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Surgical Outcomes of More Than 1300 Cases of Mohs Micrographic Surgeries from a Private Mohs Clinic in Romania

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Rezumat

Rezultatele chirurgicale a peste 1300 de intervenții de microchirurgie Mohs într-o clinică privată din România

Introducere: Cancerele de piele au o incidență în continuă creştere, avand un impact economic important. Microchirurgia Mohs este cunoscută ca *gold-standard* în tratamentul a 10 tipuri de tumori cutanate, dintre care carcinoamele bazocelulare şi spinocelulare sunt cele mai frecvent întâlnite.
Metodă: Au fost analizate dosarele pacienților trataţi prin microchirurgie Mohs pe o perioadă de 6 ani (2014-2019) şi au fost extrase informaţii demografice, precum şi informaţii despre histologia tumorală, localizarea tumorilor, numărul de stadii necesare pentru îndepărtarea completă a tumorii şi evoluţia pacienților. Am analizat informațiile cu privire la numărul şi tipul de reconstrucții efectuate.
Rezultate: Pe parcursul a 6 ani, în clinica noastră au fost tratate 1356 tumori cutanate folosind microchirurgia Mohs. Carcinoamele bazocelulare au reprezentat 80.5%, carcinoamele spinocelulare 17.6% iar alte tumori precum melanoamele in situ, dermatofibrosarcoma protuberans, boala Paget extramamară, carcinom sebaceu - 1.9% din numărul tumorilor tratate. În perioada analizată s-au înregistrat doar 4 recidive după microchirurgia Mohs, cu o rată de vindecare de peste 99,7%
Concluzii: Microchirurgia Mohs este o metodă eficientă de tratament în îndepărtarea carcinoamelor cutanate precum si a unor tumori cu indicatie speciala,cu o rată scăzută a recidivelor, reducând necesitatea unor intervenții chirurgicale succesive.

Cuvinte cheie: carcinom bazocelular, carcinom spinocelular, melanom in situ, dermatofibrosarcoma protuberans, microchirurgie Mohs.

Abstract

Background: Basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC) are the most frequent skin cancers with a continuous increasing incidence and a cause of economic impact. Mohs micrographic surgery (MMS) is known as the gold-standard of treatment of non-melanoma skin cancer.

Methods: The files of the patients treated with MMS were analysed during a 6 year period (2014-2019) and demographic information was extracted in addition to the information on tumor histology, localization of tumors, number of stages required for a complete removal of the tumors, and the evolution of the patients. We also analysed the information regarding the number and type of reconstructions performed.

Results: Over the course of 6 years, 1,356 cutaneous tumors were treated in our clinic by means of MMS. BCC represented 80.5%, SCC 17.6%, and other tumors such as melanoma in situ, DFSP, Extramammary Paget's Disease - being 1.9% of the number of other treated tumors. During the period under review, only 4 cases of post-Mohs Micrographic Surgery recurrence have been recorded, with a cure rate of over 99.7%.

Conclusions: Mohs micrographic surgery is an efficient treatment method in removing cutaneous carcinoma as well as tumors with special indications with a low recurrence rate therefore reducing the need of successive surgical interventions.

Key words: basal cell carcinoma, squamous cell carcinoma, melanoma in situ, dermatofibrosarcoma protuberans, Mohs micrographic surgery

Introduction

Although melanoma is the most dangerous skin cancer, the most frequent cutaneous cancers are basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), spanning more than 1/3 of overall cancers and are increasing in number around the world (1). This pathology economically burdens both the individual, as well as society. In less than 10 years, in the United States of America, the treatment costs for skin cancers had an average annual increase of 126.2% compared to 25.1% represented by the cost increase for all the malignant diseases (2). Hence, despite the low mortality rate, cutaneous carcinomas should not be underestimated since they are in 5th place in regards to the treatment costs for cancers in Medicare. Non-melanoma skin cancer (NMSC) accounts for 81% of the costs associated with all skin cancers, including melanoma (3,4).

