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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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INNOVATIONS IN DERMATOLOGIC SURGERY AND MELANOMA PATHOGENESIS: FROM THE PERSONALISED SURGERY TO THE CONCEPT OF GENOMIC MAPPING/ TARGETING VIA NITROSAMINES IN DRUGS: SPOTLIGHT ON CONTAMINATION OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACES) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

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Abstract.

The pathogenesis and successful surgical treatment of cutaneous melanoma remain a mystery to this day, the unraveling of which has excited clinicians and research teams worldwide. The breakthrough regarding the interpretation of the pathogenesis of skin cancer and melanoma in particular in all likelihood concerns phototoxicity and photocarcinogenesis as some of the major factors associated with its occurrence. Extremely interesting and revealing are two types of observations/indisputable facts that definitely change completely the current vision of melanoma occurrence and progression: 1) The presence of carcinogens, photocarcinogens and mutagens in more than 95% of the most widely distributed drugs worldwide. On the one hand, they are inducers of heterogeneous types of mutations and, on the other hand, potentiate phototoxicity, and 2) clinicopathological correlations demonstrating a pathogenetic link between the intake of actual/potential photocarcinogen/mutagen contaminated products and the subsequent or concurrent development of melanomas.

The categorical refusal of regulators (so far) to oblige manufacturers to officially declare the presence of photocarcinogens/mutagens/genome modifiers in medicines , remains puzzling and disturbing to say the least. This is what makes it difficult to make an accurate judgement on the specific risk of a particular nitrosamine present as a contaminant in a particular drug in a particular geographical area. The regulation of the distribution and concealment of carcinogens in medicines correlates with the occurrence of heterogeneous forms of it in the geographical regions concerned. This is a strong reason to formalize carcinogens in medicines.

Conflicting evidence on the risk of developing melanomas in one latitude/continent or another is likely to correlate with the type of photo/nitroso/contaminant involved and the concentration in which it is present in a given drug.

The official data of the regulatory authorities in America and Australia, for example, do not correspond with each other and show the different availability in different preparations with different photocarcinogens/mutagens/genome modifiers or so-called nitrosamines. For other continents, there are no epidemiological data on the subject.

It remains an open and speculative question whether genetic targeting based on so-called genetic mapping is involved in these cases in order to maximize future benefits. The issue of genetic profiling of a nation, a geographical region or a particular collective is a matter of national but also global security for every country. In recent times, it is precisely this 'policy of nation preservation' that has led to a ban on the use of US genetic databases, with the 2024 ban targeting the world's strongest export economies: that of China.

We present a patient , who developed thick nodular melanoma within a long-term treatment with sartan/ valsartan and ACE inhibitor/ Enalapril. We comment on the possibility of a personalized one-stage surgical management of cutaneous melanomas as well as aspects of a new medical concept introduced in the literature; also known as drug-induced Photo Nitroso carcinogenesis/ oncopharmacogenesis of cancer.

Key words. Nitroso-Enalapril, Nitroso-Valsartan, Nitrosamines, Nitroso-contamination, melanoma surgery, innovations, Drug related Nitroso photo carcinogenesis, skin cancer, genetic mapping, genetic targeting, genetic weapons.

Introduction.

The surgical treatment of melanomas is a subject of endless debate or lively discussion, and unfortunately the guidelines on this occasion also turn out to be quite contradictory, sometimes even confusing. The first step of the so-called standard guideline is described as excisional biopsy (Tables 1 and 2) [1,2]. The so-called ″biopsy″, sometimes turns out to be a defect that must be covered with a flap or closed with an underming plastic surgery using up to 16 skin sutures [3,4].

Table 1. *Surgical margin recommendations for primary cutaneous melanoma modificated from AJCC, Swetter et al., 2019 [1].*

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

Table 2. *Modificated from EJC recommendations (C. Garbe et al., 2022) [2].*

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

The next recommended surgical step depends on the postoperatively determined tumor thickness (AJCC/EJC recommendations) and is associated with re-excision and the application of an additional surgical field, which varies (up to 1 or 2 cm total resection field within the two sessions), combined with or without the parallel conduction of a draining lymph node (Tables 1 and 2) [1,2].

