



# Marjolin ulcer: the importance of early diagnosis and excision

## *Úlcera de Marjolin: a importância do diagnóstico e excisão precoces*

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### ■ ABSTRACT

**Introduction:** Marjolin's ulcer is a rare disease characterized by the malignancy of chronic wounds that present healing disorders, often due to chronic irritation and repetitive trauma in this area. The diagnosis is made mainly through clinical history and histopathological examination. The differential diagnoses of other diseases that course with ulcers must always be researched and ruled out. **Method:** The present work presents a bibliographic review to elucidate the subject's relevance for medical students, physicians and nurses, to assist in early diagnosis. **Results:** Nine observational studies were selected to compose the discussion. **Conclusion:** The most effective treatment for this condition is surgery, and lymph node dissection is suggested in some cases. Chemotherapy has not shown satisfactory results, while radiotherapy is used in selected cases. Given the rapid evolution, tissue damage, and worse prognosis, diagnosis, and excision should be performed early for a better clinical outcome.

**Keywords:** Carcinoma, squamous cell; Skin ulcer; Reconstructive surgical procedures; Early diagnosis; Wounds and injuries; Burns.

### ■ RESUMO

**Introdução:** A úlcera de Marjolin é uma doença rara, caracterizada pela malignização de feridas crônicas que apresentaram distúrbios cicatriciais, muitas vezes devido à irritação crônica e a traumas repetitivos nesta área. O diagnóstico é realizado sobretudo através da história clínica e de exame histopatológico. Os diagnósticos diferenciais de outras doenças que cursam com úlceras devem sempre ser pesquisados e afastados. **Método:** O presente trabalho apresenta uma revisão bibliográfica, a fim de elucidar a relevância do tema para acadêmicos de medicina, médicos e enfermeiros, com o propósito de auxiliar no diagnóstico precoce. **Resultados:** Foram selecionados 9 estudos observacionais para compor a discussão. **Conclusão:** O tratamento mais eficaz desta condição é o cirúrgico, e o esvaziamento linfonodal é sugerido em alguns casos. A quimioterapia não demonstrou resultados satisfatórios, enquanto a radioterapia é utilizada em casos selecionados. O diagnóstico e a excisão devem ser feitos precocemente para melhor desfecho clínico, visto a rapidez da evolução, o prejuízo tecidual e pior prognóstico.

**Descritores:** Carcinoma de células escamosas; Úlcera cutânea; Procedimentos cirúrgicos reconstrutivos; Diagnóstico precoce; Ferimentos e lesões; Queimaduras.

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Article received: October 27, 2021.  
Article accepted: April 7, 2022.

Conflicts of interest: none.

DOI: 10.5935/2177-1235.2023RBCP0654-EN

## INTRODUCTION

Marjolin's ulcer (MU), also called cicatricial carcinoma, is a lesion first described in 1928 by the French surgeon Jean Nicholas Marjolin after observing tumor lesions originating from burn scars. The

incidence ranges from 0.77 to 2%<sup>1,2</sup>. As for the time of progression, it is considered a chronic form when the time of evolution of the lesion is greater than 12 months. The average time of malignant transformation is generally superior to 30 years<sup>3-5</sup>. Although the evolution, in most cases, is slow, early diagnosis is essential since,

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in the initial stages, the malignant tumor is subject to excision with less complex reconstructions<sup>6</sup>.

The diagnosis of Marjolin's ulcer is made through the patient's clinical history, lesion presentation, and histopathology. Although a previous history of burns is the most frequent cause, other factors such as pressure ulcers, ulcers due to dermatological conditions, lesions due to vascular insufficiency, and ulcers due to diabetes, among others, are indicative predictors<sup>3</sup>.

Histopathologically, it can be classified into squamous cell carcinoma (SCC), the latter developed in white populations, especially after exposure to ultraviolet rays, basal cell carcinoma (BCC), melanoma, sarcoma, and other rare cell types<sup>7</sup>. It has a wide spectrum of differential diagnoses, such as ulcerative infectious diseases such as tertiary-stage syphilis, American tegumentary leishmaniasis, sporotrichosis, and leprosy.

Marjolin's ulcer treatment is a process that requires knowledge and preparation. The most specific treatment is surgery, radiotherapy is recommended in particular cases, and chemotherapy has shown little efficacy<sup>1,8</sup>.

## OBJECTIVE

The purpose of this study is to review this condition, highlighting the history, physical examination, local care, clinical and surgical treatment, and its impact on prognosis and quality of life.

