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Effectiveness of Combined (585 and 1064 nm) Laser Radiation for Treatment of Basal Cell Skin Cancer

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Background: Basal cell skin cancer is the most common skin malignancy, and its incidence has been rapidly increasing throughout the world in recent decades.
Objectives: To investigate the effectiveness of combined sequential laser radiation (585 and 1064 nm) treatment of superficial and nodular forms of basal cell skin cancer using dermoscopic and confocal microscopic *in vivo* examination.
Materials and methods: The study included 30 patients with histologically confirmed basal cell skin cancer treated using a 585-nm pulsed dye laser and a 1064-nm long-pulse neodymium laser at Consultation and Diagnostic Center of State Research Center of Dermatovenereology and Cosmetology from 2020 to 2021.
Results: Among the patients with nodular carcinoma (*n*=15), 11 underwent 1 procedure, 3 patients 2 procedures and 1 patient 3 procedures. Among the patients with superficial carcinoma (*n*=15), 2 patients underwent 2 procedures, and 13 patients 1 procedure. All included patients have now completed the treatment and are followed up every 6 months during 3 years. According to their dermoscopic and confocal microscopic results, there have been no evidence of continued growth or relapse in all patients. No side effects or adverse events have been recorded so far.
Conclusions: The combined sequential laser radiation may be an effective treatment for basal cell skin cancer with low-risk of recurrence. The results of our study indicate that the tumor can be effectively removed without scarring and may be an alternative treatment option for those patient who want to avoid traditional surgical procedures.

Keywords: **basal cell skin cancer; pulsed dye laser; neodymium laser**

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Эффективность использования комбинации лазерного излучения с длиной волны 585 и 1064 нм в лечении пациентов с базальноклеточным раком кожи

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Обоснование. Базальноклеточный рак кожи является наиболее распространенным злокачественным новообразованием кожи, и в последние десятилетия заболеваемость быстро растет во всем мире.
Цель исследования. Изучить эффективность использования лазерного излучения с длиной волны 585 нм и 1064 нм в последовательном (секвентальном) комбинированном режиме для лечения пациентов с поверхностной и нодулярной формами базальноклеточного рака кожи с помощью дерматоскопического и конфокально-микроскопического прижизненного исследования.
Методы. В исследование включено 30 пациентов с гистологически подтвержденным базальноклеточным раком кожи, получавших лечение в условиях консультативно-диагностического центра ФГБУ «ГНЦДК» Минздрава России в период с 2020 по 2021 г., с применением импульсного лазера на красителе (длина волны — 585 нм) и длинноимпульсного неодимового лазера (длина волны — 1064 нм).
Результаты. В подгруппе пациентов с нодулярной формой базальноклеточного рака кожи (n = 15): у 11 пациентов длительность курса лечения составила — 1 процедуру, у 3 пациентов — 2 процедуры, у 1 пациента — 3 процедуры. В подгруппе пациентов с поверхностной формой базальноклеточного рака кожи (n = 15): у 2 пациентов курс лечения составил — 2 процедуры, у 13 пациентов — 1 процедуру. В настоящее время пациенты завершили лечение и находятся под наблюдением с визитами каждые 6 месяцев в течение 5 лет. По данным дерматоскопического и конфокально-микроскопического исследований данные за продолженный рост и рецидив у всех пациентов отсутствуют. Побочных эффектов и нежелательных явлений не зафиксировано.
Заключение. Использование комбинированного секвентального лазерного излучения с длиной волны 585 нм и 1064 нм является эффективным методом лечения пациентов с клиническими формами базальноклеточного рака кожи, имеющими низкий риск рецидива. Результаты исследования показывают, что клиническое удаление опухоли без рубцевания может быть достигнуто альтернативным вариантом лечения в случаях, когда традиционные хирургические подходы нежелательны или недоступны.

Ключевые слова: **базальноклеточный рак кожи; пульсирующий лазер на красителе; неодимовый лазер**
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Background

Basal cell skin cancer (BCSC) is the most common skin malignancy in the United States, Australia, and Central Europe. Its annual incidence worldwide has been increasing consistently by 3–10% [1], which poses a major challenge for public healthcare systems.