The international statistics show an increase in the incidence of the NMSC (5). The data published in 2018 on GLOBOCAN regarding cutaneous carcinomas in international statistics state that in Eastern Europe the incidence is 7.1 per 100,000 inhabitants in men and 5.2 in women. In comparison, in the United States of America, the incidence is 76 per 100,000 inhabitants in men and 36.8 in women, while in Western Europe it's 34.1 in men and 18.8 in women.

Unfortunately, in Romania, the lack of reporting and of official statistics explains why the situation of non-melanoma skin cancer remains unknown. Therefore, it is possible that we have nationwide on an annual basis, 1,383 new cases of cutaneous carcinomas in men and 1,013 new cases in

women, totaling 2,400 new cases.

The treatment of choice in high-risk non-melanoma skin cancer is a surgical one. Among the surgical treatments, it has been proven that Mohs micrographic surgery attains the highest cure rates for NMSC, preserving the maximum amount of surrounding healthy tissue. Mohs micrographic surgery is the standard treatment of cutaneous carcinomas in the United States of America, Canada, New Zealand, Great Britain, the Netherlands and Israel. In these countries, there are numerous dermatologists qualified in Mohs micrographic surgery and a multitude of education and training programs for the specialists. In Europe, there are 117 Mohs surgeons certified by the European Society for Micrographic Surgery (ESMS), which are unevenly distributed across Europe, with the highest numbers in the Netherlands, Switzerland, and Belgium, where the incidence of cutaneous carcinomas is high (6).

In Romania, our clinic has experience of more than 10 years in treating NMSC by means of Mohs Micrographic surgery. As the treatment recommendation for the use of Mohs microsurgery for other types of skin cancers such as in situ melanoma or lentigo maligna (LM) was introduced, we have integrated the procedure for these types of tumors as well.

This paper exhibits the clinic's experience in Mohs micrographic surgery for the last 6 years over the period of 2014-2019.

Material and Methods

A retrospective analysis was performed on the data of the patients who underwent surgical interventions in our clinic between 2014-2019. The information was extracted from the database of the Clinic, including photographs, histopathological results, and patient charts. This information was extracted and introduced in a Microsoft Excel database. The data was classified according to the histopathological diagnostic (BCC, SCC, other tumoral types), primary or recurrent tumor, and its localization. Also, the initial size of the tumor, the number of stages, the final size of the defect, and the reconstruction type were recorded.

The cases were classified preoperatively into three categories: A - low difficulty, B - average difficulty, or C - complex cases, and according to the histopathological subtype, localization, sizes and estimated complexity of the surgical stages. This distribution facilitated establishing the days for surgery.

Mohs surgery in our clinic is an option for treating keratinocyte tumors (BCC and SCC), as well as the treatment of melanocytic tumors, melanoma in situ, dermatofibrosarcoma protuberans, extramammary Paget's disease, Merkel cell carcinomas, microcystic adnexal carcinomas, atypical fibroxanthoma, and sebaceous carcinoma.

A small biopsy is performed prior to excision in order to establish the diagnosis. The tumor is removed using the standard MMS technique. The tumor is excised at a 30-45 degree angle with an 1 mm margin for most of the tumors. For aggressive histopathologic types of BCC (micronodular, infiltrating, sclerosing), Bowen disease, lentigo maligna, the margin is at 2- 5 mm, but can be increased at up to 1 cm for dermatofibrosarcoma protuberans. The 12 o'clock position is marked with a nick on the specimen and on the skin. For larger tumors additional marks can be added.

The tumor is taken to the Mohs laboratory, a map is drawn, the tissue is marked with ink and flattened. The tissue is then fixed on a metal chuck, covered with OCT and placed in the microtome. Tissue wafers are cut horizontally 6-8 um thick with 40 um discarded between each wafer and placed on two slides. The slides are stained with an H&E staining and analyzed. Any positive margins are marked on the Mohs map. If the tumor is present, the patient returns to the procedure room and the layer corresponding to the positive area is taken and the tissue is processed as per the first stage. The process is repeated until there is no tumor is present. After the tumor is cleared, the skin defect is repaired. The whole procedure is performed

ambulatory the same day under local anesthesia.

Results

The total number of cases treated by Mohs micrographic surgery has increased gradually, from 116 in 2014 to 444 in 2019 (*Table 1*).