## METHOD

This is a literature review based on original studies and trials published between 2005 and 2020 in English and Portuguese, with or without systematization. The search was carried out in the Medline and SciELO databases, using the descriptors "Squamous Cell Carcinoma,"; "Marjolin's Ulcer,"; "Postburn Wounds." Nine articles were selected, of which 8 refer to the Medline database and 1 to the SciELO database, because they fit the requirements and are relevant to the analysis and discussion. Furthermore, data released by the Brazilian Society of Dermatology, the *Revista Brasileira de Cirurgia Plástica*, the Ministry of Health, and protocols and guidelines were consulted to enrich the discussion of this article.

## RESULTS

In total, 382 published scientific articles addressing the issue of Marjolin's ulcer were found. After reading the abstracts and information in each study, we selected 21 articles to compose and support our bibliographic

review. Of these 21, 9 articles meet the requirements of being observational, analytical, or descriptive studies, then analyzed and presented in our table of results (Chart 1).

The articles selected to compose our results were published between 2005 and 2019, originating in China, the United States of America, South Korea, Turkey, Portugal, and Brazil.

## DISCUSSION

Marjolin's ulcer is a rare and constantly aggressive disease. It develops in previously damaged and chronically affected areas and undergoes malignant degeneration in 0.77 to 2% of wounds and scars, especially after burns<sup>2,5</sup>. According to Serras et al.<sup>9</sup>, the average latency time is 23 to 37 years, there is no distribution by race or age, but it occurs, preferably in the fifth decade of life. It is more prevalent in men and occurs mainly in the lower extremities, around 40%, followed by the upper extremities, head, neck, and trunk<sup>9,10</sup>.

The pathophysiology includes several etiological factors responsible for malignant transformation. Decreased vascularity, combined with a weakened epithelium, creates a susceptibility to wound chronification, one of the main mechanisms suggested since the 1930s<sup>3</sup>.

MU can be diagnosed early through strict surveillance during the latency period<sup>3,11</sup>. When the wound healing period is prolonged due to lack of adequate treatment, it can lead to loss of immune system cells and physiological events in a way that impairs immune surveillance, resulting in the inability to recognize non-auto malignancy in the early stages, which may lead to an aggressive condition prone to metastases<sup>3,5</sup>.

Chronic irritation and repetitive trauma in this malnourished area act as promoters of degenerative changes, where there is a lack of collagen organization and impairment of the vascular supply due to fibrosis, contributing to the weakening of the new epithelium that will be formed and compromising the current immune system<sup>12</sup>.

Toxins released by tissue in necrosis can directly cause cell mutations<sup>5,9</sup>. Furthermore, mutations in the genes responsible for cell division and apoptosis cause increased carcinoma incidence in patients with MU<sup>5</sup>. However, once ulceration occurs, the irritating factor becomes indifferent due to the rapidity with which the malignancy progresses, leading to advanced-stage diseases faced by surgeons<sup>11</sup>.

The diagnosis begins with the history and clinical suspicion based on the characteristics of the

**Chart 1.** Observational studies on Marjolin's ulcer (UM).

Authors	Title	Year	Results	Type of Study
Xiang et al. <sup>1</sup>	Clinical features and treatment of 140 cases of Marjolin's ulcer at a major burn center in southwest China	2019	MU occurred mainly in men and resulted from scar carcinoma after burns. The pathological type was mainly squamous cell carcinoma. Autologous skin grafting and local skin flap repair were the main repair methods used. The skull bone was the site most susceptible to invasion.	Retrospective Study
Bang & Woo <sup>2</sup>	The Fate of Chronic Burn Wounds Suspected as Marjolin's Ulcers	2018	Histologically, chronic ulcer and pseudoepitheliomatous hyperplasia were 21%, respectively, and malignancy, including squamous cell carcinoma and leiomyosarcoma, was 58%. The mean latency period was 31.6±13.0 years, and most injuries occurred in the extremities.	Retrospective Study
Kerr-Valentic et al. <sup>3</sup>	Marjolin's Ulcer: modern analysis of an ancient problem	2009	Although burn scarring represents 76.5% of patients in the authors' review, venous stasis ulcers, traumatic wounds, osteomyelitis, and pressure ulcers are also types of wounds that can undergo malignant degeneration.	Cross-sectional study with bibliographic review
Choi et al. <sup>4</sup>	Impact of Disturbed Wound Healing after Surgery on the Prognosis of Marjolin's Ulcer	2013	The recurrence rate increases in patients with low histological grade or lymph node metastases at diagnosis. The recurrence rate is even higher when the problem occurs during wound healing after surgery.	Retrospective Study
Calikapan et al. <sup>6</sup>	Marjolin ulcer of the scalp: intruder of a burn scar	2008	Consistent with the literature, the histopathology of the tumors was squamous cell carcinoma in most patients. Although rare, mesenchymal tumor is involved in 2 out of 9 patients. The latency period of the tumor is inversely proportional to the age at the time of the burn.	Cross-sectional study
Serras et al. <sup>9</sup>	Melanoma Marjolin's ulcer in the hand: a case report	2019	Female, 74 years old, with malignant melanoma resulting from a burn scar on the right thenar eminence 14 years after the initial lesion. The lesion was excised, and a full-thickness skin graft covered the defect. At 6 months postoperatively, there are no signs of locoregional recurrence or systemic dissemination.	Case report
Xiao et al. <sup>11</sup>	A review of 31 cases of Marjolin's ulcer on the scalp: Is it necessary to preventively remove the scar?	2019	Of the 31 patients with MU on the scalp, the mean latency and post-ulceration period was 42.9 years and 37.5 months, respectively. Among them, 30 patients were diagnosed with cancer 5 years after the initial lesion, and 25 experienced a pre-ulceration period of more than 20 years. A negative correlation was identified between the post-ulceration period of the scalp MU and its pre-ulceration period.	