In 2022, the percentage of nonmelanoma skin tumors (including BCSC) in the structure of oncological diseases in Russian Federation was 10.8% at 298.9 cases per 100 thousand inhabitants [2].

Compared to two other common clinical and histological types (nodular and sclerodermiform BCSC), superficial BCSC may occur at earlier ages, and it currently accounts for 31% of BCSC cases, with the percentage almost doubled in recent 20 years [3].

Surgical excision of the tumor followed by a pathology study and an excision radicality control is still considered the standard of care for BCSC.

However faster, safer, and more effective therapeutic options ensuring acceptable aesthetic outcomes are increasingly sought for, especially with the younger population being affected.

The list of nonsurgical options includes locally destructive techniques not requiring histological control (e.g., cryotherapy, laser vaporization, and photodynamic therapy), as well as local pharmacological treatment with imiquimod or 5-fluorouracil [4]. The disadvantages of both approaches are well known: destructive methods are often characterized with complicated wound healing and questionable aesthetic outcomes compared to surgical excision (especially in cases of multiple lesions), while local pharmacological treatment relies heavily on the patient's ability to follow the prescribed regimen.

Vascular-specific selective laser destruction that employs radiation wavelengths of 578, 585-595, 1064 nm, and their combinations appears to be a viable alternative for the techniques above. The use of this approach in BCSC cases may be justified by the presence of the supporting vascular network macroscopically visible at the tumor surface. In addition to macroscopic vessels, tumor-feeding vessels are an integral part of the microvascular architecture of a tumor [5]. Microscopic studies *in vivo* confirmed that blood vessels in BCSC foci were significantly larger, than in those healthy skin [6].

The potential advantage of vascular-specific photothermal treatment compared to conventional destruction or excision techniques is preservation of the healthy tissue surrounding the tumor.

The technique is based around the concept of selective photothermolysis [7]. Selective heat damage inside the target lesion can be achieved, if we can ensure wavelength-selective absorption, sufficient power, and pulse duration shorter than the target's cooling time.

Vascular-specific selective lasers may selectively affect oxyhemoglobin and deoxyhemoglobin at various penetration depths depending on laser wavelength.

Pulsed dye laser (PDL) generating laser radiation with wavelengths of 585–595 nm, which is well absorbed by oxyhemoglobin in blood vessels with partial transformation into methemoglobin, is limited in its penetration depth to papillary dermis and used to treat port-wine stains, hemangiomas, and facial telangiectasia.

Long-pulse neodymium laser (Nd:YAG laser) generating laser radiation of 1064 nm well absorbed by deoxyhemoglobin and methemoglobin in blood vessels has a penetration depth of up to 8 mm below the skin surface and is used for coagulation treatment of venules, phlebectasia, and venous malformations.

There is a number of papers studying the use of 585/595-nm laser radiation for treatment of various BCSC types that show the complete regression of 71-92% BCSC focal lesions after 4 laser therapy sessions at 2-week intervals. Treatment effectiveness depends on histological subtype of a tumor, and the best results are observed in superficial BCSC and for a treatment mode with stacked pulse setting [8–10].

Confocal microscopic *in vivo* study in our previous paper [11] showed the persistent vascular circulation in reticular dermis both in unchanged skin and around nodular BCSC lesions following 585-nm laser treatment, which is why this technique was only used in superficial BCSC cases.

A study of 1064-nm Nd:YAG continuous wave laser therapy in 36 BCSC cases showed the cure rate of 97.3% after 2–4 sessions with a single relapse observed in 5 years post-treatment [12]. Moskalik et al. (2010) analyzed the outcomes of neodymium laser treatment in 2915 facial BCSC lesions and reported the relapse rate of 3.1% for primary basaliomas and 4.1% for recurrent basaliomas in over five years of follow-up [13], while the respective relapse rates in Markowitz et al. (2021) were 2% and 11.8% in 12 months of follow-up [14].

With these results, an assumption can be made that combined treatment with sequential PDL (585 nm) and Nd:YAG (1064 nm) laser pulses makes it possible to increase the effectiveness of tumor removal, while maintaining selectivity and minimizing the side-effects. In addition to higher penetration depth ensured by this approach, the transformation of oxyhemoglobin into methemoglobin after PDL pulses creates the second target chromophore for Nd:YAG laser. 1064-nm laser radiation is well absorbed by methemoglobin and penetrates deeper-seated vessels. This technique makes it possible attack the anomalous vascular network of BCSC lesions at two levels.

