New aspects of surgery for cutaneous malignancies

Ph.D. Thesis

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Table of contents

LIST OF PUBLICATIONS 3
1. ABBREVIATIONS 5
2. INTRODUCTION 6
2.1. Epidemiology of skin malignancies 6
2.2. Surgical treatment of skin malignancies 7
2.3. Aims 10
3. PATIENTS AND METHODS 11
3.1. Melanoma 11
3.1.1. Patients with thin melanoma 11
3.1.2. Patients with thick melanoma 12
3.1.3. Histopathology 12
3.1.4. Surgical procedure of sentinel lymph node biopsy 13
3.1.5. Statistical methods 13
3.1.5.1. Thin melanoma 13
3.1.5.2. Thick melanoma 14
3.2. Reconstruction of alar-perialar defects 14
3.2.1. Patients 14
3.2.2. Surgical procedures 15
3.2.3. Result evaluation methods 18
4. RESULTS 19
4.1. The role of sentinel lymph node biopsy in thin melanoma 19
4.2. The role of sentinel lymph node biopsy in thick melanoma 24
4.3. Successful alar-perialar reconstruction and good aesthetic results with our method 26
5. DISCUSSION 30
5.1. Sentinel lymph node biopsy and prognostic factors in thin melanoma 30
5.2. Benefits of sentinel lymph node biopsy in thick melanoma 34
5.3. Reconstruction of alar-perialar defects and application of our novel method 38
6. CONCLUSION 39
7. ACKNOWLEDGEMENTS 41
8. REFERENCES 42

List of full papers related to the subject of the dissertation

I. **Kocsis A**, Karsko L, Kurgyis Z, Besenyi Z, Pavics L, Dosa-Racz E, Kis E, Baltas E, Ocsai H, Varga E, Bende B, Varga A, Mohos G, Korom I, Varga J, Kemeny L, Nemeth IB, Olah J: Is it Necessary to Perform Sentinel Lymph Node Biopsy in Thin Melanoma? A Retrospective Single Center Analysis. Pathology and Oncology Research 2020; 26 (3): 1861-1868. doi: 10.1007/s12253-019-00769-z.

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II. Mohos G, **Kocsis Á***, Erős G, Korponyai C, Varga Á, Bende B, Varga J: Reconstruction of alar-perialar defects with a combined subcutaneous and cutaneous pedicled rotation-advancement nasolabial flap. Journal of Investigative Surgery 2020; 33(7):666-672. doi: 10.1080/08941939.2018.1538397 Mohos G and Kocsis Á contributed equally to the work

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III. **Kocsis Á***, Mezőlaki N*, Porkoláb D, Mohos G, Kis E, Varga J, Baltás E, Ócsai H, Korom I, Varga E, Németh IB, Kemény L, Oláh J: Őrszemnyirokcsomó áttét kimutatása vastag melanomában esélyt ad ígéretes adjuváns kezelésre Orvosi Hetilap 2020 (accepted for publication)

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1. ABBREVIATIONS

NMSC	Non-melanoma skin cancer
MM	Malignant melanoma
AJCC	American Joint Committee on Cancer
TNM	Tumor Node and Metastases
SLN	Sentinel Lymph Node
SLNB	Sentinel Lymph Node Biopsy
FDA	Food and Drug Administration
MSLT	Multicenter Sentinel Lymphadenectomy Trial
BCC	Basal cell carcinoma
SCC	Squamous cell carcinoma
NCCN	National Comprehensive Cancer Network

2. INTRODUCTION

2.1. Epidemiology of skin malignancies

Non-melanoma skin cancer (NMSC) and malignant melanoma (MM) are the most common form of cancer in the Caucasian population, and the incidence of both subtypes is increasing worldwide. According to the Hungarian National Cancer Register (2016), 19-20.000 patients are registered with skin cancers annually, placing a considerable economic burden on the healthcare system [1].

However, the benefits of adjuvant and curative target and immunotherapy are largely improving, surgical treatment remains in the mainstream of therapy.

Although malignant melanoma is not as frequent as the non-melanoma skin cancer, but accounting for 90% of the deaths associated with skin malignancies and therefore is the most lethal form of skin cancer, with 2742 newly diagnosed cases in Hungary according to the National Cancer Registry 2016and the incidence is increasing [1,2].

The NMSC refers to all skin cancers that do not arise from melanocytes. Squamous cell carcinomas and basal cell carcinomas (BCCs) account for 99% of cases. The incidence of basal cell carcinomas is 3 to 5 times that of squamous cell carcinomas [3].

Metastasis of a BCC is a rare case in the literature [4], while in the case of SCCs, metastases occur in 3% [5].

These tumours derive from epidermal cells, usually on sun-exposed areas, according to a recent study, the most common site of BCCs is the head and neck region (80%) [6,7]. The BCCs usually grow slowly and may present as superficial, nodular, morphoeic, or ulcerated [8], while SCCs may develop more rapidly. However, both types of tumours may cause significant local destruction, asymmetry or disfigurement. There are various treatment modalities available depending on size, location, clinical and histological features, age, and comorbidities. Nevertheless, surgical excision with a proper surgical margin is still the gold standard treatment [6], because it provides an accurate diagnosis by histological examination, and information on the completeness of the excision is also obtained. Complete removal of the tumor is essential to local tumour control and results in healing in the vast majority of patients.

According to a recent study, the nasal region (31,82%) was the most common site of BCC, followed by the periorbital (13,64%) and cervical (12,5%) units [6]. In this study, half (50%) of the nasal BCCs affected the alar region.

2.2. Surgical treatment of skin malignancies

The concepts of surgical treatment of melanoma have changed vastly in the past. Until the 1960s-1970s, extensive local wide resection with a 5-cm margin in all directions was advised, usually accompanied by elective lymph node dissection. In 1969 Clark et al. defined levels of invasion of the dermis and subcutaneous fat, which inversely correlated with survival. In 1970 independently from Clark, Breslow evinced that tumor thickness was a reliable measure of prognosis. According to these findings, prophylactic lymph node dissection was advised to Clark level III to V or Breslow thickness of 1.5 mm or thicker lesions. Over the past few decades, similar to breast cancer patients, the mechanical approach has been replaced by a biological approach in the surgical treatment of melanoma.

The 1990s has also brought a significant change and a paradigm shift in the treatment of melanoma and the care of regional lymph nodes. The aggressive resection with a safety margin of 5 cm has been replaced by an excision adjusted to the tumor thickness with a surgical safety margin up to 2 cm [9].

The 1st version of the American Joint Committee on Cancer (AJCC) Tumor Node and Metastases (TNM) Melanoma Staging system provided a different approach to surgical treatment instead of the prophylactic radical selective regional block dissection [10]. Several randomized trials showed that narrower surgical margins (2 cm between Breslow 1 and 4 mm or 1 cm for 2 mm or less) did not result in increased local recurrence or decreased overall survival. In 1992 Morton described the technical details of sentinel lymph node biopsy (SLNB) [10]. Based on the Multicenter Sentinel Lymphadenectomy Trial (MSLT) – 1 sentinel lymph node biopsy was found biologically relevant in intermediate thickness melanoma, and the sentinel lymph node positivity was found to be the single most important factor in overall survival [11]. From the end of 90s high dose interferon and high dose bolus IL-2 were applied as adjuvant therapy, but both drugs were withdrawn from the market in 2020. The latest and most important advancement in the therapy in the 2010s was the FDA approval of checkpoint inhibitor immunotherapy and a few years later, the targeted therapy in metastatic melanoma. In the adjuvant setting, for patients with high risk resected melanoma

immun checkpoint therapy such as PD-inhibitor is the preferred drug of choice. After multimetastatic (>3 positive lymph nodes) block dissection or resected lymph node metastasis with capsular involvement, additional irradiation also should be considered [12,13].

The recommended surgical margins for surgical excision in primary melanoma are well established.

However, for histological diagnosis excision with a 3-5 mm safety margin is advised and the reexcision is performed according to the histological parameters.

The indication of SLNB has changed several times over the decades because its beneficial effect on overall survival has been mostly demonstrated in intermediate-risk primary melanoma (with an absolute tumor thickness of 1–4 mm) [2,14]**.**

On the other hand, a debate has been going on in the literature about the need of sentinel lymph node biopsy in case of thin (<1mm) and thick (>4mm) melanomas.

However, most authors agree that SLNB may be recommended in these cases after a thorough discussion with the patient of the potential benefits and risk of harms associated with the procedure [15].

The predictive role of sentinel lymph node positivity in thin melanoma has been investigated and reported by several authors [16-20]. There is a consensus in the literature that the metastatic involvement of regional lymph nodes is still one of the most important prognostic factors of thick and thin cutaneous melanomas as well. However, the criteria and the indications of thin melanomas for SLNB are inconsistent and the results both contradictory and incoherent [21].

In 2009, the American Joint Committee on Cancer (AJCC) published the 7th edition of the staging system for melanomas, which relies on thickness, ulceration, and mitotic rate in the dermis. According to AJCC 7th recommendation, SLNB should be considered in the case of melanomas ≤1mm in thickness, with ulceration or with even a single mitotic figure [22]. The local guidelines for thin melanomas were modified at our department in early 2011 and the AJCC 7th adopted, as SLNB was offered not only if ulceration was present but if mitotic rate ≥1/mm2 of the tumour area. According to the new AJCC 8th guidelines, which was published in 2017, the tumour thickness measurements should be recorded to the nearest 0.1 mm, not 0.01 mm. The definitions of T1a and T1b tumours were revised (T1a <0.8 mm without ulceration, T1b 0.8-1.0 mm with or without ulceration or <0.8 mm with ulceration), and the dermal mitoses are not considered for pT1b, however, mitotic activity should be noted as an

independent prognostic factor. There have been other key changes in the N and M classification as well [23].