The implied two-stage proposal for the treatment of cutaneous melanomas, however, also hides a number of drawbacks, such as 1) the frequent non-compliance with the primary resection field and the conduct of an uncontrolled and undefined one, 2) the lack of possibility to control the first (but also the second) surgical intervention due to the lack of obligation for video or photographic control, 3) the delay of the second surgical intervention beyond the implicitly and imprecisely defined deadlines in the guideline itself (2-4 weeks?), 4) the lack of a sufficient number of qualified centers to perform sentinel biopsies, 5) the gradual loss of therapeutic relevance of sentinel determination in patients with thin and thick melanomas, etc. (it has more of a diagnostic orientation) [5-7].

All of the aforementioned arguments open the door wide for dermatosurgeons regarding the possible introduction of a personalized and overall more adapted, flexible and dynamically oriented approach to patients and the health care system-namely that of a single-stage or one step surgical intervention in patients with cutaneous melanoma (Table 3) [8].

Table 3. *Personalized One step Melanoma surgery (OSMS) recommendations. Updated version 2025.*

Breslow thickness	**Recommended surgical margins**
Melanoma in situ	1.0 cm **/PREOPERATIVELY/**Mandatory: clinical/dermatoscopic evaluation obligate/ if possibility for echographical examination-from benefit/ when possible - confocal microscopy additionally)
<1mm	1.0 cm **/ PREOPERATIVELY/** Mandatory: clinical/dermatoscopic evaluation obligate/ if possibility for echographical examination-from benefit/ confocal microscopy additionally)
1.01- 2.0 mm / Class A	**2.0** cm **/PREOPERATIVELY/:** (with SLNB), (Mandatory: clinical/ dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/ when possible - confocal microscopy additionally, CT contrast, PET SCAN, echography lymph nodes)
2mm- 4 mm /Class B	2.0 cm **/PREOPERATIVELY/:** (with SLNB), (Mandatory: clinical/ dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/ when possible-confocal microscopy additionally, CT contrast/ PET SCAN, echography lymph nodes)
>4mm	2.0 cm complete surgical margin or less with / without SLNB to be discussed on tumour board. **/PREOPERATIVELY/:** Mandatory: clinical/ dermatoscopic evaluation, echographic tumour thickness measurement preoperatively/ when possible-confocal microscopy additionally, CT contrast, PET SCAN, echography lymph nodes)

Personalized or single-stage/ one step melanoma surgery is determined by the patient's current status, but measured preoperatively: clinical findings, dermatoscopy of the primary lesion, preoperative measurement of tumor thickness, CT contrast/ PET SCAN and echography for determination of the possible dissemination to locoregional lymph nodes/distant metastases , the tumor localization, and it is this complex assessment that remains the guide for whether a single- or two-stage surgical approach should be useful for the patient accordingly (Table 3) [8-13].

We describe the application of one step melanoma surgery in a patient with thick nodular melanoma and discuss certain clinical management options.

Case report.

A 74-year-old male presented with primary complaints of a slow-growing mole on his back, which had been stable for over 30 years but had shown significant changes and enlargement in recent months (as of august 2024).

His medical history includes arterial hypertension, hiatal hernia, hepatic steatosis, liver cyst, cholelithiasis, right-sided nephrolithiasis, parenchymal cysts in both kidneys, mesenteric lymphadenopathy, colonic diverticula, spondylosis, polyarthrosis, partial prostatectomy, and hip replacement.

The patient has been on systemic therapy with valsartan 160 mg twice daily and lercanidipine hydrochloride 10 mg once daily since 2019 and rosuvastatin 5 mg once daily for the past month. His previous long-term antihypertensive therapy included verapamil 120 mg once daily and enalapril maleate 10 mg from 2005 to 2019.

Dermatological examination revealed a solitary, nodular, pigmented tumor measuring 2.6x2.5 cm, with a rounded shape, well-defined borders, and a lobulated surface with increased pigmentation, located on the left back (Figure 1a,b). Enlarged lymph nodes were not palpable.