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**Chart 1.** Observational studies on Marjolin's ulcer (UM).

Authors	Title	Year	Results	Type of Study
Shen et al. <sup>12</sup>	Clinical characteristics and therapeutic analysis of 51 patients with Marjolin's ulcer	2015	Among patients with squamous cell carcinoma, 30.23% had metastasis to the sentinel lymph node, and 11.63% had distant metastasis. Among patients with melanoma, 66.67% had sentinel lymph node metastases, and 33.33% had distant metastases.	Retrospective Study
Costa et al. <sup>10</sup>	Epidemiology and treatment of pressure ulcers: experience of 77 cases	2005	Forty-five patients with 77 ulcers were evaluated during this period. Regarding sex, a 4:1 male predominance was found. 32.47% of the ulcers were located in the sacral region, 32.47% in the trochanteric region, and 15.58% in the sciatic region. Mostly young (mean age 34.78 years), with spinal cord injuries (100% of patients), victims of firearm injuries (60% of patients), chronic (93.3%), and grade IV injuries (67.53%).	Prospective Study

ulcer: raised, hardened edges, fetid odor, vegetative appearance, occasional purulent discharge associated with pressure or venous ulcers, and burn scars. Collecting samples from the center and edges of the ulcer is recommended for later histopathological analysis and diagnostic confirmation<sup>5</sup>.

Furthermore, it is essential to deepen the patient's history because poorly healed burns during childhood may be the causal factor of the current injury<sup>12,13</sup>. There is a risk of metastases to regional lymph nodes, and in case of clinical suspicion of lymph node involvement, these should be qualified for surgery. Sentinel lymph node biopsy is highly sensitive and is recommended to identify metastases<sup>5</sup>.

With the possibility of involvement of noble structures, lesion recurrence, and metastases, early diagnosis is of paramount importance<sup>14</sup>. The delay in seeking and receiving medical care and inadequate treatment due to an error in diagnosing the wound postpones the therapeutic approach, which is essential for a good prognosis<sup>9</sup>.

The SCC leads as the most common histological type and is formed by cells that mimic those of the normal epidermis; however, with disorganized architecture, nuclear atypias, and typical and atypical mitoses<sup>8,15</sup>. It is common to identify horny pearls, where keratin condensation occurs in the center of cell clusters, an indication of good differentiation from squamous cell carcinoma<sup>8</sup>. BCC is the second most common neoplasm<sup>7</sup>. It arises in the basal cells found in the deepest layer of the epidermis. Melanoma, which ranks third in the incidence of MU, is a highly malignant tumor that originates from melanocytes in the basal layer of the epidermis and infiltrates the dermis<sup>15,16</sup>.

Another important differential diagnosis is pseudoepitheliomatous or pseudocarcinomatous hyperplasia<sup>17</sup>. It is a benign disease characterized by hyperplasia of the epidermis and adnexal epithelium, which simulates SCC<sup>17</sup>. It is found in several heterogeneous diseases<sup>2,18</sup>. Also known as "invasive acanthosis" and "verrucous epidermal hyperplasia," it can be misinterpreted as SCC, especially in cases where the primary process located in the dermis is not easily seen, or when the biopsy is superficial and does not include a sufficient portion of the dermis<sup>18</sup>.