More recently, it has even been questioned whether the extension of radical node dissection is necessary in cases with histologically positive sentinel lymph nodes. Nowadays, more and more high-level evidence supports the fact that complete radical node dissection, which is associated with increased morbidity, improves neither the overall survival nor the progression-free survival of patients with melanoma [24,25]. Instead of the radical surgical treatment of lymph nodes, systemic therapies are becoming more relevant.

The indication for the modern adjuvant therapy of melanoma cannot be established without the histological assessment of sentinel lymph node biopsy; thus, this staging method is more and more recommended in the guidelines. Earlier, the use of interferon alpha-2a or alpha-2b was the only adjuvant therapeutic option, which could be administered in case the tumor thickness was identified. Nowadays, stage III melanoma (i.e., melanoma with metastatic involvement of the regional lymph nodes) is the prerequisite for both targeted and immuno-oncological adjuvant therapies.

The aim of surgical treatment in the case of NMSCs is the complete resection of the tumour with preserving the function and achieving the best possible cosmetic result. There are well established surgical principles both in case of low risk and high-risk tumours. In the case of low-risk tumours the recommended safety margin for BCCs and SCCs is 4 and 6 mm, respectively. In case of high-risk NMSCs Mohs-surgery or excision with wider surgical margin is recommended. However, this margin is not generally specified, mostly individual and depending the exact subtype of the tumour [26].

In our practice, in case of tumours when primary closure of the defect is not possible slow Mohs-surgery or multistage technique is performed.

However, this process is slower, takes 24-48 hours, but the histological samples prepared in this way are histologically superior to frozen sections and, therefore, easier to evaluate [27,28]. The defect of the removed tumor in this procedure is closed only after tumor-free margins are proved, with delayed coverage. This technique provides reliable surgical care in a tissue-friendly manner, with acceptable speed and outstanding cost-effectiveness [29].

Considering the behaviour of BCCs SLNB is not recommended [4].

However, there is some debate in the literature about the role of SLNB in case of SCCs, it is not proposed by most authors [30-32]. In the case of palpable regional lymph node or radiologically detected abnormal lymph nodes fine-needle biopsy or core biopsy is indicated.

In the event of positive histology, regional lymphadenectomy followed by chemo-radiotherapy is recommended [26,33].

According to the epidemiological data the tumours in the alar region of the nose are relatively common and should be considered high risk according to the 2018 NCCN Guidelines, therefore wider surgical resection margin or Mohs (or slow Mohs) – surgery is recommended [26].

After the removal of the tumour in the alar region, the remaining defect usually involves multiple cosmetic units, destroying the supra-alar, alar-facial groove, and the melolabial fold [34]. Traditionally, the defined C- shaped perialar area includes the superior labial tissue, melolabial fold, medial cheek, and nasal tissue superior to the nasal alar crease [35]. If the defect is localized to a single esthetic unit and side-to-side closure is not possible, owing to the size, V-Y advancement island pedicle flap is the most frequently chosen technique [36]. It is an important principle that if the defect affects more than 50% of an esthetic subunit, the whole subunit is advised to be reconstructed with the excision of the remaining subunit [37]. Maintenance of the natural curvatures and facial symmetry without impaired airflow is an important factor when performing flap closure in the alar region [37]. Defects localized to the nasal ala and C-shaped region usually require multiple combined flaps and further additional procedures (e.g. pedicle plasty in case of interpolational flap or correctional procedures to obtain optimal esthetic result).

2.3.Aims

1. In our retrospective study, we aimed to investigate the predictive value of mitotic rate and to analyse further clinicopathologic predictors of positive SLNB by examining the common feature of these metastasizing cases in order to prevent the majority of the T1b melanoma patients from undergoing SLNB. Cases were also reassessed according to the AJCC8th guideline and additional statistical analyses were performed to re-evaluate the prognostic value of the well-known histological parameters considering AJCC8th.

2. Even though the treatment of the disease in Hungary is tied to specified dermato-oncological centers, the surgical treatment of melanoma cannot be considered standardized. The surgical approach of the centers designated for the treatment of melanoma is not completely uniform. There are centers where sentinel lymph node biopsy has been largely omitted in the treatment of melanomas thicker than 4 mm. Since the risk for distant metastasis development is high in this patient group, the early administration of systemic therapy is essential. Currently available clinical data suggest that the detection of clinically occult metastases is the only option to indicate targeted and immuno-oncological adjuvant therapies; thus, the failure to perform sentinel lymph node biopsy significantly should reduce patient survival. Given the Hungarian situation, the question arises of how many patients with thick melanoma at high metastatic risk might be unable to take advantage of novel adjuvant therapies because sentinel lymph node biopsy has not been performed. At the Department of Dermatology and Allergology, University of Szeged, we have consistently performed sentinel lymph node biopsy in patients with melanoma thicker than 4 mm; therefore, we decided to evaluate the proportion of sentinel lymph node positivity in this high-risk patient group.

3. Since the BCCs are frequent in the alar and perialar region, our aim was to introduce a variation of cutaneous-subcutaneous pedicled rotation-advancement flap for the reconstruction of the thin alar and adjacent deep perialar defects in a single step procedure with an appropriate cosmetic result.

3. PATIENTS AND METHODS

3.1.Melanoma

3.1.1. Patients with thin melanoma

The Department of Dermatology and Allergology, University of Szeged, is a regional centre for the management of cutaneous malignancies, being responsible for melanoma care for the 1.5 million inhabitants of south-eastern Hungary. A retrospective review was conducted

involving patients treated at our department with thin melanomas (<1mm) between January 2011 and December 2014 *(Ethical approval: MEL-RETRO-001; number: 3521, 40/2015)*. During these four years, 625 consequtive primary melanomas were diagnosed at our department. Four hundred and three pT1 melanoma patients entered our study; among these cases, 152 patients suffered from pT1b ulcerated or mitotic rate $\geq 1/mm^2$ melanomas according to the AJCC7th staging system. We also planned to evaluate the common and characteristic features of primary melanomas among thin melanoma cases with sentinel node involvement. On the basis of the histopathological results of the primary tumours, a multidisciplinary tumour board approved a therapeutic plan and the choice of SLNB was discussed with patients in all cases. SLNB was offered to most eligible patients with pT1b melanomas as part of their surgical management in the absence of clinically evident nodal disease, or known distant metastases. SLNB was not advised if any sign of dissemination was detected in the case of high biological age, severe comorbidities or pregnancy. Some patients had declined surgery. Seventy-eight cases of SLNB were included in the study based on the criteria which are listed below.

3.1.2. Patients with thick melanoma

In our retrospective study, the medical records of newly diagnosed melanoma patients with tumor thickness over 4 mm were reviewed at the Department of Dermatology and Allergology, University of Szeged over a 5-year period (from 2007 to 2011). The parameters evaluated included prognostic factors, such as gender, age, Breslow's depth and localization, and histological assessment of the sentinel lymph node. Data were obtained from the institute's MedSol database in accordance with current ethical regulation and GDPR requirements (ethical approval: MEL-RETRO-001:3521, 40/2015 SZTE).

3.1.3. Histopathology

A standardized histopathological examination was performed on samples of primary melanoma, re-excision and sentinel lymph node dissection. Specimens were fixed in 4% buffered formaldehyde embedded in paraffin, and 4µm sections were placed on silanized slides. In addition to routine haematoxylin eosin staining (Leica ST5020), further immunohistochemistry (Leica Bond Max Autostainer) involved Melan-A (DAKO; mouse clone A103), HMB45 (Biocare; mouse monoclonal), and occasionally S100 (DAKO, rabbit

monoclonal) antibodies in a dilution of 1:300, 1:200, and 1:2000, respectively. At least three serial sections were prepared from sentinel node specimens.

3.1.4. Surgical procedure of sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) for the staging of melanoma was first described in detail in 1992. We perform combined radiotracer and blue dye mapping as usual. On the day before the surgery, dynamic lymphoscintigraphy is performed with human albumin colloid (Sentiscint; FJC Institute, Budapest, Hungary, Medi-Radiopharma Ltd., Érd, Hungary) labelled with 99mTc pertechnetate, with 80% of the particles sized 100 to 600nm. As part of the double staining, 0.5 to 2.0ml vital blue dye (Byk-Gulden, Konstanz, Germany) is injected 15–20 minutes before the incision. During the operation, a handheld gamma probe (C-Trak, AEA Technology, Darwin House, Birchwood Park, Warrington and Navigator GPS System; RMD Instruments Corp. Watertown, MA 02472 USA) is used to identify the hot spots. The nodes with significant activity or with vital blue stain are considered sentinel lymph nodes. The radiotracer activity of these nodes is measured ex vivo and compared to the bed from which they were removed. A radioactive lymph node is defined as positive and removed until the background counts are <10% of the hottest node removed. If the postoperative histology reveals metastasis in the lymph nodes, completion lymph node dissection is offered to the patient.