In this respect, **the objective of the present study** was to investigate the therapeutic effectiveness of combined sequential laser radiation (585 and 1064 nm) in patients with superficial and nodular types of BCSC, using dermoscopy and confocal microscopy *in vivo*.

To investigate the therapeutic effectiveness of the laser treatment in focal BCSC lesions, 30 patients with 15 superficial and 15 nodular basaliomas were treated, and pathophysiological changes observed during treatment and post-treatment were assessed, using real-time dermoscopy and confocal laser scanning microscopy (CLSM).

Methods

The study included 30 patients with 30 histologically confirmed focal BCSC lesions, who received combined pulsed dye laser and long-pulse neodymium laser treatment at the facilities of Consultati and Diagnostic Center of the State Research Center of Dermatovenerology and Cosmetology from 2021 to 2022.

Dermoscopic examination, CLSM examination *in vivo,* and skin biopsy with subsequent pathological analysis were performed in patients with suspected BCSC. Skin biopsy samples were taken from the most pronounced focal lesions, including from the edges and the center of neoplasms.

With the diagnosis confirmed, the patients were informed about the proposed therapy, and their informed consent was requested.

Inclusion criteria:

- Age of 18 or above;
- Availability of an informed consent form documenting that the patient was properly informed about all significant aspects of the study signed by the patient in person and citing the signature date;
- The patient's willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other procedures relevant to the research;
- Confirmed diagnosis of superficial or nodular BCSC with lesions not exceeding 20 mm in diameter for torso and extremities (excluding hands, feet, and periungual areas) and 10 mm for neck, scalp, forehead, and cheek.

Noninvasive verification of neoplasms using confocal microscopy was performed before skin biopsy, right after laser treatment sessions, 4 weeks after treatment completion under condition of complete re-epithelialization of the laser treatment site, 6 months post-treatment, and later, if prescribed due to clinical and dermoscopic signs of relapse during the 3-year follow-up.

Exclusion criteria: focal lesions exceeding 2 cm in diameter, infiltrative growth pattern of the tumor, and recurrent lesions.

Treatment technique in patients with basal cell skin cancer

The patients were divided into two groups based on the histological BCSC subtype (superficial or nodular).

The intended treatment for the patients included in the study was sequential high-intensity selective laser (585 and 1064 nm) coagulation.

Sequential selective laser coagulation technique is based on simultaneous sequential use of radiation with short interpulse delay. The effect of 585-nm laser radiation on oxyhemoglobin is 60% coagulation and 40% methemoglobin transformation. Methemoglobin is 3–5 times as effective in absorbing the energy of 1064-nm laser radiation, which allows reducing pulse energy density to make the procedure safer for the patient. Higher absorption and penetration depth improve the therapeutic effect.

The regimen included one to three sessions at 3-week intervals depending on the therapeutic effectiveness. The parameters were as follows: pulse energy density at 585 nm was 8 J/cm^2; pulse duration 3 ms; pulse energy density at 1064 nm was 60 J/cm^2; pulse duration 10 ms; interpulse delay 250 ms; laser beam diameter 7 mm; pulse overlap rate 10%; dynamic cooling level 4; number of passes 2.

Effectiveness criteria for the parameters selected were as follows: visible purpura, darkening or grey pigmentation at the laser treatment site including at least 5 mm of healthy tissue around the tumor.

Laser treatment sessions were followed by repeated CLSM examinations *in vivo* of the focal lesions to check circulation persistence in tumor vessels. Additional session was performed if such blood circulation was observed.

Characteristics of patients included in the study

The studied sample included 30 patients with histologically confirmed BCSC, who received laser treatment at the Consultative and Diagnostic Center from 2020 to 2022.

The study was approved by the Local Ethics Committee, certificate of approval no. 1 dated January 31, 2022.