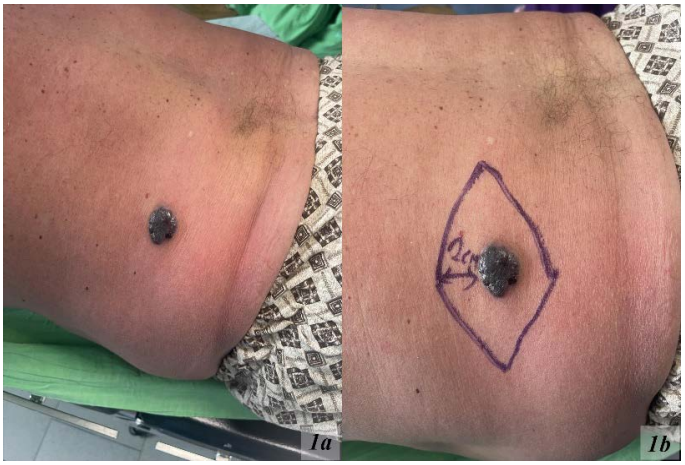

Figure 1a,b. *A solitary, nodular, pigmented tumor measuring 2.6x2.5 cm, with a rounded shape, well-defined borders, and a lobulated surface with increased pigmentation, located on the left back.*

Contrast CT scan of the head, neck, thorax, abdomen, and pelvis revealed hiatal hernia, hepatic steatosis, liver cyst, cholelithiasis, right-sided nephrolithiasis, parenchymal cysts in both kidneys, mesenteric lymphadenopathy, and colonic diverticula.

In the back area, a tumor formation suspicious for melanoma (differential diagnosis pigmented basal cell carcinoma) was excised under local anesthesia with 2% lidocaine. An elliptical excision was performed with a 2 cm surgical margin in all directions (Figure 2a-c), following the patient's informed consent and his refusal of sentinel lymph node excision despite being informed of the associated risks. The wound edges were adapted using single interrupted sutures (Figure 2d).

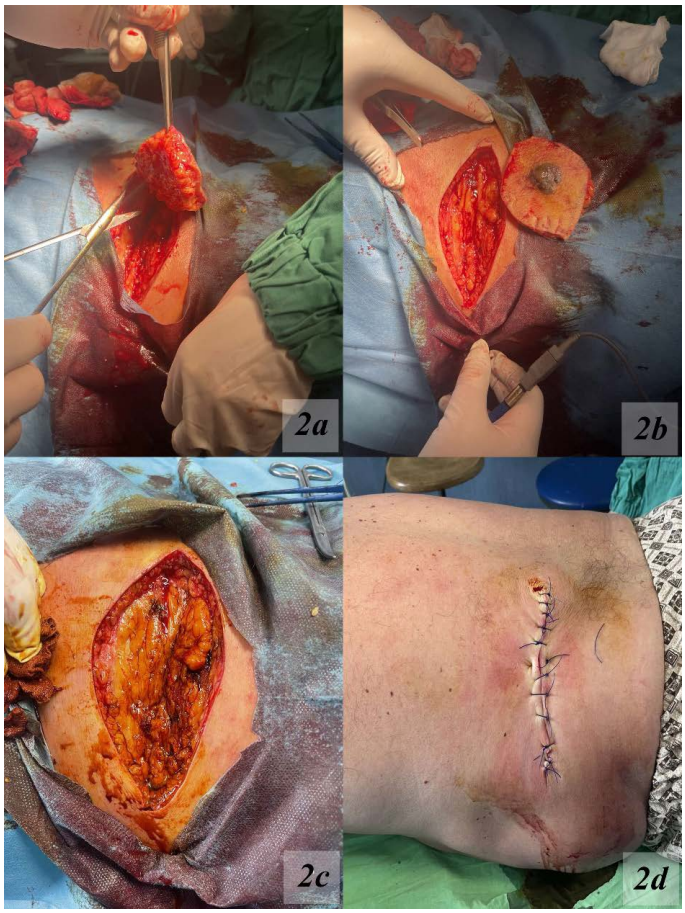

Figure 2a-d. *Intraoperative view: a tumor formation excised with an elliptical excision (a-c) with a 2 cm surgical margin in all directions. The wound edges are adapted using single interrupted sutures (d).*