Between 2014 and 2019, the majority of the treated tumors were basal cell carcinomas (1091 cases, 80.5%),followed by squamous cell carcinomas (239 cases, 17.6%).Other tumoral types benefitting from Mohs micrographic surgery are lentigo maligna melanoma (5 cases, 0.4%),rare tumors as extramammary Paget's disease, Dermatofibrosarcoma protuberans, microcystic adnexal carcinoma, atypical fibroxanthoma (21 cases, 1.5%).

The indications for Mohs micrographic surgery were then documented. These indications included aggressive histopathological subtypes, recurrence of tumors after non-surgical treatment or classical excision, tumors localized on high-risk areas, such as the H-zone of the face, the genital area, the periareolar area, hands, feet, and legs, if the tumor was previously excised completely, tumors of large sizes, tumors with perineural invasion, and patients with immunosuppression.

Most of the surgical interventions were performed in a single day and frozen-section tissue processing technique was employed (1,329, 98.1%). For the rest of the cases, the "slow" Mohs method, which involves embedding the tissue in paraffin was used. This technique was used in the case of rare tumors, lentigo maligna, or in circumstances when additional immunohistochemistry (IHC) staining was required. The average number of stages required in order to obtain the complete removal of the tumor was 1.59.

The surgical interventions were performed under local anesthesia by the dermatologists working in our clinic. The HP interpretation was performed by the pathologist. The reconstruction was made by the dermatologists, and for the complex cases it was performed by plastic surgeons - 11 cases. All the interventions performed by fellows from the ITMP-MOHS Program were supervised and guided by Fellowship Manager.

Table 1. Annual number of treated tumors, localization and type of tumors treated by MOHS micrographic surgery during 2014-2019 in the clinic

Number of tumors treated per year		
2014	116	8.6%
2015	148	10.9%
2016	175	12.9%
2017	195	14.4%
2018	278	20.5%
2019	444	32.7%
Type of tumors		
Total (N, %)	1356	
CBC	1091	80.5%
CSC	239	17.6%
Melanoma (in situ/lentigo maligna)	5	0.4%
Others	21	1.5%
Localization of tumors		
"H"-zone of the face n (%) (Nose, Lips, Eyelids, Temples, Ears)	951	70.1%
Face (outside the "H"-zone) n (%)	254	18.7%
Scalp and neck n (%)	79	5.8%
Torso (excluding the special areas) n (%)	32	2.4%
Body special areas (Genital, Perianal, Periareolar, Hands and Feet) n (%)	19	1.4%
Anterior face of the leg n (%)	21	1.5%
Unknown n (%)	0	0.0%

The cutaneous defects resulted after the complete removal of the tumors were linearly closed in 495 of the cases (54.0%). Full thickness skin grafts (FTSG) were used in 24 cases (2.6%). In 809 (59.6%) cases, the reconstruction required the use of cutaneous flaps. According to the type of flap, the most frequently used were rotation flaps 112 (12.3%), advancement flaps 90 (9.8%), transposition flaps 33 (3.6%), and island flaps 52 (5.7%). Three cases required paramedian flaps, 12 cases needed vermilionectomy and in one case a toe amputation was necessary. In 11 cases, the healing was per secundam. Nineteen patients needed combined reconstructions (flap and FTSG or linear closure and FTSG) (*Table 2*)

The postoperative complications, reduced in number, were managed by each attending physician, but they haven't been centralized into a database. The complications were seroma, partial flap necrosis, bleeding, and vicious scarring. There was no record of severe

Table 2. Types of reconstructions

Direct closure	495	54.0%
Skin graft	24	2.6%
Paramedian transposition flap	3	0.3%
Bilobed flap	8	0.9%
Advancement flap	90	9.8%
Rotation flap	106	11.6%
Transposition flap	33	3.6%
Islanded flap	46	5.0%
Keystone flap	2	0.2%
Per secundam	11	1.2%
Purse string	3	0.3%
M-Plasty	22	2.4%
S-Plasty	13	1.4%
Z-Plasty	22	2.4%
V-Plasty	1	0.1%
O-T-Plasty, O-Z-Plasty and A-T-Plasty	6	0.7%
Vermilionectomy	12	1.3%
Amputation	1	0.1%
Combined reconstructions	19	2.1%

complications or complications that might endanger the patient's life.