3.1.5. Statistical methods

3.1.5.1. Thin melanoma

The SLN positivity rate was the primary outcome. The clinicopathological features analysed were age, sex, melanoma type, location, ulceration, Breslow thickness, Clark level, mitotic rate, regression, and SLN status. The relationships between SLN positivity and each of the clinical and histopathological parameters were assessed with Chi-square test, Student's t-test and Fisher's exact test. Potential risk factors for SLN metastasis were analysed by multivariate logistic regression models with the enter method, and odds ratios (OR) and 95% confidence intervals (CI) were calculated for categorical variables. The predictive value of the multivariate logistic regression model was measured with the Nagelkerke R Square method. The relationship between the re-evaluated pT stage and the SNL status was assessed by Mann Whitney U test. P values <0.05 were considered to be statistically significant and all p values

were two-sided. All statistical analyses were performed with the IBM SPSS Statistics Version 23.0 program.

3.1.4.2. Thick melanoma

Fisher's exact test and Mann-Whitney U test were applied to analyze the data.

3.2. Reconstruction of alar-perialar defects

3.2.1. Patients

Ten patients were included in this study, mean age was 77 years (ranges from 66 to 84years, 6 males, 4 females). Skin defect was localized to the alar region, the alar-facial groove, the upper lip and the cranial part of the nasolabial fold after the tumor was removed (Figure 1A). The extent of the defects following tumor excision ranged from 1.8cmx1.8cm to 2.6x2.9cm. Histological examination revealed basal cell carcinoma with tumor-free margins in all cases. Reconstruction was only performed once final histological result was obtained. This took 2–3days, during which period a temporary coverage was used (Epigard, Biovision GmbH, Ilmenau, Germany). The mean follow-up was 7.5months (ranges from 5 to 15months). Prior to the intervention, all participants have given their informed consent in writing which granted the authors to use their photographs for scientific purposes.

3.2.2. Surgical Procedures

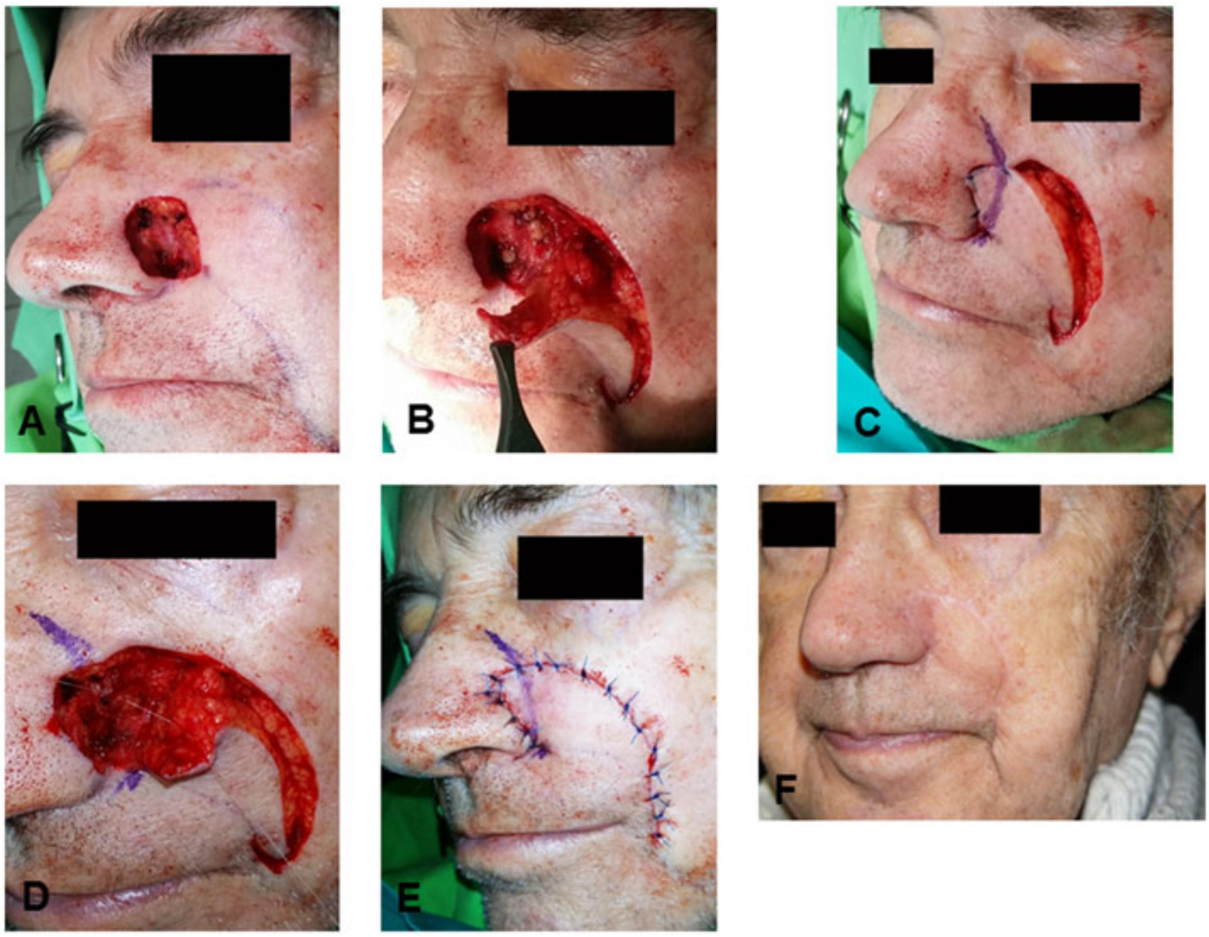

Figure 1. Different steps of the operation. A: preoperative status, B: dissection of the subcutaneous and cutaneous pedicled flap, C: temporarily situated flap, blue ink shows the position of alar-facial groove on the skin flap, D: alar-facial groove is fixed with 5/0 absorbable sutures, E: the flap is sutured into the defect, F: late postoperative status.

Both the removal of the tumor and the reconstruction were performed under local anesthesia. The flap was designed by marking the nasolabial fold and a curved line from the cranio-lateral part of the defect according to the relaxed skin tension lines. These lines matched in a distal point, marking the size and shape of the flap. Incision was performed on the lateral line, followed by subcutaneous tissue dissection and mobilization of the lateral wound edge, if necessary. It is important not to undermine the flap during the preparation and mobilization of the pedicle and to keep the perforator branches of the facial artery intact to preserve the vascular supply of the flap (Figure 1B). The cutaneous branches from the medial part and the subcutaneous perforator branches from the inferior part of the flap were hereby preserved.

The flap was pulled to the cranial point of the defect. If necessary, a cut back was performed distally in the nasolabial fold so that the flap could be easily placed into the defect. Following temporary fixation of the proximal part a marking was performed on the flap according to the alar-facial groove (Figure 1C).

Figure 2. Reconstruction in another patient. A: preoperative status, B: preparation of the flap, C: positioning of the flap, D: early postoperative status, E and F: late postoperative status.

The flap was thinned proximally from this marking. This part was used to cover the alar fragment of the defect. The prospective fold can be fixed to its base in the alar-facial groove with one or two 5/0 absorbable sutures if the flap is elevated (Figure 1D). Wound closure was performed with 5/0 absorbable and 5/0 permanent sutures (Figure 1E). Drainage or compression was not necessary. Scars were treated with silicone-ointment. Massage of the

flap was advised after 4 weeks postoperatively (Figure 1F). Figures 2–4 demonstrate the steps of operation in three other patients. Patients were discharged on 2nd–3rd postoperative day.