The use of non-surgical therapies is still controversial. The use of cisplatin, 5-fluorouracil, and bleomycin showed partial or complete remissions<sup>2</sup>. However, the effects of chemotherapy and cytotoxic radiotherapy are still doubtful, and there are divergences in the literature<sup>16</sup>. The radiotherapy effects are questioned due to the little vascularization around the ulcerated tissue<sup>6</sup>; however, radiotherapy is often indicated in inoperable patients or as a post-surgical consolidation treatment<sup>16</sup>. Among the indications for radiotherapy, there are:

- (1) metastasis from dead regional lymph nodes;
- (2) grade 3 lesions with positive lymph nodes after nodal dissection;
- (3) tumors greater than 10 cm in diameter and with positive lymph nodes after regional lymph node dissection;
- (4) grade 3 lesions with tumor diameter greater than 10 cm and negative lymph nodes after regional lymphatic dissection; and
- (5) head and neck lesions with positive lymph nodes after regional lymph node dissection<sup>5</sup>.

Currently, the most effective and used treatment is surgery<sup>1</sup>. Several authors suggest prophylactic lymph node dissection due to the aggressive progression profile<sup>1,2</sup>. This is based on the histological grade of the tumor or the indication for sentinel lymph node dissection and, according to recommendations, is performed only in clinically positive lymph node chains or in cases of histologically positive lymph nodes after fine needle aspiration puncture<sup>2</sup>. It is very commonly debated that positron emission computed tomography (PET-CT) findings in combination with ultrasound-guided biopsy have a good accuracy rate for searching for metastases in lymph nodes<sup>12</sup>.

Surgical intervention requires extensive tissue excision with margins of 2 cm<sup>4</sup>. In some cases, an extension of 5 cm from the edge of the wound is recommended<sup>1</sup>, possibly improving the prognosis by reducing post-surgical recurrence<sup>19</sup>. Radical excision is necessary because malignant transformation occurs mainly at the edges of ulcers during secondary intention healing. The chance of a false-negative biopsy, due to the focal nature of the malignant alteration, also suggests excisional oncological clearance of the primary lesion, with horizontal safety margins of 2 to 4 cm and vertical margins close to uninvolved barrier structures<sup>2</sup>.

The depth of resection depends on the level of tumor cell invasion. The superficial layer of the deep fascia, the muscle tissue, and the periosteum are structures possibly affected by neoplastic cells<sup>1</sup>. In most cases, debridement at the facial level is a minimum requirement, and insufficient resections can lead to impaired healing and recurrence<sup>2,19</sup>.

However, deep tissue and/or bone invasions make radical resection of the lesion difficult. Amputation is indicated in cases of very extensive resections<sup>2,19</sup>. Deep muscle involvement demands greater excisions and may affect the periosteum and cortical bone<sup>2,19</sup>. The structures' excision is also indicated to avoid recurrence due to residual tumors<sup>1</sup>. Amputation is also considered in cases of joint infeasibility.

After ulcer resection, adequate repair and functional reconstruction should be instituted to improve the patient's quality of life through options such as skin grafting and flaps<sup>20</sup>. Grafts are indicated in situations that demand monitoring of possible recurrences—flaps, for covering important structures and maintaining function<sup>1,2</sup>. The microsurgical flap is indicated for cases with extensive resection, with the possibility of postoperative radiotherapy<sup>20</sup>.

Quickly recognizing the signs of cancer recurrence after surgical excision is paramount for a better prognosis. An active diagnosis through additional physical examinations, general radiographs, computed tomography, and magnetic resonance imaging, among

others, may be necessary to obtain early confirmation of recurrence.

The triggering factors for recurrence are still poorly understood; however, the pre-surgical histological grade of the carcinoma, healing disorders, and lymph node metastases are factors that suggest a relationship with possible recurrence. The recurrence rate is still being researched. Some studies have shown recurrence in 8 out of 12 patients, 4 to 5 months after surgery, with an average of 3 to 10 months<sup>4</sup>.

## CONCLUSION

In short, UM is a rare but highly aggressive malignant neoplasm that needs to be better studied and assisted. It has a wide differential diagnosis, which must be known so that other hypotheses are discarded. The most effective treatment is surgery. Radiotherapy may be indicated in specific preoperative cases or as postoperative adjuvant therapy, and chemotherapy has not shown good results. In the initial stages, the malignant tumor is subject to simple excision, and in late cases, resection, as it is wide, can lead to high morbidity. That said, early diagnosis and adequate treatment are the keys to the good evolution of MU.

## COLLABORATIONS

- NNR** Analysis and/or data interpretation, Conceptualization, Data Curation, Final manuscript approval, Project Administration, Supervision, Writing - Review & Editing.
- LRAD** Analysis and/or data interpretation, Investigation, Writing - Review & Editing.
- ISG** Analysis and/or data interpretation, Conceptualization, Writing - Review & Editing.
- IHS** Analysis and/or data interpretation, Investigation, Writing - Review & Editing.
- LOM** Analysis and/or data interpretation, Investigation, Project Administration, Writing - Review & Editing.
- MPSN** Final manuscript approval, Project Administration, Supervision.

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