The patients were under supervision for 12 to 24 months (mean 20.2 months on average). Age and sex stratification was as follows: 9 males (30%) aged 53 to 88 (mean 66) and 21 females (70%) aged 38 to 76 (mean 63.8). The largest subgroups in the superficial BCSC group were the patients aged 60–70 and over 71 (7 (46%) patients to comprise 92% of the studied cohort). The largest subgroup in the nodular BCSC group included the patients aged 50–60 (7 (46%) patients). Skin phototype stratification was as follows: phototype I was 10 (30%); phototype II was 14 (46%); phototype III was 6 (24%).

Based on clinical, dermoscopic, and pathomorphological descriptions of focal lesions, the following distribution by clinical BCSC types was obtained: 15 (50%) superficial lesions (the most common type) and 15 (50%) nodular lesions. Lesions varied from 5 to 20 mm in diameter (the average of 8 mm), with the ones under 10 mm observed in 12 (40%) cases being the most common and the ones over 15 mm or under 5 mm observed in 4 (15%) cases each were the rarest.

The most common locations of focal lesions were back and chest in 12 (40%) and 7 (23%) cases respectively, the other areas affected were facial skin in 1 (3%) case, abdominal area in 3 (10%) cases, upper limb in 3 (10%) cases, and lower limb in 4 (14%) cases (Table 1).

Results

The total of 30 BCSC patients were included in the study. Age and sex stratification was as follows: 9 males (30%) aged 53 to 88 (mean 66) and 21 females (70%) aged 38 to 76 (mean 63.8).

Skin phototype stratification was as follows: phototype I was 10 (30%); phototype II was 14 (46%); phototype III was 6(24%).

The stratification in the nodular BCSC group (n = 15) was as follows: 6 males (40%) with the average age of 65 and 9 females (60%) with the average age of 56. The regimen included one session in 11 patients, two in 3 patients, and three in 1 patient. All patients have completed their treatment and attend routine visits every 6 months during the 5-year follow-up. According to dermoscopy and confocal microscopy findings, no evidence of continued growth or relapse was found in the patients. No side-effects and adverse events were observed as well (Fig.1).

The stratification in the superficial BCSC group (n = 15) was as follows: 12 females (80%) their mean age 69.6 and 3 males (20%) their mean 67. The regimen included two sessions in 2 patients and one session in 13 patients. According to dermoscopy and confocal microscopy findings, no evidence of continued growth or relapse was found in the patients. No side-effects and adverse events were observed as well (Fig. 2).

Laser treatment turned out to have only temporary side-effects. The immediate effect in the form of purpura was indicative of effectively selected laser radiation parameters and was observed in all sessions. Gradual reduction of the emerging erythema and purpura was observed, when the regimen included more than one session. The patients, who received the regimens of more than one session, developed temporary hyperpigmentation.

Discussion

The use of 585 and 1064-nm laser radiation shows promise as a BCSC therapy due to its ability to affect tumor

Table 1. Characteristics of lesions of examined patients (n = 30, abs.)
Таблица 1. Характеристика патологических очагов обследованных пациентов (n = 30, абс.)

Parameter		Value	
		abs	%
Location	Face	1	3
	Chest	7	23
	Abdomen	3	10
	Back	12	40
	Upper limb	3	10
	Lower limb	4	14
Size, mm	Under 5	4	15
	Under 10	12	40
	Under 15	10	30
	>15	4	15
Histological type	Nodular	15	50
	Superficial	15	50

