

# Systematic Review of Modern Case Series of Squamous Cell Cancer Arising in a Chronic Ulcer (Marjolin's Ulcer) of the Skin

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**PURPOSE** Marjolin's ulcer is an aggressive cutaneous malignancy that arises in chronic nonhealing wounds. A review of modern series describing Marjolin's ulcer would be helpful in defining optimal management strategies and expected outcomes.

**METHODS** A systematic review was performed on October 18, 2018, by querying Medline and EMBASE. Key inclusion criteria were as follows: human studies, English language, published in 2000 or later, > 10 patients, and at least 80% of the patients having squamous cell carcinoma (SCC) histology.

**RESULTS** There were 599 patients in 14 case series from 10 countries; 82% of patients were from low-income and middle-income countries, and 48% were women. Overall, 65% of the ulcers were preceded by burns. Mean latency ranged from 11 years to 41 years (median, 28 years). Lower extremities were the most common site (62%). Differentiation was reported as well differentiated (64%), moderately differentiated (27%), or poorly differentiated (9%). Almost one third of cases were clinically node positive, though only 7% of all cases (24 of 334) were confirmed to be pathologically involved. Distant metastasis rates were reported in only 7 series, with median rate of 5% (range, 0%-27%). The main treatment modality was surgical excision (71%), followed by amputation (24%), primary radiotherapy (2%), and chemotherapy (< 1%). Outcomes data varied in content and quality. Mortality rates were 12%, 24%, and 37% in the three series reporting between 2 and 3 years of follow-up.

**CONCLUSION** Marjolin's ulcer with SCC histology is an aggressive cancer with a notable potential for lymph node metastasis and distant metastasis. Comprehensive staging is recommended, with management optimally having a multidisciplinary context. Low- and middle-income countries are overrepresented in reports of Marjolin's ulcer, and there may be opportunities for prevention and early detection.

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## INTRODUCTION

Marjolin's ulcer is an aggressive cutaneous malignancy that arises in chronic nonhealing wounds. It is uncommon in high-income country settings, though it may be more common in lower-resource settings, given the role of chronic wounds arising from situations that involve suboptimal management at time of primary injury.<sup>1</sup> The natural history of a Marjolin's ulcer includes the initial insult, which results in a nonhealing or recurrent ulcer.<sup>2,3</sup> The latency period is defined as the time from initial injury to the diagnosis of Marjolin's ulcer. The average latency period varies widely, but it is typically greater than a decade.<sup>2</sup> The cause of the malignant transformation is not well defined. Squamous cell carcinoma (SCC) is the most common histology for Marjolin's ulcer.<sup>2,4</sup> There are limited data that systematically review management and outcome in the era of cross-sectional imaging or more advanced

forms of systemic therapy and radiotherapy. We set out to review clinical features of Marjolin's ulcer with SCC histology in modern case series so that management strategies and expected outcomes could be better defined.

## METHODS

### Study Eligibility

To identify all published case series on Marjolin's ulcer, we performed a systematic review using the Ovid database and including EMBASE and Medline. The goal was to identify modern case series describing contemporary management, so only studies published in the year 2000 or later were retained, with year of individual patient diagnosis ranging from January 1, 1995, to October 18, 2018. Additional inclusion criteria were English language; > 10 patients; inclusion of information on staging, management, and/or

## ASSOCIATED CONTENT

### Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

To perform a systematic review of modern case series describing Marjolin's ulcer, a skin malignancy that occurs after a chronic nonhealing wound. This would help define optimal management strategies and expected outcomes.

### Knowledge Generated

Marjolin's ulcer with squamous cell carcinoma histology is an aggressive cancer with a notable potential for lymph node metastasis and distant metastasis. Mortality is substantial. Low- and middle-income countries are overrepresented in reports of this disease.

### Relevance

Comprehensive staging of Marjolin's ulcer is recommended, with management optimally having a multidisciplinary context. There may be opportunities for prevention and early detection of Marjolin's ulcer, especially in low- and middle-income countries.

outcomes; and at least 80% of the patients having SCC histology.

### Search Algorithm

Keywords were used to simultaneously search EMBASE and Medline: "marjolin," "scar neoplasm," "scar cancer," or "chronic ulcer." Details of the search strategy are provided in Appendix [Figure A1](#). Study results were supplemented by hand searches of key article reference lists for other articles.