During the analyzed period of time, only 4 relapses were recorded (0.29%) - three recurrent infiltrative BCC and one poorly differentiated SCC and were treated using MMS. In each situation, photographs were taken during the surgical intervention, the patient charts and histopathology slides were carefully re-examined. In the case of two basal cell carcinomas, the recurrence occurred due to a discontinuous tumor spread, given that they were carcinomas with numerous previous surgical treatments. The third BCC developed on an actinic keratosis near the postoperative scar in a patient with numerous NMSCs. In the case of the SCC, the histopathological subtype was difficult to highlight by frozen-section tissue processing and at the subsequent surgical treatment, paraffin sections were also performed for further examination.

Discussions

Mohs micrographic surgery is a surgical technique associated with very high cure rates, particularly employed in case of tumors with a high recurrence risk, asymmetrical tumors, irregular margins, and aggressive histopathological subtypes since it offers the possibility of microscopic examination of all margins. Furthermore, the healthy tissue is maximally preserved, making this technique useful in areas of aesthetic and functional importance (7,9).

The cutaneous tumors that frequently benefit from this surgical technique are basal cell carcinomas and squamous cell carcinomas. Those in the high-risk tumor category are lesions localized in the H-zone of the face, the genital area, hands, feet, areolar region, recurrent tumors or the ones incompletely treated, tumors with aggressive histopathological subtypes, tumors with perineural invasion, tumors exceeding 1 cm in diameter on the face or neck and 2 cm on the torso and limbs, or in patients with immunosuppression (8) (*Fig. 1A, 1B*).

Among the surgical treatments, Mohs micrographic surgery is proven to have the highest rates of healing NMSC. Two reviews which analysed the rate of recurrence after various treatments for BCC have reported

Figure 1A. A nodular tumor appeared 6 weeks before on the ala nasi of this 71 y.o. patient. A shave biopsy was performed and the diagnosis was keratoacanthoma.

Figure 1B. Several stages of Mohs micrographic surgery were needed in order to remove the tumor completely.

lower recurrence rates of the tumors treated by Mohs micrographic surgery. In case of primary tumors, the recurrences were of 1% for Mohs and 10.1% for the classic excision and in case of recurrent tumors 5.6% for Mohs surgery compared to 17.4% for the classic surgical excision, and 40% for curettage and cauterization (10,11). Another study carried in the Netherlands has reported that the rates of recurrence in 10 years in cases of primary and recurrent carcinomas are three times lower when treated with Mohs as opposed to surgical excision (11). Very low recurrence rates have also been recorded in cases of cutaneous tumors treated by Mohs micrographic surgery in our clinic (0.29%).

The low recurrence rates are due to an integral verification of the tumoral margins. The main difference between the two types of treatment – the standard surgical excision and Mohs micrographic surgery – consists of the histopathological examination of the margins. In the case of classic surgical excision, the margins are evaluated by random vertical sections. This way, only 1% of the margins are being examined (12,13). By contrast, in the case of the Mohs micrographic surgery, the tissue is flattened and horizontal sections are made. This way, the margins are verified integrally, on 100% of the surface (12) (*Fig. 1C*).

Another advantage of the Mohs technique is the preservation of the healthy tissue neighboring the tumor. The sizes of the final defect might decrease by 50% in cases of infiltrative basal-cell carcinomas treated by Mohs (14). The excision of the tumor by Mohs micrographic surgery is made with a margin of 1 mm, as opposed to 4-5 mm in case of classic surgical excision of the nodular or superficial basal cell carcinomas, or up to 6 mm in case of aggressive histopathological subtypes. Additional excisions are made if the margins continue to be positive in the area where the tumoral tissue persists. The smaller defects can be easier to reconstruct at the end generating better aesthetic and functional results (14) (*Fig. 1D, 1E*).