The histological examination revealed a compact nodular melanocytic proliferation with orthohyperkeratosis, epidermal atrophy with focal upward spreading, and consumption of the overlying epidermis by large, atypical melanocytes exhibiting pronounced pleomorphism and large, bright cytoplasms. These cells formed artificial acantholysis and variegated nests, interspersed with necrotic zones, and infiltrated into the dermis, extending to the superficial hypodermis. Lympho-vascular and perineural invasion was present, and a high mitotic index with atypical mitoses was noted. Ulceration was absent. The tumor was classified as Clark level IV with a Breslow thickness of 14mm, consistent with stage II B (T4aN0(X)M0) nodular melanoma (Figure 3a-c).

Daily dressing changes were recommended, along with an S100 immunohistochemical study. Due to inconclusive findings on the CT scan regarding enlarged mesenteric lymph nodes, PET scanner was recommended to determine infiltrate density and exclude tumor infiltrates from cutaneous located nodular melanoma. BRAF testing of the primary melanoma tissue was recommended for outpatient management to plan target treatment for possible progression.

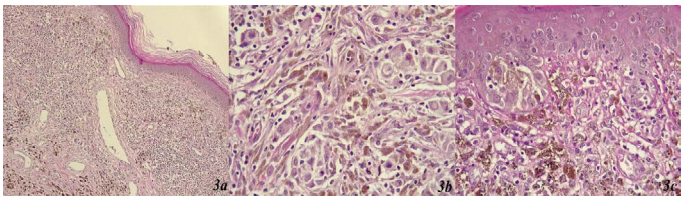

Figure 3a-c. *Histology panel: A compact nodular melanocytic proliferation with orthohyperkeratosis, epidermal atrophy with focal upward spreading, and consumption of the overlying epidermis by large, atypical melanocytes exhibiting pronounced pleomorphism and large, bright cytoplasms. These cells form artificial acantholysis and variegated nests, interspersed with necrotic zones, and infiltrated into the dermis, extending to the superficial hypodermis. Lympho-vascular and perineural invasion is present, and a high mitotic index with atypical mitoses is noted. Ulceration is absent.*
3a: *Nodular melanoma x HE x 100*
3b: *Nodular melanoma x HE x 200*
3c: *Epidermal component of NM x HE x 200.*

Results and Discussion.

Surgical treatment of thick melanomas or those with tumor thickness greater than 4 mm is associated with a surgical margin of safety of no more than 2 cm according to both standard and innovative guidelines for personalized melanoma treatment [1,2,4] (Tables 1-3). In both cases, a total resection margin is referred to here: for standard guideline- within two sessions (Tables 1 and 2) [1,2] and for innovative guideline- within one session (Table 3) [6-8].

Baseline criteria for this excision field could be selected both after the first excision/standard guidelines [1,2], i.e., based on the postoperative Breslow tumor thickness, but also preoperatively (Table 3), based on the complex evaluation of a combination of parameters that are determined entirely preoperatively/ personalized guideline for melanoma surgery: from clinical findings, dermoscopy, tumor thickness determination / ultrasonography / and conducting CT with contrast / Pet scanner to exclude metastases for example (Table 3).

There are several arguments in favour of the one-stage/one-step model of surgery for thick melanomas, and they mainly depend on the absence or presence of locoregional or distant dissemination. The last could be clarified by CT with whole-body contrast and/or PET scanner. This model could be applied in more than 90% of melanoma patients.

The clinical and dermatoscopic findings of nodular melanomas are more than suggestive of the dignity of the disease, and they can be supported by cytological analysis, confocal microscopy and/or preoperative determination of tumor thickness with ultrasonography (Table 3).