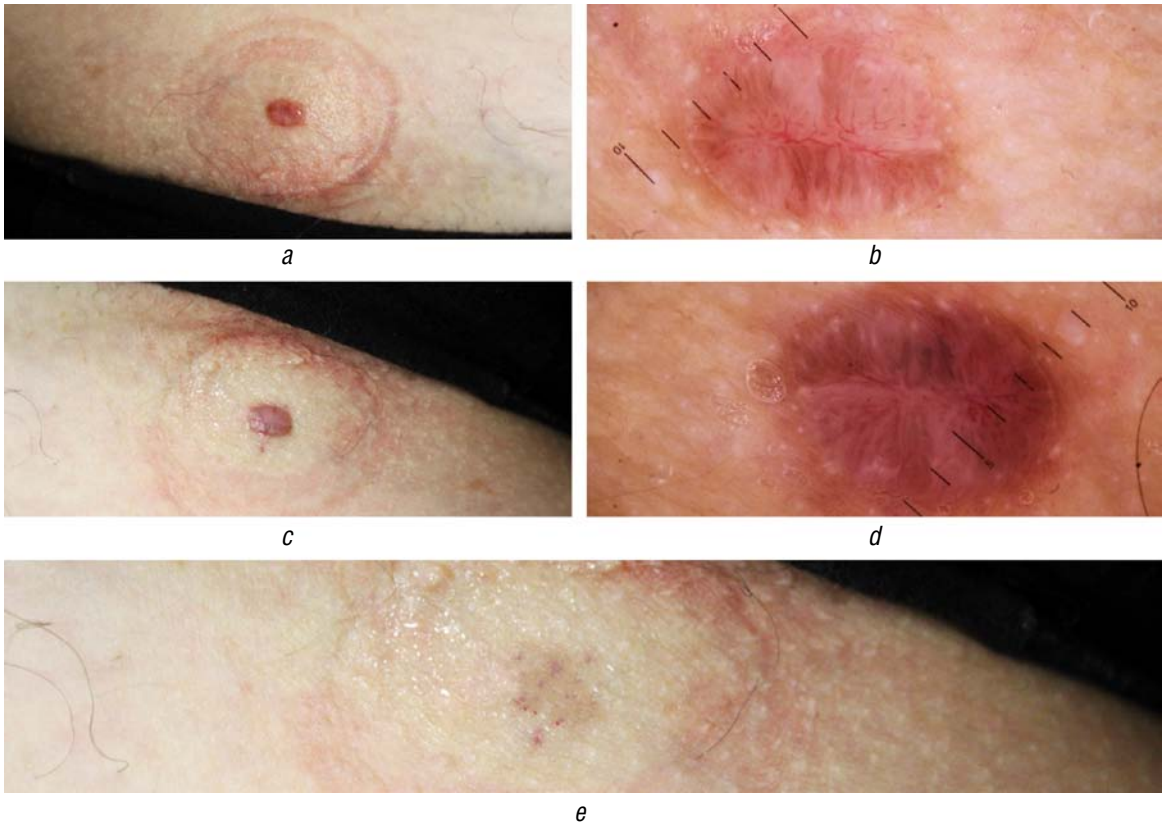

Fig. 1. Clinical and dermoscopic dynamics during the treatment of the nodular basal cell carcinoma: *a*, *b* – before treatment; *c*, *d* – immediately after the procedure; *e* – 1 month after treatment
Рис. 1. Динамика клинической и дерматоскопической картины при лечении нодулярной формы базальноклеточной карциномы в процессе лечения: *a*, *b* — до лечения; *c*, *d* — сразу после процедуры; *e* — через 1 месяц после лечения