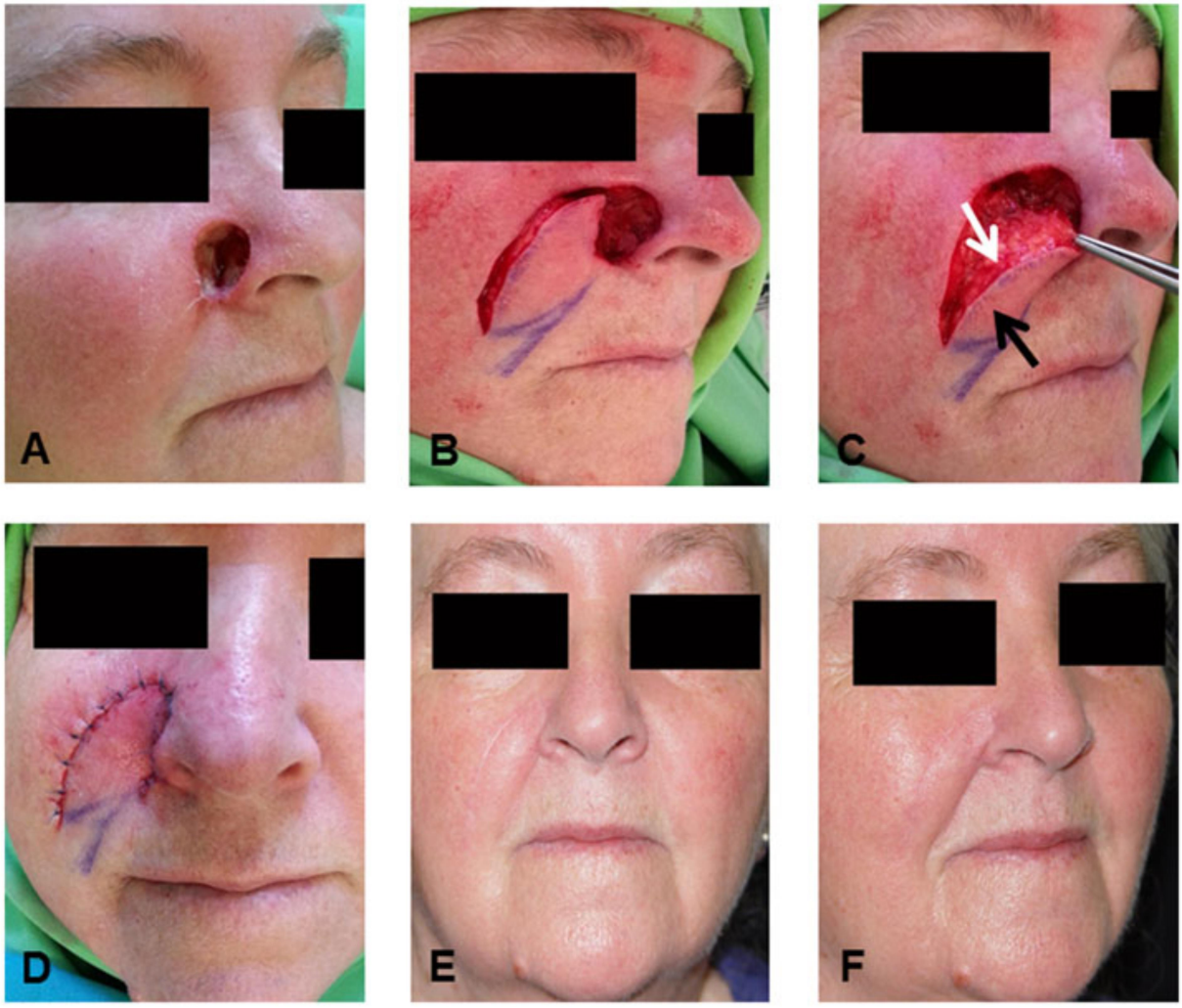

Figure 3. Application of the combined flap in a third patient. A: preoperative status, B: dissection of the flap, C: positioning of the flap, white arrow: the subcutaneous part of the flap via which perforators enter the flap, black arrow: direction of the cutaneous branches from the medial part of the flap, D: early postoperative status, E and F: late postoperative status.

An examination was performed 10 days after the surgery, stitches were removed this time. The second examination was in the 3rd postoperative week. Following this, the patients were

examined in each 3 months. During the postoperative period, different complications were monitored and evaluated as described below. If it was necessary, antibiotic therapy was launched which involved daily 1.000 mg cefuroxime (2x500 mg) administered orally.

3.2.3. Result evalaution methods

Laser Doppler Flowmetry

Laser Doppler flowmetry was chosen for the determination of the microcirculation since it is an accepted and reliable method for this aim [38]. Perfusion of the flaps was monitored by means of the PeriFlux System 5000 (Perimed, J€arf€alla, Sweden), as described in a previous study [39]. The sensor was fixed to the tissue with a sterile adhesive strip provided by the manufacturer. Measurements were performed at five different time points: before the incision (baseline), after preparation of the flap, after fixation of the flap, 1 day after surgery and 3 weeks after surgery. At each time point, recordings were made for 5 minutes. Perisoft for Windows software was used for data collection, storage and analysis. The data are presented as perfusion unit (P.U.).

Evaluation of Complications

The following signs and aspects were monitored: edema, erythema, hematoma, trap-door deformity and need for resuturing/reoperation (Table 1). Complications were evaluated with a semi quantitative scoring system. Briefly, 0: the given sign is not present; 1, 2, 3: mild, moderate, and severe manifestation of the given sign, respectively.

Patient Satisfaction

Each patient was asked to complete a patient satisfaction questionnaire in the 6th postoperative month. Eight questions were given concerning the postoperative pain and the satisfaction with the results of the intervention (Table 2). Patients were asked to rate the pain on a 10-point scale: no pain (=0), unbearable pain (=10) while a 5-point Likert scale was suggested for the other questions: very satisfied (=5), relatively satisfied (=4), fairly satisfied (=3), relatively dissatisfied (=2), and very dissatisfied (=1).

Statistical Analysis

Data analysis was performed with SigmaStat for Windows (Jandel Scientific, Erkrath, Germany). Friedman repeated measures analysis of variance on ranks was applied for the evaluation of the data obtained from laser Doppler flowmetry. Time dependent differences from the baseline were assessed by Dunn's method. In Figure 5, median values (M) with the 25th and 75th percentiles (25p and 75p, respectively) are given, $p<0.05$ was considered statistically significant. Scores describing the complications and patient satisfaction are presented as mean values (m) and standard deviation (S.D.).

4. RESULTS

4.1. The role of sentinel lymph node biopsy in thin melanoma

According to AJCC 7th 152 patients with pT1b melanoma entered our study. Among these 152 cases, 74 patients underwent only local wide excision with a 1cm safety margin. In addition of local wide excision SLNB was also performed in 78 cases. Twelve patients were excluded for previous cutaneous or other malignancies; the remaining patients were not involved due to high biological age, severe comorbidities or pregnancy, or because they had simply declined the procedure. Lymphoscintigraphy successfully identified the draining lymphatic basin and sentinel node in all 78 patients. The majority of patients were sentinel node-negative (n=69); in nine cases (11.5%) metastasis was detected in the regional lymph nodes. The location, Clark level and mitotic rate of the tumour, the presence of ulceration, and regression were examined and compared. Complete lymph node dissection (CLND) was performed in 7/9 positive SLN cases. Additional metastatic L.N.s were found in two cases.

Site of the primary tumour and SLN

With regard to the location of the primary melanoma, the majority of these tumours were found on the lower extremities in women and on the trunk in men, as we expected.

Location	Overall male (n=75)	Overall female (n=77)	SLNB male (n=34)	SLNB female (n=44)
Head and neck	5	5	3	1
Trunk ventral	10	12	4	7
Trunk dorsal	33	21	14	13
Upper extremity	19	16	8	6
Lower extremity	7	22	4	16
Acral	1	1	1	1

Table 1. Location of primary tumours among all patients and in the SLNB group

Among patients who underwent SLNB, the most frequent location of the primary tumours was the dorsal region of the trunk (27/78 overall, 14/34 in men and 13/44 in women); however, a high proportion of the tumours were located on the lower limbs in the women (16/44). In our series, the SLN positivity was independent of the location of the primary tumour (Fisher's exact test p=0.9312).

As regards the location of the sentinel nodes, 46 patients had axillary SLNB, in seven cases from both sides. Six of these 46 patients had metastatic lymph nodes. Three patients had sentinel nodes from both the axillary and inguinal regions; one of these patients had a positive sentinel node. In 22 cases, the nodes were removed from the inguinum (1 positive) and in the case of two patients from the popliteal region as well (1 positive). Four patients had sentinel nodes in the neck, and one patient had a sentinel node at an atypical site (over the scapula).

Age and gender

The overall male/female ratio was 1:1. Of the patients who underwent SLNB, 43.5% were male, and the median age was 48.5 years (range 20–77 yrs). The onset of melanoma diagnosis did not differ significantly in the node-negative (48.8 yrs) and node-positive (46.3 yrs) groups. However, the mean age with pT1b/nodal involvement was 58.2 and 31.5 years among men and women, respectively. Moreover, in the younger age group (<35 yrs) the SLN

positivity rate was 22.2%, which is higher than the average in all cases. Demographic and histopathological characteristics of the SNLB group are shown in Table 2.

Variable	All patients with SLNB	SLN-positive	SLN-negative	p value	OR
Total no.	78	9	69		
Age mean (years)	48.526	46.33	48.812	0.614 b	
<35	18	4	14	0.136 a	
36–49	21	0	21		
50–64	32	4	28		
>65	7	1	6		
Gender				0.492 a	1.724 (0.426–6.985) c
Male	34	5	29		
Female	44	4	40		
Histological type					
Superficial spreading	72				
Nodular	4				
Acral lentiginosus	2				
Location				0.9312 a	
Head and neck	4	0	4		
Trunk ventral	11	2	9		
Trunk dorsal	27	4	23		
Upper extremities	14	1	13		
Lower extremities	20	2	18		

Acral	2	0	2		
Thickness (mean)	0.716	0.714	0.717	0.966 b	
Ulceration				0.586 a	0 c
Present	8	0	8		
Absent	70	9	61		
Mitotic rate (mean)	2.25	1.89	2.29	0.494 b	
Clark level				0.715 a	1.5 (0.368–6.114) c
II	28	4	24		
III	50	5	45		
Regression				0.044 a	4 (0.916–17.459) c
Present	29	6	23		
Absent	49	3	46		
Reclassified stage (AJCC8th)				0.566 d	
pT1a	37	4	33		
pT1b	41	5	36		

a: Fisher's exact test

b: Student t-test

c: OR (95% CI)

d: Mann Whitney U

$\alpha = 0.05$

p two-sided

Table 2. Demographic and histological characteristics of the primary tumours with SLNB

Multivariate logistic regression model	SLN positivity	
Variable	OR (95% CI)	p
Age	.958 (.916; 1.002)	0.059
Gender	.651 (.152; 2.782)	0.562
Breslow	1.626 (.036; 72.656)	0.802
Clark	.560 (.112; 2.807)	0.480
Mitosis index	.723 (.348; 1.502)	0.385
Regression	5.796 (1.046; 32.123)	0.044 *
OR : odds ratio		
CI : confidence interval		
* p<0.05 significant		
method=enter		

Table 3. Multivariate logistic regression model of the clinicopathologic parameters

Multivariate logistic regression modelling demonstrates the association between SLN positivity and age, gender, Breslow, Clark level, and regression. The presence of regression in the primary tumour increases the probability of sentinel positivity by 5.796-fold. There was a significant correlation noted between histological regression and sentinel lymph node positivity, however, no significant relation between the other characteristics examined (age, gender, Breslow, Clark level, mitosis index; Nagelkerke R square=0.7). After reassessing the pT stage according to the AJCC8th guideline, 37 patients were reclassified from pT1b into pT1a category. By repeating the statistical analyses there was no significant association between reclassified stage and SLN positivity indicating that regression may have independent prognostic value on the lymphatic spread of melanoma.

