margins/AJCC
Melanoma in situ	0.1-0,3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve **0,5-1 cm total surgical margin**
< 1 mm	0,1-0.3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve **1 cm total surgical margin**
1.01-2.0 mm	0,1-0,3 cm primary excision/excisional biopsy, followed by secondary excision with variable resection surgical field in order to achieve **total surgical margin between 1-2 cm/with parallel performance of SLNB**
2 mm-4 mm	0.1-0,3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve total surgical margin of 2 cm in all directions/with SLNB
> 4 mm	0.1-0,3 cm primary excision/excisional biopsy followed by secondary excision in order to achieve a **total surgical margin of 2 cm in all directions** – with or without SLNB, a matter of discussion

Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histologic margins as measured by the pathologist.

Reciprocity between clinically and histopathologically measured surgical margins is not required! Always in 2 surgical sessions. Mentioned in the update from 2021, but it is still not required.

but less than 2 mm and those with a thickness of more than 4 mm could in some cases be identical-i.e. with 2 cm surgical margin [5, 6] (Table 1, 2). Even in certain cases of medium thick melanoma of 1.1 mm, for example, surgery should be much more aggressive than that of cutaneous melanoma with a tumor thickness of more than 4 mm, when the latter does not require the removal of a draining lymph node [1, 5, 6] (Table 1, 2). The total resection field in these two categories could be set at 2 cm, and sentinel lymph node biopsy in intermediate thickness melanomas should be recommended, in contrast to those tumors over 4 mm in thickness, in which sentinel lymph node biopsy may be avoided [1, 5, 6] (Table 3). In parallel, reaching this "total resection field" should be achieved within "as many as two" surgical sessions [5-7].

Following the initially announced guidelines in 2019 [5], and after dozens of critical publications on the subject [1-4] concerning the lack of reciprocity between clinically measured and histopathologically established resection fields, additional studies by the same team of co-authors led to a correction of some of the inaccuracies concerning the reciprocity between clinical and histologic findings [6]:

˝For histologically negative margins on the WE specimen, ICCR and CAP guidelines do not require reporting the microscopically measured distances between tumor and labeled lateral or deep margins, and this measurement should not generally impact clinical decision-making (see "WE for Invasive Cutaneous Melanoma," page 370). However, narrow pathologic margins (particularly of the invasive component) are associated with higher risk of local recurrence, and this information may warrant consideration of further surgical resection (ME-E, page 367) [6].˝

As can be clearly seen from the recommendation revisons of the AJCC/2021, they are once again subject to interpretation, which may lead to variability in the treatment of cutaneous melanomas at the same stage, i.e. using different resection fields/surgical margins [6], (Table 1, 2). The responsibility for deciding whether there is a correspondence between clinically measured and histologically established resection margins is, for the first time, subtly shifted to the clinicians, though not obligatory [6]. The primary goal of clinicians should be the logically justified surgical treatment of melanoma in each stage [4-7].

In contrast to the recommendations of the AJCC for surgical melanoma treatment, the EJC guidelines give better accuracy in the treatment of medium thickness melanomas, i.e. those between 1.01 and 2 mm in tumor thickness (Table 3) [7]. According to the EJC recommendations, these should be removed with a total resection margin of 1 cm, accompanied by a draining lymph node in a second session (Table 3), [7]. The main disadvantage lies in the fact that the recommendations of both the EJC and the AJCC are to be performed within 2 surgical sessions (Table 1, 2, 3), [1, 5-7].

The EJC guidelines also do not mention the need for reciprocity between clinically marked (preoperatively) and histologically measured (postoperatively) surgical margins (Table 3) [5, 6, 7]. In practice, it turns out that melanomas of the same tumor thickness may be treated surgically using different resection margins [1].

The Personalized One Step Melanoma Treatment (OSMS) guideline uses radically different baseline parameters that define and support the approach, namely: 1) clinical features, 2) dermatoscopic findings, which should be indicative of melanoma, and 3) preoperative ultrasound determination of tumor thickness, and, if clinically and dermatoscopically indicated, 4) confocal microscopy for medium thickness and thick melanomas, those with areas of regression, and non-pigmented melanomas (Table 4) [1-3].

In practice, this personalized surgical approach for the treatment of melanoma achieves the same end

Table 3. Modified from EJC recommandations (C. Garbe et al., 2019), [7]

Breslow thickness	Recommended surgical margins/EJC
Melanoma in situ	0.1-0.3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve **total surgical margin of 0.5 cm** in all directions
< 2 mm	0.1-0.3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve t**otal surgical margin of 1 cm** in all directions
> 2 mm	0.1-0.3 cm primary excision/excisional biopsy, followed by secondary excision in order to achieve **total surgical margin of 2 cm** in all directions

Sentinel lymph node biopsy – is performed in patients with tumour thickness ≥ 1.0 mm or ≥ 0.8 mm with additional histological risk factors (ulceration, 1 mitosis/mm^2, microsatellites).