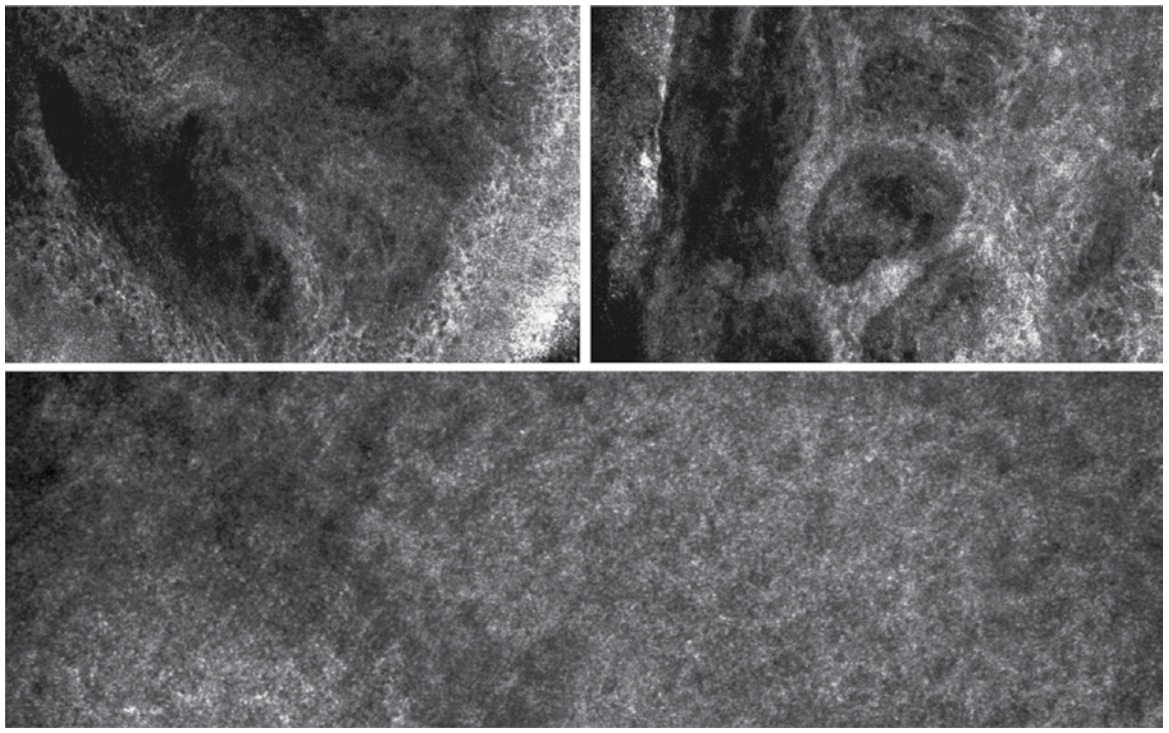

Fig. 2. Confocal microscopy of the lesion before treatment (top row), 1 month after treatment (bottom photo)
Рис. 2. Конфокальная микроскопия очага поражения до лечения (верхний ряд), через 1 месяц после лечения (нижнее фото)

arteries. To date, most papers on therapeutic options for BCSC based on selective laser coagulation have focused on 585-nm PDL.

According to various authors, PDL therapy resulted in complete regression of 71 to 92% BCSC focal lesions after four sessions at 2-week intervals. Treatment effectiveness depended on histological subtype of the tumor, with higher effectiveness observed in superficial BCSC cases and in those treated with stacked pulse setting [8–11]. 585-nm laser radiation is well absorbed by hemoglobin and oxyhemoglobin, but the penetration depth is limited to reticular dermis, which makes it possible to effectively use this approach to attack superficial BCSC focal lesions.

1064-nm laser radiation is characterized by higher penetration depth (up to 8 mm), which makes it possible to use it in nodular BCSC focal lesions. The relapse rate in post-treatment BCSC patients during the 5-year follow-up was 3.1% for primary basaliomas and 4.1% for recurrent basaliomas [13], and the respective values in Markowitz (2021) were 2% and 11.8% during the 12-month follow-up [14].

The use of combined sequential (585 and 1064 nm) laser radiation as a BCSC therapy was described by Jalian et al. (2013). The total of 10 patients with 13 BCSC focal lesions received up to 4 laser treatment sessions at 2–4-week intervals. Almost half of all focal lesions showed full response to 4 sessions (n = 7/12; 58%). Given the size, 75% of all tumors under 1 cm in diameter (n = 6/8) were fully responsive [15].

The present study showed the effectiveness of 100% primarily due to post-treatment confocal microscopy examinations *in vivo* making it possible to monitor the effectiveness of tumor vessel destruction and perform additional laser therapy sessions, if persistent capillary circulation is observed in the focal lesion. The present paper only cites the preliminary results of the study, because only 24 months of the follow-up period have passed.

Conclusions

The combined sequential laser radiation is an effective treatment option for patients with clinical types of basal cell skin cancer characterized by low risk of recurrence. The results obtained show that the described alternative option can be used for clinical tumor removal without scarring, when the use of conventional surgical techniques is complicated.

Research limitations

Since the effectiveness of laser therapy was only studied in superficial and nodular BCSC subtypes, the effectiveness of the technique cannot be extrapolated to the aggressive (infiltrative and morpheaform) subtypes based on the results obtained.

In addition, BCSC focal lesions were restricted to small tumors only, which limits our potential for generalization, while the effectiveness of laser treatment in a wider diversity of tumors appears to be of great interest.

Finally, the follow-up period of at least 5 years is defined by the design of the study, and final conclusions on recurrence probability can only be made when it passes.

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