4.2. The role of sentinel lymph node biopsy in thick melanoma

Between January 1, 2007 and December 31, 2011, we diagnosed 1133 patients at our Department with melanoma; out of these patients, 116 had a thick (Breslow's depth >4 mm) primary tumor (10%). We removed 9 cases with thick melanoma from our research register as their available data were insufficient (e.g., patients were lost to follow-up after the removal of the primary tumor or we consulted on histological samples with other institutions, etc.); thus, we included the data of 107 patients in this analysis. Table 4 summarizes our findings. We performed sentinel lymph node biopsy in 78 cases. In 19 cases, the presence of palpable metastatic lymph node had already made the assessment of the sentinel lymph node unnecessary. In addition, in 7 patients, the advanced age/presence of comorbidities disallowed us from performing the intervention. In 2 cases, there was a technical failure, and one patient refused to undergo the intervention. The mean age of the patients with thick melanoma was 60.97 years (n=107) at the time of the diagnosis, whereas it was slightly lower (57.89 years) in cases that were subjected to sentinel lymph node biopsy (n=78). This finding is consistent with the fact that we did not perform the intervention in 7 cases with a higher age (>80 years). We detected no significant difference concerning the age of histologically positive (57.64 years) and negative (58.769 years) patients. The localization of sentinel lymph nodes showed the following distribution (n=88): 51 (57.9%) in the armpit, 24 (27.2%) in the inguinal region, and 6 (6.8%) in the neck. Otherwise, so-called atypical sentinel lymph nodes were detected in the popliteal region in 4 cases, and so-called in-transit nodes on the back of 3 patients.

Of the 78 sentinel lymph node biopsies, 28 (36%) had no histologically detectable melanoma metastasis, whereas 50 (64%) had histologically detectable lymph node metastases. These patients gave almost two thirds of the cases, and that is a remarkably high rate. The last 50 patients could be classified into stage IIIC, according to the latest (8th) edition of AJCC TNM. The mean Breslow's depth was 6.79 mm in high-risk melanoma patients (n=107), 6.40 mm in patients undergoing sentinel lymph node biopsy (n=78), 6.254 mm in patients with positive sentinel lymph node biopsy, and 6.67 mm in patients with negative sentinel lymph node biopsy.

Surgical complications, mostly seromas (n=10) and infections (n=3), were identified in 17 cases (21.7%).

	SLNB negative	SLNB positive	Altogether	p
Patient (n)	28 (35.89%)	50 (64.1%)	78 (100%)	
Mean age (year)	58.36	57.1	57.55	0.501 a
Mean age – men (year)	53.94	56.05	55.06	0.739 a
Mean age – women (year)	65.18	57.74	59.69	0.025 a
Men (n)	11(27%)	31(73%)	42	
Women (n)	17(48%)	19(52%)	36	0.062 b
Primary tumor in head and neck region	2 (50%)	2 (50%)	4	
Primary tumor in trunk	12 (32%)	25 (67%)	37	
Primary tumor in extremities, or pectoral and pelvic girdles	14 (38%)	23 (62%)	37	0.681 b
Average of Breslow's tumor thickness (mm)	6.671	6.254	6.4	0.237 a
Clark I.	0	0	0	
Clark II.	2 (50%)	2 (50%)	4	
Clark III.	9 (30%)	21 (70%)	30	
Clark IV.	10 (29%)	24 (71%)	34	
Clark V.	7 (70%)	3 (30%)	10	0.089 b
Ulceration	8 (25%)	24 (75%)	32	
Non-ulcerated	20 (43%)	26 (57%)	46	0.149 b

a: Mann–Whitney test

b: Fisher's exact test

Table 4. Demographic and histological characteristics of thick primary melanomas with SLNB

4.3. Successful alar-perialar reconstruction and good aesthetic results with our method

We performed a combined cutaneous and subcutaneous pedicled rotation-advancement skin flap, contrary to the widely applied subcutaneous island pedicle flap. With this method, there is no (or short) incision in the nasolabial fold. This preserves the vascular supply better and provides more preferable cosmetic results with fewer scars.

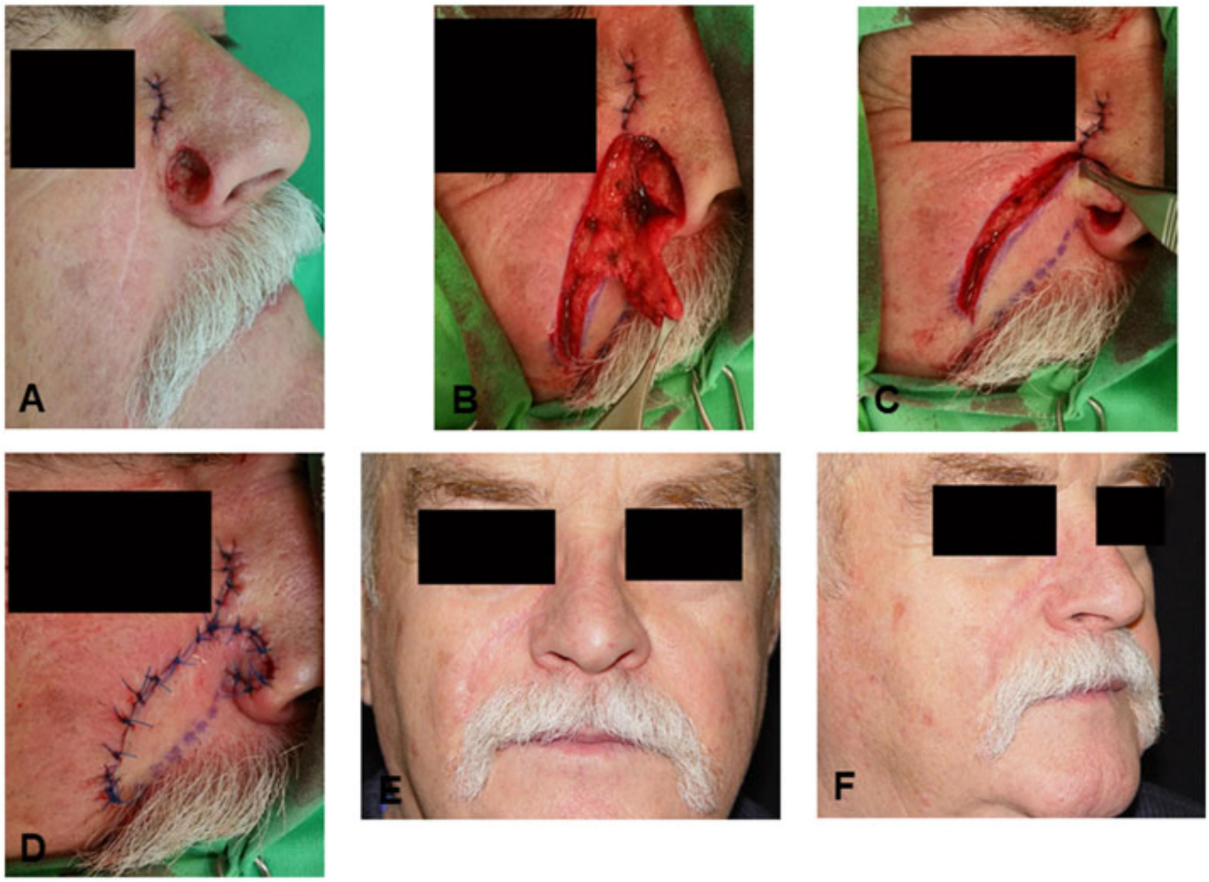

Figure 4. A further patient with the combined flap. A: preoperative status, B: preparation of the flap, C: positioning of the flap, D: early postoperative status, E and F: late postoperative status.

As concerns perfusion of the flaps, laser Doppler flowmetry has revealed a significant decrease in the blood flow after preparation of the flap (M1⁄4 36.57 P.U., 25p 1⁄4 22.02, 75p 1⁄4 58.03) and fixation of the flap (M1⁄4 49.49 P.U., 25p 1⁄4 29.1, 75p 1⁄4 77.99) as compared to the baseline (M1⁄4 237.59 P.U., 25p 1⁄4 152.89, 75p1⁄4 331.2). However, microcirculation has shown a considerable improvement during the 1st postoperative day. Day 1 perfusion values (M1⁄4 200.32 P.U., 25p1⁄4 106.34, 75p1⁄4 260.59) did not differ significantly from

baseline. Sufficient blood flow was observed in the later period, as well. Week 3 values (M1⁄4 173.39 P.U., 25p 1⁄4 132.59, 75p 1⁄4 222.94) did not display significant difference as compared to the baseline (Figure 5).