Mohs micrographic surgery and the reconstructions are performed with local anesthesia. The data claims that this type of anesthesia is safe, efficient, and well tolerated by patients (15). Between the stages of the surgical intervention, the patients can wait in the waiting room with the wound covered by a sterile dressing. For each surgical stage, the anesthesia is repeated. The reconstruction

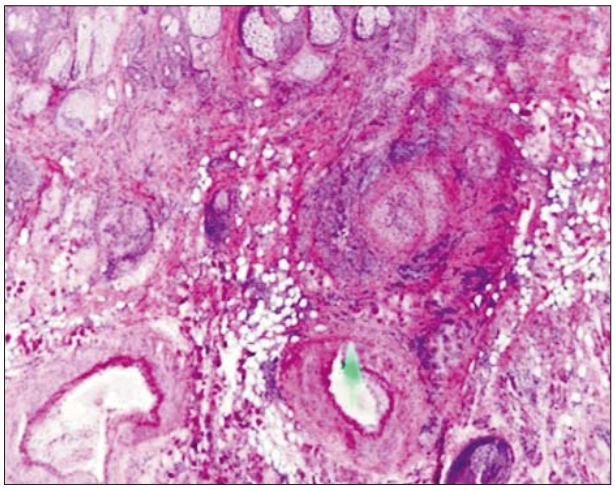

Figure 1C. The HP examination revealed an important perineural infiltrate. Six stages were needed in order to reduce it significantly. The tissue was also processed in paraffin and IHC was performed in order to exclude the presence of tumor cells in the perineural inflammatory infiltrate.

Figure 1D. A paramedian forehead flap was used to reconstruct the defect. A template of the operative wound was obtained using a sterile foil and was transferred on the forehead, delineated and marked. The flap was incised along the margins and the portion of the flap that became the nasal tissue was elevated from the frontalis muscle. After that, the rest of the flap and the pedicle were elevated just above periosteum. A cartilage graft was harvested from the antihelix and gently sutured into position. The flap was meticulously thinned and turned over to envelope the cartilage graft.

in most of the cases was performed by the dermatologist. In special circumstances, when the cutaneous defects were complex, they involved an extended surface – more than 50% of the cosmetic unit surfaces – for instance, at the level of the eyelid they required amputation, the reconstructions were then performed by the plastic surgeon.

Figure 1E. Before and after result.

Aside from basal cell carcinomas and squamous cell carcinomas, in our clinic the Mohs micrographic surgery was successfully used in treating melanocytic tumors - melanoma in situ, dermatofibrosarcoma protuberans, extramammary Paget's disease, Merkel cell carcinomas, microcystic adnexal carcinomas, atypical fibroxanthoma, and sebaceous carcinoma (16).

Lentigo maligna is a subtype of melanoma in situ characterized by extended horizontal growth, where the neoplastic melanocytic remains at the dermal-epidermal junction level without invading the dermis. These lesions appear on the sun-exposed areas, particularly on the head and neck, having an important subclinical extension and may evolve to invasive melanoma. A study published in 2005 has analysed the size of the cutaneous defects resulted after treating lentigo maligna by "slow" Mohs and determined that these are 2 to 10 times larger compared to the clinical size (17). Evidence was provided that the 5 mm oncologic safety margin recommended for the excision of melanoma "in situ" was the most time insufficient and in one quarter of the cases initially diagnosed as melanoma "in situ" following the partial biopsy, invasive components were identified. As a result, the surgical treatment is the treatment of choice in case of melanoma "in situ" imprecisely delimited and localized on sun-exposed areas (18). Mohs micrographic surgery offers the possibility of integrally examining the margins and the rate of recurrences is significantly lower when using this technique (0-3,6%, by Mohs micrographic surgery, as opposed to 6-20% in case of classic excision) (18).

The frozen tissue processing by Mohs technique has certain limitations, the freezing artifacts and background actinic changes make the examination difficult. In order to increase the accuracy of the diagnosis,

immunohistochemistry (IHC) staining was introduced and can be used on the frozen-section processed tissue. Among these, MART-1/Melan A are more sensitive compared to HMB-45 and S-100 and the working protocols are reproducible (19,20). However, false positive results leading to a useless extension of the cutaneous defect have been recorded in the case of presence of pigmented actinic keratosis or on sun-damaged skin. Therefore, given the difficulty to examine frozen sections, even by use of IHC the sections embedded in paraffin and the "slow" Mohs technique are preferable (18). This is also the technique used in our clinic for treating melanoma "in situ" on the sun-exposed areas. During 2014-2019, five cases of lentigo maligna have been treated, with no recurrences recorded to date.