### Data Extraction

After completing the search algorithm, the identified studies were reviewed. Data were abstracted using a standardized form. Abstracted variables for each study were as follows: number of patients from each study, study period, mean age at diagnosis, proportion of patients who were female, mean latency period, percent SCC histology, grade, site of lesion, size of ulcer, injury type, treatment types used (surgery, chemotherapy, or radiation), use of imaging, presence of metastasis at diagnosis, use of lymph node dissection, outcomes, recurrences, and re-treatment.

### Data Analysis

The abstracted data were reviewed by three independent investigators (M.A., M.Y., T.P.H.). Consensus was reached when there were differences in abstracted data. Data were summarized in the form of categorical variables, frequency tables, and summary figures. Given heterogeneity and limited availability of study data, meta-analysis of outcomes was not deemed feasible or appropriate.

## RESULTS

The systematic review was performed on October 18, 2018. Details of the literature search are provided in [Figure 1](#). Fourteen case series met inclusion criteria.

### Demographic Data

There were 599 patients total in the 14 identified series ([Table 1](#)). Women were 48% of the patient group (n = 289). The mean age at diagnosis of Marjolin's ulcer ranged in

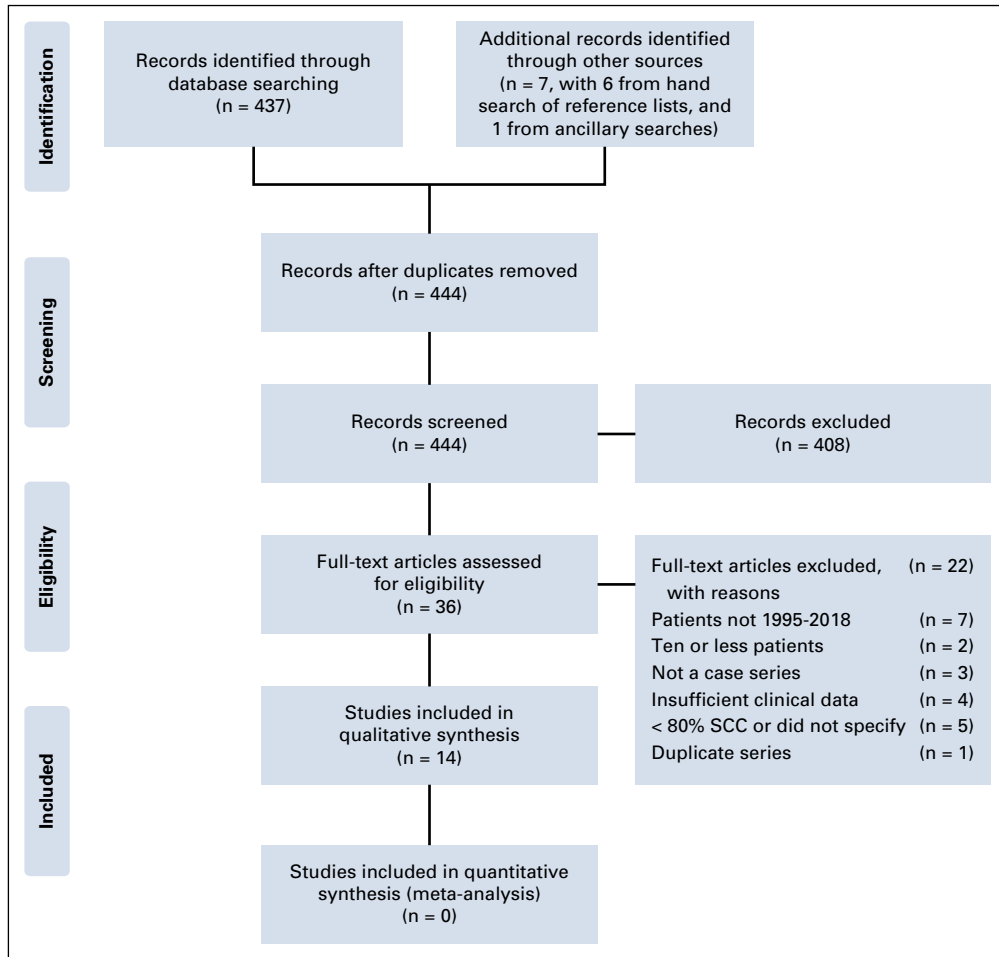
studies from 30 to 76 years, with a median value of 51 years. Series included patients from Das<sup>3</sup> (n = 46 patients), Smith<sup>6</sup> (n = 21), Shen<sup>12</sup> and Yu<sup>1</sup> (n = 68), Combemale<sup>13</sup> (n = 80), Reich-Schupke<sup>10</sup> (n = 30), Shala<sup>17</sup> and Sadegh Fazeli<sup>15</sup> (n = 102), Kadir<sup>16</sup> (n = 48), Tahir<sup>11</sup> (n = 36), Chalya<sup>8</sup> (n = 56), and Karasoy Yesilada,<sup>9</sup> Aydogdu,<sup>7</sup> and Oruc<sup>14</sup> (n = 112; [Fig 2](#)). Except for France and Germany, all series were for patients (n = 489) from low- or middle-income countries (LMICs) according to the World Bank Country Income Classification for 2010.<sup>5</sup>