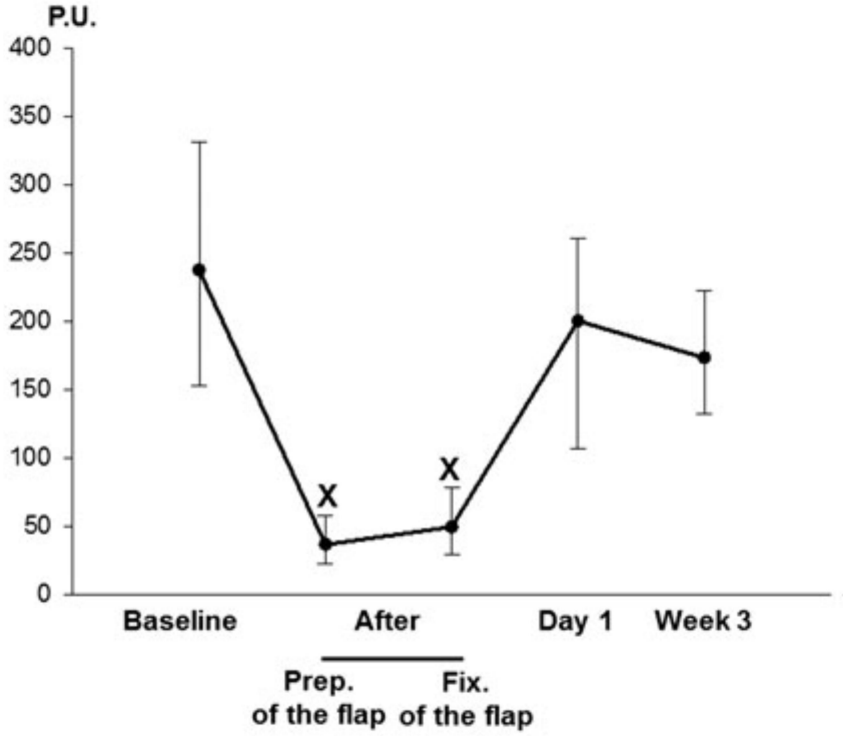

Figure 5. The blood flow of the flaps before the operation, during the intervention and in the postoperative period.

(Prep. of the flap: preparation of the flap, Fix. of the flap: fixation of the flap.)

Median values with 25th and 75th percentiles are demonstrated. X: p<.05 vs. Baseline.

Mild edema was noticeable in three cases during the 2nd-8th postoperative weeks (score: m = 0.3; SD=0.48) that was resolved with scar treatment and massage of the flap. In two cases, mild erythema was observed (score: m = 0.2; SD=0.42) which ceased after the antibiotic therapy. Mild trap-door deformity was found in one case (score: m = 0.1; SD=0.32). Hematoma was not observed and none of the patients required reoperation/resuturing (Table 5).

	Severity of the sign		
Sign	Mild	Moderate	Severe
Edema	3	0	0
Erythema	2	0	0
Hematoma	0	0	0
Trap-door deformity	1	0	0
Need for reoperation/resuturing	0		
	Number of patients displaying the given sign is presented.		

Table 5. Frequency and severity of the postoperative complications

The 6-month postoperative cosmetic result was outstanding. There were no further complications or need for additional correction (Figures 1F, 2E, 2F, 3E, 3F, 4E, 4F). Table 6 summarizes the findings of the patient satisfaction survey. The majority of the patients reported only mild or moderate postoperative pain. They were also satisfied with the esthetic and the functional results of the intervention. Moreover, they have received positive feedback from other people.

Question	Score
Q1: Could you rate the pain you felt after the intervention on a scale 0-10?	m=3.25; SD=3.4
Q2: Are you satisfied with the esthetic result of the intervention?	m=4.5; SD=0.58
Q3: Are you satisfied with the functional result of the intervention?	m=4.75; SD=0.5
Q4: Are you satisfied with the feedback of	m=5.0; S=0

other people (relatives, acquaintances, etc.) concerning the result of the intervention?	
Q5: Are you satisfied with the present shape of your nose?	m=4.75; SD=0.5
Q6: Are you satisfied with the healing of the wound and the scar?	m=4.5; SD=0.58
Q7: Do you find the breathing through your nose satisfactory?	m=5.0; SD=0
Q8: Would you decide to undergo this intervention for reconstruction, if a facial tumor was removed again?	m=4.75; SD=0.5
For question 1, the answer was given on a scale 0-10, no pain (Ľ0), unbearable pain (Ľ10). concerning questions 2-8, a 5-point likert scale was applied: very satisfied (Ľ5), relatively satisfied (Ľ4), fairly satisfied (Ľ3), relatively dissatisfied (Ľ2) and very dissatisfied (Ľ1). m: mean value, SD: standard deviation.	

Table 6. Patient satisfaction questionnaire

5. DISCUSSION

5.1.Sentinel lymph node biopsy and prognostic factors in thin melanoma

SLNB has become standard procedure for the staging of the regional nodal basin in patients diagnosed with thin melanoma and remains one of the most important predictive factors of the outcome for these patients [16-20]. However, Morton et al. reported that local complications occur in approximately 10% of SLNBs, a percentage which is not higher than other elective, clean surgeries [40]. Several previous authors have attempted to identify predictive risk factors for nodal metastases in thin melanomas, including Breslow thickness, ulceration, regression, Clark level, age, and tumour-infiltrating lymphocytes to prevent overtreatment of these patients. However, no widely accepted consensus exists as to which patients are at risk for nodal metastases.

In our study, we aimed to assess how efficiently melanoma staging systems can predict the occurrence of nodal metastases in thin melanoma and whether there are any other additional criteria to improve this rate.

Age and Gender

Younger patient age is associated with a higher nodal metastasis rate among melanoma patients in general [20,41,42-45]; however, the available studies in thin melanoma are inconsistent on this factor, and there is no widely accepted specific age cut-off value under which SLNB should be performed. Kretschmer et al. reported that young patients (<40 years) in a series of 0.75–1.00mm thin melanoma patients had a significantly higher SLN positivity rate than older age groups [46]. Sondak et al. have also reported that relatively young age (besides M.R. and Breslow depth) is associated with positive SLNs in melanoma patients [43]. In our study, we did not apply a particular cut-off age for SLNB (range 20–77 years). We placed emphasis on the characteristics of the tumour rather than on comorbidities or biological age. Corresponding to findings by Balch et al., male patients were slightly older than female patients (49.5 vs. 47.7 yrs.) [47]. However, our study did not identify any significant difference with regard to age among the SLN-positive and -negative groups. On the other hand, a marked difference was observed between male and female patients with metastatic SLNs. The mean age of SLN-positive men was 58.2 years versus 31.5 years among

women. This might be the result of the small sample size of patients involved, and further investigation may be required.

Breslow thickness

The thickness of melanoma is generally considered the most useful prognostic factor in patients with thin melanoma. In a study of 121 thin melanoma cases, Hinz et al. [17] found that all SLN-positive patients belonged to the subgroup of tumour thickness range 0.9–0.99 mm. Han et al. [48] reported that a Breslow thickness of ≥0.76 mm is associated with a 4.9–12.8% rate of SLN metastases. However, according to these studies, only 0–2.3% of melanomas <0.76mm is associated with nodal disease. Our results are similar for thin melanomas <1 mm (11.5 %) but we have found a relatively high positive sentinel rate (8%) for primary melanomas <0.8 mm. While Murali et al. [42] reported that patients with thin melanomas of <0.50 mm have negative SLN stage, Bagaria et al. reported that melanomas of <0.50 mm are identified as a factor of worse prognosis in term of SLN metastases [49]. In our series, 1/9 cases of primary melanoma <0.50mm had nodal metastasis. Interestingly, corresponding to results by Mitteldorf et al. [18], we found no significant difference in sentinel nodal metastases between the <0.76 mm and the 0.76–1.00 mm groups.

Ulceration

According to the latest two AJCC Melanoma Staging and Classification schemes, thin melanomas continue to be classified as T1b by the presence of ulceration [22,23]. Several studies have reported that ulceration is a rare event (1–15%) in thin melanomas [41, 50-52]. In our series, only 12 melanomas were ulcerated among the 152 pT1b tumours (7.9%). In the group of patients that underwent SLNB, 8/78 primary tumours (10%) showed ulceration. In their study of 147 thin melanoma patients, Yonick et al. found that ulceration (and Breslow thickness) was an independent predictor of nodal disease [53]. A study of 77 patients by Oliveira Filho et al. confirmed this result [54]. However, most studies have not shown ulceration as a significant predictor [19,20,42,53,55-57]. Kesmodel et al. reported that 181 thin melanoma patients with positive SLNs showed no signs of ulceration in the primary tumour [55]. Our results are consistent with these findings. None of the primary thin melanomas showing ulceration had nodal metastasis.

Mitotic rate

Mitotic rate (M.R.) is defined as the maximum number of dermal mitoses per mm². According to the staging system for melanomas in the AJCC7th edition, even a single mitosis can be categorized as T1b in the case of a small dermal tumour area, and, therefore, SLB should be considered [22,58]. However, with only one mitotic figure being the cut-off point, this method may be unreliable even with an additional immunohistochemistry [59]. Several authors have reported that primary melanoma mitoses predict SLN status [19,43,55]. Furthermore, Sondak et al. have found young patients (<35 years) that showed an M.R. correlation with a positive SLN. Interestingly, this was not the case with Breslow thickness [43]. Other studies showed no such association, even revealing that up to one-third of SLN-positive thin melanomas have zero mitosis [41,42,60]. In our study, there was no observable significance in mitotic rate between the node-positive and -negative group (Student t-test; t=-0.688; df=76; p=0.494).