Reciprocity between clinically and histopathologically measured surgical margins not required/not mentioned! Always in 2 surgical sessions.

Table 4. Modified, updated from: Personalized One step Melanoma surgery (OSMS) recommendation (Tchernev et al.) [4], updated version

Breslow thickness	Recommended surgical margins
Melanoma in situ	1.0 cm (clinical/dermatoscopic evaluation obligate/if possibility for echographical examination-from benefit/when possible – confocal microscopy additionally)
< 1 mm	1.0 cm (clinical/dermatoscopic evaluation obligate/if possibility for echographical examination-from benefit/confocal microscopy additionally)
1.01-2.0 mm/Class A	2.0 cm (with SLNB), (Mandatory: clinical/dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/when possible – confocal microscopy additionally)
2 mm-4 mm /Class B 2.0 cm (with SLNB), (Mandatory: clinical/dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/ when possible-confocal microscopy additionally)	
> 4 mm	2.0 cm complete surgical margin or less with/without SLNB to be discussed on tumour board. Mandatory: clinical/dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/when possible-confocal microscopy additionally)
With the requirement for reciprocity between preoperatively clinically measured and histopathologically established/ postoperatively surgical margins. Always in 1 surgical session	

results that are achieved within two surgical sessions using the guidelines of AJCC and EJC (Table 4) [3, 5-7]. In addition to being single-stage, OSMS guidelines from 2021 require reciprocity with respect to clinically and histologically established surgical margins (Table 4). Another advantage of the guidelines for personalized surgical treatment of cutaneous melanomas is the unification of the treatment of moderately thick class A and B melanomas with that of thick melanomas, with a total resection margins of 2 cm in all directions (in accordance with the AJCC recommendations) (Table 4), and in over 98% of cases, this complies with the recommendations of the AJCC and the EJC (Table 1, 2, 3). A serious premise for the application of this method is the presence of excellent clinical and dermatoscopic evaluation, as well as thorough knowledge in the field of skin ultrasound.

Using the idea of innovative personalized surgical treatment of melanoma, we presented 2 patients in whom this procedure was performed successfully in a single surgical session: patient 1 (Fig. 1, 2, 3) and patient 2 (Fig. 4). In both cases, in which there was suspicion of melanoma in situ, thin melanomas, or severely dysplastic nevus, a single surgical procedure was performed with a total resection margin of 1 cm, corresponding to the final or total resection margin according to AJCC/EJC recommendations, but achieved in one rather than two surgical sessions (Figs. 1, 2, 3, 4). Thus, in both of the presented cases, the application of the new methodology led to a reduction in the number of surgical interventions, which according to the AJCC/EJC guidelines should be two for melanomas in situ or thin melanomas [4-7].

To further illustrate the above issue, we also presented patient 3 – with multiple dysplastic nevi and suspicion of thin melanoma or melanoma in situ, treated according to the guidelines of AJCC/EJC (Fig. 5, 6, 7, 8). After obtaining the histological diagnosis indicating melanoma in situ from a lesion located on the back, the need for reexcision became clear, and an additional procedure was carried out in accordance with the guidelines of AJCC/EJC – resulting in 2 surgical sessions [5-7].

Not insignificant is the financial impact of the recommendations for innovative personalized melanoma surgery under the OSMS, which in practice generally leads to the elimination of between 200,000/300,000-350,000 initial excisions per year due to the merger of two surgical interventions into one [4, 8].

CONCLUSIONS

By presenting these three cases, we want to emphasize the clear benefit of applying the innovative personalized approach to the one/ single step treatment of melanoma (OSMS), applicable to all stages of the disease, but of particular importance for dysplastic nevi, melanoma in situ, thin and medium thickness melanomas.

Timely one step surgical removal, followed by full congruence between clinically measured and histopathologically established resection fields, would

be a great starting point. The application of the innovative treatment of OSMS with a field of operative safety of 1 cm in all directions in one surgical session in the first two patients led to a rapid surgical solution within one operative session. At the same time, this approach saves additional mental stress and financial costs for the patients and reduces the risk of complications associated with secondary surgery. The third patient we presented, treated by the currently known AJCC/EJC guidelines, required a second surgical intervention, which could have been avoided using OSMS guidelines. This information highlights once again the need to review and update the guidelines used until now for the treatment of melanoma.

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