Dermatofibrosarcoma protuberans is a rare soft tissue tumor, characterized by slow growth and low metastasizing rates, but with an aggressive local invasion and high recurrence rates (21). In a study published by Ratner, an important subclinical growth of DFSP was highlighted, thus the tumor extends to 1 cm around the clinical margins in 70.7% of the cases, to 2 cm in 39.7%, to 3 cm in 15.5% and to 5 cm in 5.2% of the cases. Moreover, even a 10 cm margin around the tumor in some cases wouldn't have led to complete excision, despite the large surface of sacrificed tissue (22). This data explains the high rates of DFSP recurrence in cases of classic excision (*Fig. 2A*). Recurrence rates of 41-47 % have been reported when the excision was performed with a margin of up to 2-3 cm and between 7-20% when the oncologic safety margin was between 3 and 5 cm, as opposed to 1.7 % in case of Mohs micrographic surgery (0% rate of recurrence for the primary tumors and 4.8% in case of the recurrent ones) (22,23). Given the reduced rates of recurrence and the possibility of preserving the healthy tissue, Mohs micrographic surgery is the treatment of choice in case of DFSP. In our clinic, five cases of dermatofibrosarcoma protuberans have been treated by "Slow" Mohs technique. The patients continue to be on follow-up appointments and during this time no recurrence was recorded (*Fig. 2B, 2C, 2D, 2E*).

Figure 2A. This 20 y.o. male patient had a recurrence after DFSP and was surgically treated one year before. The tumor was marked and was removed at the 1 cm border for biopsy. After that, the margins were removed with "slow Mohs" technique at 1 cm and markings were made on the skin and on the tissue. The sample was sent to the pathology lab where permanent sections were made, along with IHC.

The extramammary Paget's disease is a rare tumor, usually localized on the epidermis level and the invasive tumors are associated with a poor prognosis. These lesions show a slow increase and imprecise margins, making Mohs micrographic surgery suitable for treating them. A retrospective analysis on 207 patients with extramammary Paget's disease treated by Mohs micrographic surgery versus wide-margin excision demonstrated that the recurrence rates are lower for the first category (9% compared to 34%) (24).

Merkel cell carcinoma is an aggressive cutaneous tumor, associated with high rates of recurrence, and an increased risk of metastasis. The classic excision, with an oncologic safety margin of up to 3 cm was associated with recurrence rates of 26-44% of the cases, while in case of the tumors treated by Mohs micrographic surgery no

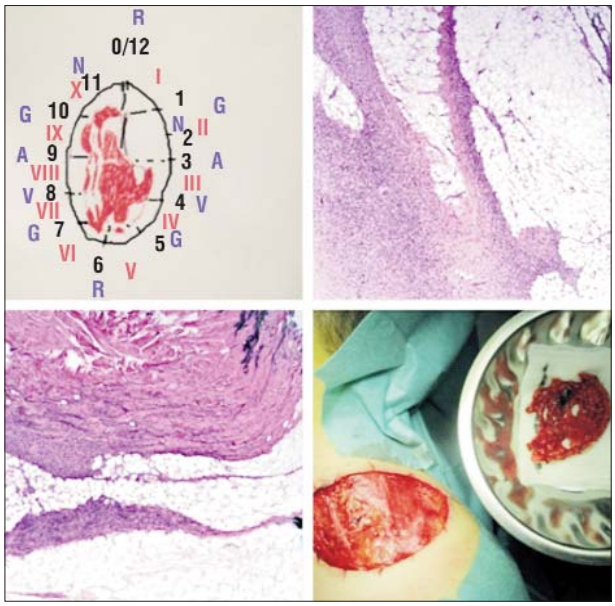

Figure 2B. The anatomopathological examination indicated that the tumor was still present in the base of the wound and another stage was performed.