Regression

The clinical significance of clinical and histological regression in melanoma is still debated, with numerous studies reporting a higher rate of metastasis in thin, regressed melanomas [61,62]. In our previous study [57], we also found that tumour regression predicts a higher risk of sentinel node involvement in melanomas <2.0mm in a series of 134 melanoma patients. Other authors showed no association with recurrence or survival [45,63]. This contradiction could be explained in part with the lack of a uniform definition for regression. Without these uniform criteria, the reproducibility of the results may be difficult. At our department, we used the criteria suggested by the Pathological Group of the World Health Organization Melanoma Programme for the definition of regression. This includes the presence of a zone of tumour-free epidermis and dermis in which there is fibrosis, often along with inflammation and dilated vessels, flanked on one or both sides by a tumour (Figure 6). These criteria for regression are also involved in the study by Botella-Estrada et al. [64] regarding (i) decrease or absence of melanoma cells in the dermal component of the tumour, presence of (ii) fibrosis, (iii) inflammatory infiltrate, (iv) melanophages, (v) neovascularization, (vi) epidermal flattening and (vii) keratinocytic/melanocytic damage. Features (i–v) together are considered obligatory elements for the diagnosis of regression. The extension of regression was horizontally evaluated and divided into focal or main categories; the cut-off point was a percentage of 75% in the horizontal extension of primary melanoma.

In our recent study using univariate and multivariate logistic regression analysis, regression turned out to be the only significant independent predictor of SLN metastases (OR=5.123). These results confirm our previous findings that patients with Breslow <2.0mm but regressing melanomas have a four-time higher relative risk of developing nodal metastases than patients with non-regressing melanomas. This may verify our previous hypothesis that histological regression can result in a decreased Breslow thickness measurement and thus in some cases an erroneously more favourable prognostic estimate. In contrast, the overvaluation of early regression signs may also result in false regression data for statistical analyses.

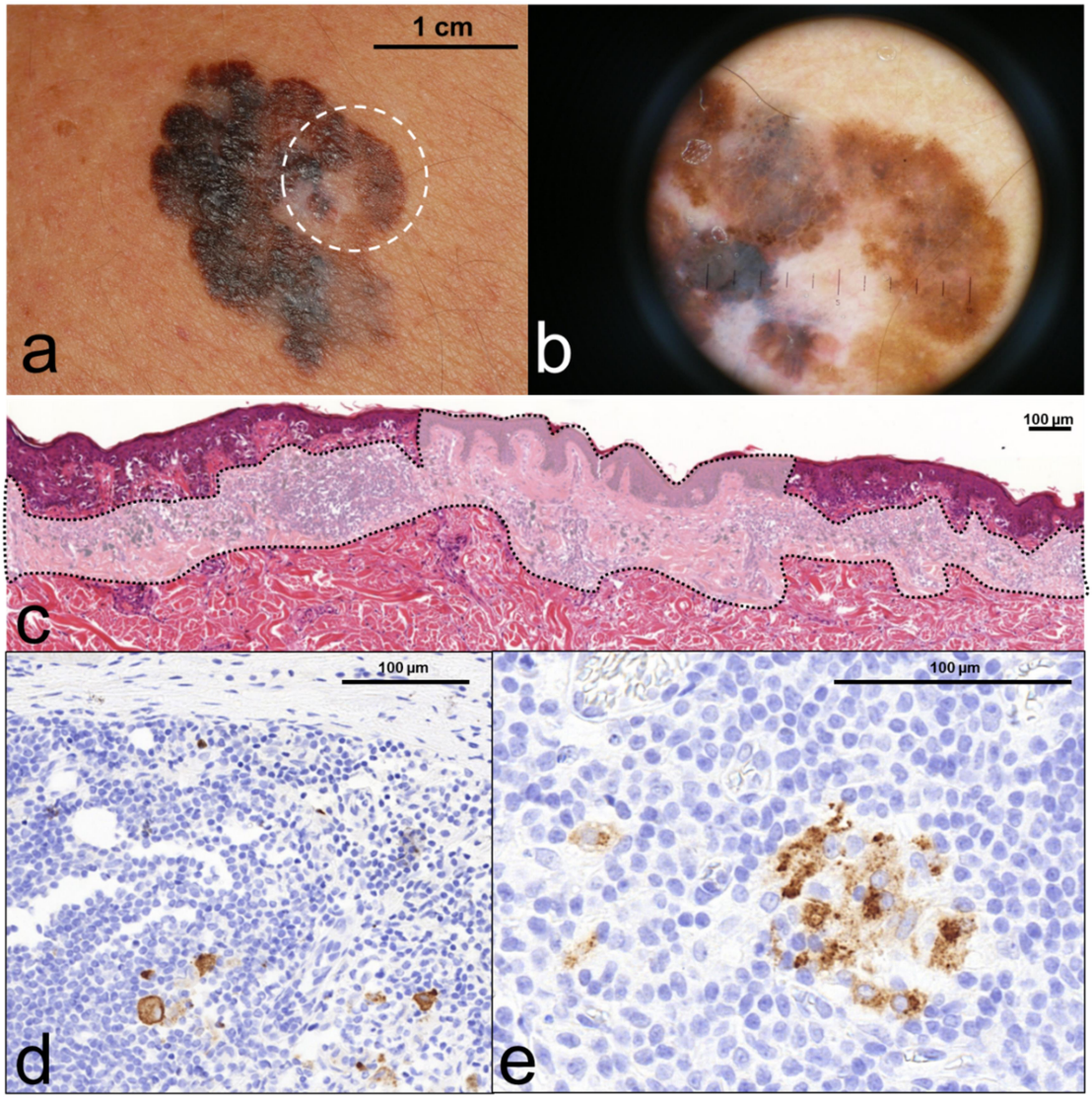

Figure 6 shows a case report of a male patient aged 71, presenting regressing superficial spreading melanoma on his back region (a). At dermoscopy, the centre of the polychrome

plaque displayed greyish-whitish area with peppering sign which is characteristic for regression (b). After the surgical removal of tumour, the histopathology showed extensive vanishing of junctional and dermal melanoma cells replaced by fibrosis, accumulation of melanophages and lymphocytic infiltrate together with focal neovascularisation (c - circumscribed faded area). Only the edges of the presented section contained atypical residual microinvasive melanoma cells within the regressive microenvironment. Although calculated Breslow thickness from the residual melanoma counterpart showed only 0.532 mm, dermal mitotic activity together with the adverse regression indicated SLNB. During the histopathological processing right axillary SLN contained scattered metastatic melanoma cells (d) which were also present in two other lymph nodes in the right axillary dissection sample (e).

5.2. Benefits of sentinel lymph node biopsy in thick melanoma

Over the five-year study period, 1133 melanoma patients were diagnosed and treated at the Department of Dermatology and Allergology, University of Szeged, Hungary. According to the Hungarian Cancer Registry, it is one-tenth of the 9862 melanoma patients diagnosed during the same time period in Hungary [1].

Our institute is the center responsible for the care of dermato-oncology patients in the region of the Southern Great Plain. Whereas the Kecskemét County Hospital plays a significant role in the surgical treatment of melanoma patients in Bács-Kiskun County, in accordance with the highest professional expectations. However, the decision about the systemic treatment of the majority of patients treated by the Kecskemét County Hospital is determined by the multidisciplinary dermato-oncology team at the Department of Dermatology and Allergology, University of Szeged.

During the study period, 1268 newly diagnosed melanoma patients were reported to the Hungarian Cancer Registry in the three counties of the region (Bács-Kiskun, Csongrád, and Békés Counties), 90 percent of whom were treated at our Department. In light of this, we can conclude that our data are suitable for assessing the region's surgical care of melanoma. Based on the data of melanoma patients treated at our department, there are up to hundred of advanced melanoma patients with absolute tumor thickness over 4 mm every year who may

need to be treated with adjuvant therapy or are expected to respond more effectively at conducting adjuvant therapy with innovative agents.

Since the turn of the millennium, with the advancement in molecular sciences, it has become known that alterations in the RAF-MEK-ERK signaling pathway play a major role in the development of this type of tumor [65].

In patients with metastatic melanoma with V600 mutation of the BRAF gene, BRAF-MEK inhibitors are the current standard of care. For BRAF wild-type metastatic tumours, immunotherapy is the first-line treatment, with PD-inhibitors being the preferred drug of choice [12,13].

As a result of these treatments, the survival rate of melanoma patients has improved remarkably, and nowadays, every third patient treated with metastatic melanoma is still alive after five years, which is a significant improvement compared to the previous, very modest average survival of a few months.

In recent years, clinical research has changed the systemic treatment of unresectable metastatic melanomas as well. The first report on favorable progression-free survival data for adjuvant treatment of high-risk melanoma with ipilimumab was published in 2016; however, due to the high rate of grade 3 or more severe adverse reactions (45.9%), this treatment has not become widespread [66].

In the phase III CheckMate238 trial, efficacy and safety of nivolumab was compared to ipilimumab as an adjuvant therapy in stage IIIB, IIIC, and IV melanoma. In stage IIIB and IIIC melanoma patients, the 12-month relapse-free survival was 72.3% in the nivolumab group and 61.6% in the ipilimumab group. In stage IV melanoma, this rate was 63.0% and 57.5% in nivolumab and ipilimumab, respectively [67].

COMBI-AD was the first prospective phase III placebo-controlled trial which demonstrated that BRAF-MEK inhibitor combined treatment as a 12-month adjuvant therapy significantly improves relapse-free survival after complete resection in stage III melanoma with V600 mutation. This study results showed that the estimated 3-year relapse-free survival in the dabrafenib–trametinib combination group was significantly higher compared to the placebo arm, 58% and 39% ($p<0.001$), respectively [68]. In 2018, Eggermont et al. published the results of the phase III, randomized, double-blind, placebo-controlled EORTC 1325 trial (Keynote 054), in which 200 mg of pembrolizumab administered every three weeks was evaluated in the treatment of resected stage III melanoma with high risk of recurrence [69].