Finding or confirming a tumor thickness of more than 4 mm (similar to the case we presented) leaves hanging the question/ dilemma of whether it is appropriate to localize and remove the sentinel lymph node afterwards or rather the clinician's position

should be one of waiting/ wait and see strategy. With evidence of metastasis/dissemination of any kind (local/locoregional or distant), the identification of the sentinel lymph node loses its prognostic/specifying significance, as its sentinel role is in all likelihood now rather compromised, or the tumour has metastasised along pathways that seems to be parallel to those that drain the sentinel lymph node(s).

In the absence of evidence of dissemination (preoperatively), the patient should be informed of the need or possibility of 2 or one surgical interventions, combined or not with the sentinel lymph node removal. In cutaneous melanomas with a tumor thickness of more than 10 mm or 14 mm, for example (such as the one we described), and intact lymph nodes (clinically and instrumentally) for example, it could be considered that the determination of a draining lymph node is at least controversial or cannot be considered as highly advisable. Either this issue remains a matter for the collective decision of the oncology committee, the dermatosurgeon and the patient's own wishes. The wait-and-see position remains a reasonable decision.

The reason for this hesitation is precisely the fact that micrometastases are in all likelihood/ probably present and a second surgical procedure could be seen as a rather aggravating action for the patient's general condition. But an action in line with the guidelines, which are recommended but not mandatory.

In practice, the patient's choice in this situation is ″cautiously directed″ towards a potential refusal of the localization and removal of the sentinel lymph node, but with respect to the total resection margin of 2 cm, and ″this compliance″ could be carried out within 1 surgical session.

The reason for these somewhat ″guiding decisions″ is driven by 1) clinical experience and 2) common sense, the main goal being 1) to spare the psycho-emotional state of the patient (by reducing the stress originating within two operations), but also 2) to drastically reduce the costs of health insurance systems worldwide.

In practice, for a large proportion of patients with thick melanomas, sentinel lymph node detection and removal could generally go by the wayside due to 3 facts/arguments:

1) Available and clinically and/or instrumentally proven dissemination.

2) Suspicion of micrometastases that could not be detected at the time of diagnosis (even with a PET scan).

3) As well as an explanatory discussion with patients about the importance of the sentinel for melanomas over 4 mm thick and the possibility of merging the two sessions into one (whether or not the sentinel would remain as an option). In practice, the sentinel is gradually losing its informative/ prognostic significance in a certain category of patients.

In the patient we have described, there are in practice two options of clinical approach depending on the interpretation of the mesenteric lymph node finding in CT:

In the case of a confirmatory (after performing a PET scan) finding regarding suspected metastasis- initiation of e.g. target/ and or immunotherapy (after braf testing of the primary tumor tissue).

In case of negative finding regarding metastasis: clinical observation regarding possible progression. In this aspect, the article is confirmatory regarding the different possibilities that single stage/ one step melanoma surgery offers to clinicians. These possibilities are greatly simplified and logically conditioned, requiring an intensive conversation with the patient. Because of this fact, they should not be overlooked as an option.

Another, not unimportant information that could be analyzed on the basis of the case we have presented, although to some extent it could be considered (according to a number of authors) also as controversial / or hypothetical, is that of the intake of 3 drugs that could also be considered as closely related to drug-triggered nitrosogenesis / carcinogenesis, photo-nitroso carcinogenesis, namely: ACE inhibitors (enalapril in our described patient, but not only) [14-16], sartans-(valsartan, but not only)[10,17-25], and calcium antagonists (lercanidipine) [26,27].

Particularly revealing in these cases remains the fact that the intake of these drugs is associated (also according to international data) with the development of both melanocytic and keratinocytic skin tumours [28,29].

This nonspecificity of affected patients with respect to skin cancer (after intake of potentially contaminated drugs) also affects areas primarily exposed to solar radiation, being associated with the concept of phototoxicity [28-30]. That is, there should be factors present that can be defined as photocarcinogens, and these are precisely the so-called nitrosamines.

Interestingly, each of these drugs is already represented in the FDA list of nitrosamine-contaminated preparations [31]. That is, even in patients who have developed melanomas, one could speak of nitroso-phototoxicity or nitroso-mediated photocarcinogenesis in the context of medication/drug intake [17-18,26].