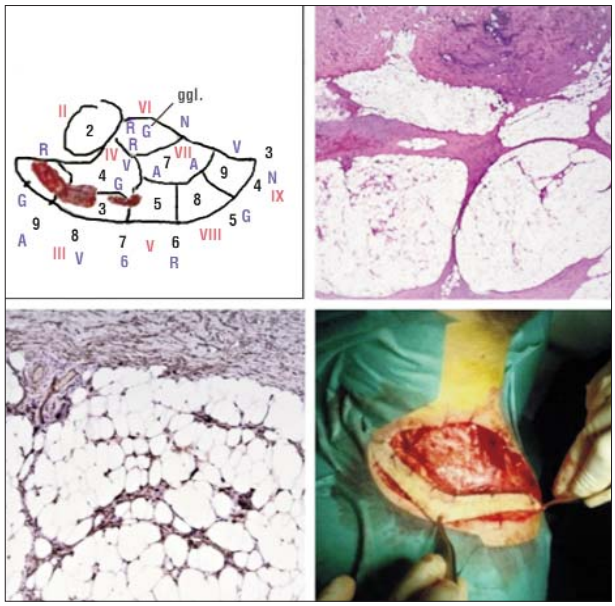

Figure 2C. The tumor was still identified on H&E staining and using IHC- CD34+ and another stage was needed.

recurrence was recorded (16).

The Mohs micrographic surgery also proved to be superior to classic surgical excision in the case of microcystic adnexal carcinoma, where the recurrence rates were 10% as opposed to over 50% in cases where the excision with oncologic safety margins of up to 5 cm (16), but also in cases of the atypical fibroxanthoma, when after the Mohs micrographic surgery, no relapses were recorded. In our clinic, a total of 16 cases of extramammary Paget's disease, atypical fibroxanthoma, trichoblastic carcinoma, microcystic adnexal carcinoma, eccrine porocarcinoma, and hidradenocarcinoma were treated by "Slow" Mohs and up until the publishing of the article no recurrences were recorded.

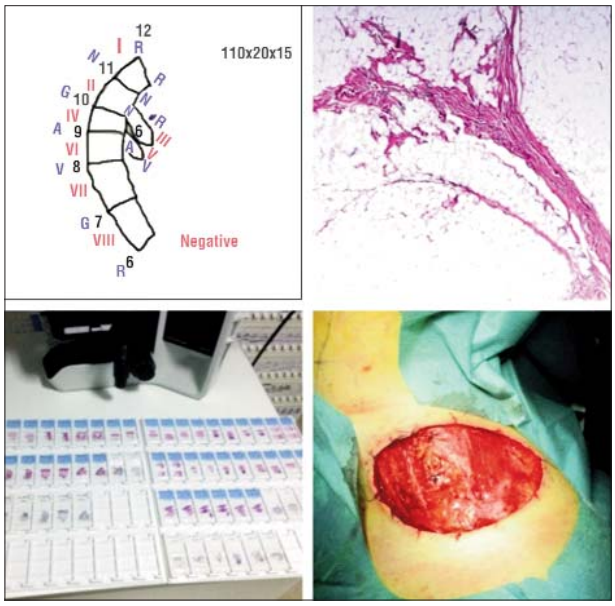

Figure 2D. The tumor was completely resected. This image is of the final defect.

Conclusions

In conclusion, Mohs micrographic surgery is the treatment of choice for non-melanoma skin cancer, providing 100% control of the tumoral margins and offering the highest cure rate. Other skin tumors with specific indications are the best candidates for this high rate healing method. The increasing incidence of this pathology as well as a more accurate understanding by physicians and patients regarding the efficiency of the treatment has led to a constant increase in the number of cases. Within the clinic, the multidisciplinary approach of patients and the collaboration

Figure 2E. Post-surgery and follow-up.

between the dermatologist, the anatomopathologist, and the plastic surgeon or oncologic surgeon have ensured high cure rates for cutaneous tumors with remarkable functional and aesthetic results. The accurate reporting, knowing the real number of affected patients, and the understanding of the results of cutaneous carcinoma treatment in the long term are important in public health policies.

Ethics Approval and Consent to Participate

Patients who participated in the study signed the consent form, giving their agreement free of any coercion or pressure.

Conflict of Interest

The authors declare no conflicts of interests.

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