In the clinical study above, patients were classified for TNM based on AJCC 7th edition. Accordingly, 1019 patients with histological stage IIIA, IIIB, or IIIC who underwent R0 resection and complete regional lymph node dissection following sentinel lymph node positivity were randomly assigned in 1:1 ratio to one of the study arms. Only patients with stage III melanoma were enrolled whose metastases had a maximum diameter larger than 1 mm. Patients received pemrolizumab or placebo 18 times in total in approximately 1 year or until recurrence or the development of unacceptable side effects. After a median follow-up of 15 months, pembrolizumab was found to be associated with a significantly higher recurrence-free survival (RFS) compared to placebo. The 1-year RFS with pembrolizumab was 75.4% [95% confidence interval {CI}, 71.3–78.9], while it was 61.0% in the placebo group ([95% CI, 56.5–65.1]). The hazard ratio (H.R.) of recurrence and / or death was found to be 0.57 (98.4% CI, 0.43–0.74; $p<0.001$).

In the subgroup analysis of 853 patients with PD-L1-positive tumors, the 1-year RFS was slightly higher (77.1% [95% CI, 72.7–80.9]) than in the whole pembrolizumab arm. The beneficial effects of pembrolizumab on progression-free survival were observed in both the BRAF wild-type group and the BRAF mutant group. Serious adverse events (grade 3–5) were reported in 14.7% of the patients treated with pembrolizumab compared to 3.4% of the patients treated with placebo.

In our study, the mean age of patients with thick melanoma was around 60 years. It means that the number of productive work years lost in this patient group is expected to be high, which implies that the importance of effective adjuvant treatments is significant, not only for the individual but also economically to the society.

One-tenth of our patients with melanoma had a tumor thickness over 4 mm, with an average of 6.79 mm. In a recent publication, Argentinean authors have evaluated their biopsy results of sentinel lymph nodes in patients with thick melanoma. In their study, 6.7% of the patients with melanoma had a thick tumor, which is lower than the 10% of the patients with melanoma treated in our department [70].

The proportion of thick tumors in our region remains high. Since the clinical signs of melanoma are recognizable by macroscopic examination, the wide dissemination of the information to the lay public about the suspicion of skin cancers will continue to be essential.

In our study, we found a very high proportion of positive sentinel lymph nodes, in almost two-thirds (64%) of the patients, which ranges on a wide scale from 22% to 64% based on various literature data [14,71-73].

In the above-mentioned study, Otero et al. have found sentinel lymph node positivity of 56% in thick melanoma [70].

Kachare et al. have observed positive SLNB test in 32.3 % of 2746 patients in their study of thick melanoma [74], Ribero et al. have reported 47.1% positivity, and Vermeeren et al. have found a 64.5% positive SLNB rate similar to ours in a smaller population [75,76].

Nonetheless, numerous studies confirm the role of SLNB in the treatment of thick melanomas, which have a significant role in the disease-specific survival, length of relapse-free period, and overall survival [77-79].

In thick melanoma, the main argument for not performing sentinel lymph node biopsy is that in these tumors, in particular, the hematogenous spread of the disease is a determinant of the disease course, and according to these researchers, performing SLNB has no effect on the recurrence or mortality [80].

There are also counterarguments because of the morbidity of the intervention the literature on which is diverse: reports of complication rate ranges between 1.8% and 33% [81].

In the present study, 21.8% of the patients, which is considered an average rate, experienced surgery-related complications, predominantly seroma formation and infection. Oana-Diana Persa et al. have investigated postoperative seroma formation and other complications in 615 patients with SLNB with a median follow-up of 115 weeks. In their study, complications occurred in 20.4% of the patients. The most common morbidity associated with SLNB was postoperative seroma formation, which was present in 19.6% of the cases. This complication was significantly more common in the inguinal region and in men [82].

In a 52.5-month follow-up study of 124 patients with SLNB by Espinosa-Pereiro et al., 30.9% of patients experienced surgery-related morbidity. In their study, the most frequent complications were scarring and wound infection (10% each), whereas seroma formation and lymphedema were observed in 5% of the cases each [83].

5.3.Reconstruction of alar-perialar defects and application of our novel method

The reconstruction of nasal soft tissue defects localized to multiple esthetic subunits is a challenging task for plastic surgeons. The combined reconstruction of alar and perialar regions is difficult. The alar region has a rigid structure and low mobility, while the perialar soft tissues are different. Preserving the natural alar contours and concavities of the alar crease also keeping the respiratory function and symmetry with the contralateral side is important [37]. There are various reconstructive techniques available that can be used in this region, including direct closure, skin grafts, local flaps, regional pedicled flaps or combinations of these [84]. Direct closure is only preferable in case of small defects, because it can easily cause alar rim distortion. Skin grafts may result in depressed scars and impaired nasal valve patency when used to repair deeper alar defects [85]. Almost all local and regional flaps have significant drawbacks. The single staged nasolabial transposition flap results in a deformed alar groove thus producing an obvious asymmetry with the contralateral side [84]. The conventional subcutaneous pedicled island flaps may also lead to distortion and more frequently pin-cushioning or trapdoor effect due to the all-round incision of the flap [36,86]. The combination of these procedures or multiple correctional surgeries can also be laborious and costly. Our aim was to find a one-step intervention which fulfills all the above mentioned requirements with the least complications. The blood supply of our flap is dual. It can be considered as the combination of the unipedicle melolabial advancement flap and the melolabial island advancement flap described by Baker [87]. Contrary to the above mentioned ones, our flap receives blood supply from two different directions. On the one part, cutaneous vessels enter the flap from the area of the nasolabial fold (because the flap is not incised medially). Furthermore, the flap is not undermined (except the cranial part) therefore it has subcutaneous perforators, as well. For the better mobilization, cutback can be performed hereby making a hatchet flap, however it is not necessary in most cases. This technique allows the reconstruction of alar and perialar defects localized to more esthetic subunits. As concerns preparation of the flap, two different movements shall be performed. The flap is first moved to the inferior part of alar rim like an advancement flap. This is the pivot point around which the cranially thinned flap is rotated into the remaining part of the defect. Regarding the results of the follow-up, there were no partial or complete flap losses. This may originate in the above mentioned advantageous blood supply which involves both cutaneous branches and subcutaneous perforators. Although surgical intervention itself may lead to a decrease in capillary flow during the early postoperative period, this parameter shows regeneration then

[88]. Neither hematoma, nor recurrence of the tumor was observable. Although in two cases sign of infection was detected, this may originate in the age and the comorbidities of the patients. Symmetry with the opposite side remained intact with no significant distortion or disfiguring of facial folds or creases. Large defects may be accompanied with the risk of temporary or permanent distortion of upper lip and melolabial fold. The biggest defect in our study was 2.6x2.9cm which has not led to such problem. However, each case shall be judged individually, and our elderly patients possess a skin laxity which may facilitate the procedure. However, a slight edema of the flap was seen in some cases but this resolved with scar treatment and massage of the flap by the end of the 8th postoperative week. Mild trap-door deformity was found in one case and there was no need for a second operation in any of the cases. Furthermore, the patients were satisfied with the results of the intervention. Planning of the flap is easy and with cautious dissection and trimming of the cranial part of the flap, the vascular supply can be fully preserved. Our study involves mainly elderly patients since extended basal cell carcinoma is rare in younger patients. Elder skin may differ from that of younger patients in terms of laxity and microcirculation. Lax skin may facilitate positioning of the flap. Microcirculation often displays impairment with the age, but we have found good postoperative regeneration of blood flow and optimal flap survival. Nevertheless, our future aim is to increase the number of cases in order to gain more reliable data on this technique.

6. CONCLUSIONS

According to the large, multicentre studies, thin melanomas (<1.00mm) have a low, but significant risk for SLN metastases; however, these studies often apply various criteria for staging and performing SLNB. Prospective standardized multicentre trials with standardized clinicopathologic and demographic criteria for performing SLNB in thin melanomas are needed to specify widely accepted, reliable predictors.

Compared to the numerous multicentre studies published recently, the benefit of our results may be the uniform criteria for diagnosis and treatment, as all the cases were managed at a single institution, with uniform surgical techniques and standard histology protocols processing and evaluating primary melanomas and SLNs.

Our analysis supports the recent AJCC8th classification that **mitotic rate alone is not a sufficiently powerful predictor of SLN status in thin melanomas.** If strict histopathological

definition criteria are applied, **regression might be an additional adverse feature** that aids in identifying those T1 patients most likely to be SLN-positive, therefore sentinel lymph node biopsy might be considered in the case of patients with widely regressive thin (<0.8 mm) melanomas.

To summarize our results in thick melanomas, we can conclude that the **proportion of both thick melanoma and sentinel lymph node positivity is high in our region.** Since, approximately the 10% of the nationwide newly diagnosed melanoma cases are treated at our Department, the number of patients with thick primary melanoma in Hungary can be up to ten times of our thick melanoma patients, so we estimate that **sentinel lymph node biopsy**, which helps to **determine the exact pathological stage, may be essential for optimal treatment in up to a hundred patients a year nationwide**. All these data further support the concept that surgical treatment of melanoma should be performed only in the centers where personal and technical requirements for performing sentinel lymph node biopsy can be met.

Reconstruction after NMSC in the alar-perilar region is a frequent task in the facial oncoplastic surgery. **Our flap design in this region provides the benefits of the combined vascular supply of subcutaneous and cutaneous pedicled flaps without the disadvantages of all-round incisions, causing trapdoor deformities.** It is suitable for the reconstruction of both deeper perialar and thinner alar defects with the appropriate cosmetic result.

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