The problematic arises precisely from the fact that nitrosamines are on the one hand genotoxic substances, mutagens/carcinogens, and on the other: so also photocarcinogens.

The synergistic action of these two properties could provide a solid explanation for the dilemmas of 1) what causes skin cancer and 2) how this risk could be linked in medication intake.

Phototoxicity has been known for decades as a nonspecific property of nitrosamines [32]. Even more disconcerting are the confirmatory data on gene and phototoxicity of nitrosomorpholine [33], recently discovered as a contaminant in some drugs [34].

Little or no is known about the phototoxicity of other nitrosamines in drugs. This phototoxicity has an additional genotoxicity-enhancing effect on nitrosamines and is not accounted for by the tests proposed by regulators to determine carcinogenicity in bacteria (Ames test) and rodents (CPCA test). It is also because of this fact that multiple skin tumours are found even after ingestion of carcinogens with the drugs, which probably do not exceed the so-called acceptable daily intake doses. Tests for carcinogenic activity in bacteria and rodents cannot be regarded as reciprocal or equivalent with respect to human DNA.

The presented scientific work opens 1) new horizons/visions regarding the understanding of melanoma pathogenesis, but also 2) hints seriously what new/innovative could be considered in relation to its surgical treatment- in order to alleviate patients' suffering.

Seriously focusing on and analysing these two steps could 1) lead to a drastic drop in the incidence of melanoma worldwide, but also, possibly 2) lead to a significant improvement in terms of its surgical treatment.

Last but not least, it should be mentioned that one of the most serious genetic bioweapons/targets worldwide appears to be the nitrosamines in drugs known as genome modifiers [35]. They could also prove to be the most effective and elegant genetic targeting weapon created precisely on the basis of genetic mapping.

It is not in vain and not without reason that in 2024 the US Congress and the Pentagon made the difficult decision to stop the most powerful Chinese companies (which collect data on the genetic profile of Americans) from accessing the genetic database, as this could lead to a threat to national security [36,37]. Could it be that the US security forces see in these cases precisely the threat of subsequent large exports of drugs and food to America that contain the genome modifiers also known as nitrosamines?

The collection and evaluation of genetic material are seen as campaigns of paramount importance for global economic growth, even if this growth is based on questionable foundations [38].

Even the journal Nature is only now, in 2024, leaning on the dangerous idea of genetic scanning/targeting as a very serious danger globally [39].

A huge puzzlement for clinicians and academics is the lack of willingness, or lack of ability, on the part of regulators worldwide, to introduce full elimination regimes on proven mutagens, carcinogens and phototoxic substances (also known as nitrosamines) in drug preparations.

This also suggests that 'the genie has long been out of the bottle', and that the warnings of Jan van Aken and Edward Hammond from as far back as 2003 remain once again overlooked [40]. And by now hard to control.

The latest generation of genome modifiers are the so-called nitrosamines. They are the substances that are about to rewrite the medical textbooks. This kind of modifier was already mentioned in 2004 [41]. Unfortunately, the focus on them remains, for the moment, shifted.

But the data on the subject are objective and revealing, as long as attention is paid to them. The lack of adequate control over the spread of carcinogens in drugs has led to a dramatic rise in the incidence of not only skin cancer (non-melanocytic) but also cancer in general [42], despite endless advertisements about medical advances and the curability of heterogeneous diseases worldwide. Again, according to international data, there is a similar trend regarding the startling estimated incidence of melanoma worldwide [43].

Even more interesting, and at the same time startling, is that the patients who have been recorded with increasing polymedication intake or polypharmacy over the past 20 years are predominantly diabetic patients and those taking cardiac medication [44]. These are also the patients most severely affected by contamination, for whom our collective has been presenting innovative data regarding drug-mediated photo nitroso carcinogenesis for the past 7 years [45,15]. Polypharmacy, polycontamination with genomic modifiers, and cancer remain inextricably linked. This is more than evident from a review of the above-mentioned comparative database analyses.

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