### Wound Characteristics

In the identified case series, burn injury was the most common form of injury, occurring in 65% of all cases with a described mechanism (387 of 598 patients). This was followed by venous ulcers (115 of 598 patients) and trauma (44 of 598 patients). The remaining cases could be classified as infection (14 of 598 patients) or other causes (38 of 598 patients; eg, human bite, pressure sore, diabetic foot, radiation, surgical scar, or electrical injury). Notably, all cases reported in the 2 high-income country case series involved venous ulcers (n = 105). The most common site of Marjolin's ulcer for cases with a reported site (n = 589) was the lower extremities, at 62% (366 of 589 patients), followed by scalp and face at 16% (95 of 589 patients), upper extremities at 12% (72 of 589 patients), and torso at 10% (56 of 589 patients). Overall, 92% of the lesions were SCC. Differentiation was reported for 74% (441 of 599 patients). The majority were well differentiated (64%), with the remainder moderately differentiated (27%) or poorly differentiated (including undifferentiated or anaplastic, 9%).

### Clinical Presentation

Cases typically had a nonhealing ulcer that has been present for many years. Mean latency ranged from 11 years to 41 years, with a median value of 28 years. The median value of mean latency was 22 years for the case series from high-income countries and was 29 years for the series from LMICs.



**FIG 1.** PRISMA flow diagram for identifying studies of modern case series of squamous cell cancer arising in a chronic ulcer (Marjolin's ulcer) of the skin.

## Imaging

Information on imaging use was incomplete when provided and was not reported in 8 of 14 series. All series reporting on imaging used cross-sectional imaging (computed tomography, magnetic resonance imaging, or positron emission tomography/computed tomography). In most cases, it was not specified how many patients in the series had disease staged with these techniques. Plain film x-rays and/or ultrasound were used in all series reporting on imaging.

## Disease Extent at Diagnosis

When reported, the involved primary areas were large. The 2 series reporting median ulcer size reported a median of 16 cm (range, 7-32 cm) and 14 cm (range, 5-30 cm), respectively.<sup>6,7</sup> The 2 series reporting on median tumor size reported a median of 8 cm (range, 2-16 cm) and 10 cm (range, 2-25 cm), respectively.<sup>8,9</sup>

The presence of deep invasion was described in 4 series. Direct extension to muscle or bone occurred in a median of 36% of cases, ranging from 3% of cases in a high-income country series to 95% in an LMIC series.<sup>6,10,11,13</sup>

Lymph node status was reported for 507 patients from 12 case series (Table 2). Almost a third (30%) of cases was assessed to have clinical involvement—though, among the 8 series reporting on pathologic status of lymph nodes considered clinically involved, only 7% of patients (24 of 334 patients) had pathologically involved disease.<sup>1,3,6,9,10,12-14</sup> Specifically, only 28% of patients undergoing biopsy and/or dissection for clinically involved nodes had pathologic involvement (24 of 85 patients). There was little difference in reported lymph node status between the 2 high-income country cases series and the 12 series from LMICs. Clinical node positive rates were 32% and 30% of patients ( $P = .69$ ), and pathologic node positive rates were 6% and 8% ( $P = .51$ ), for high-income countries and LMICs, respectively. Compared with later series (earliest case reported from 2000-1010), earlier series (earliest case report date, 1995-1999) demonstrated higher rates of clinical node positivity (44% v 20%;  $P < .001$ ) despite similar pathologic node positive rates (6% v 4%;  $P = .30$ ).

Distant metastasis at diagnosis was described in 7 series, representing 342 patients; 8% had distant metastasis (29 of

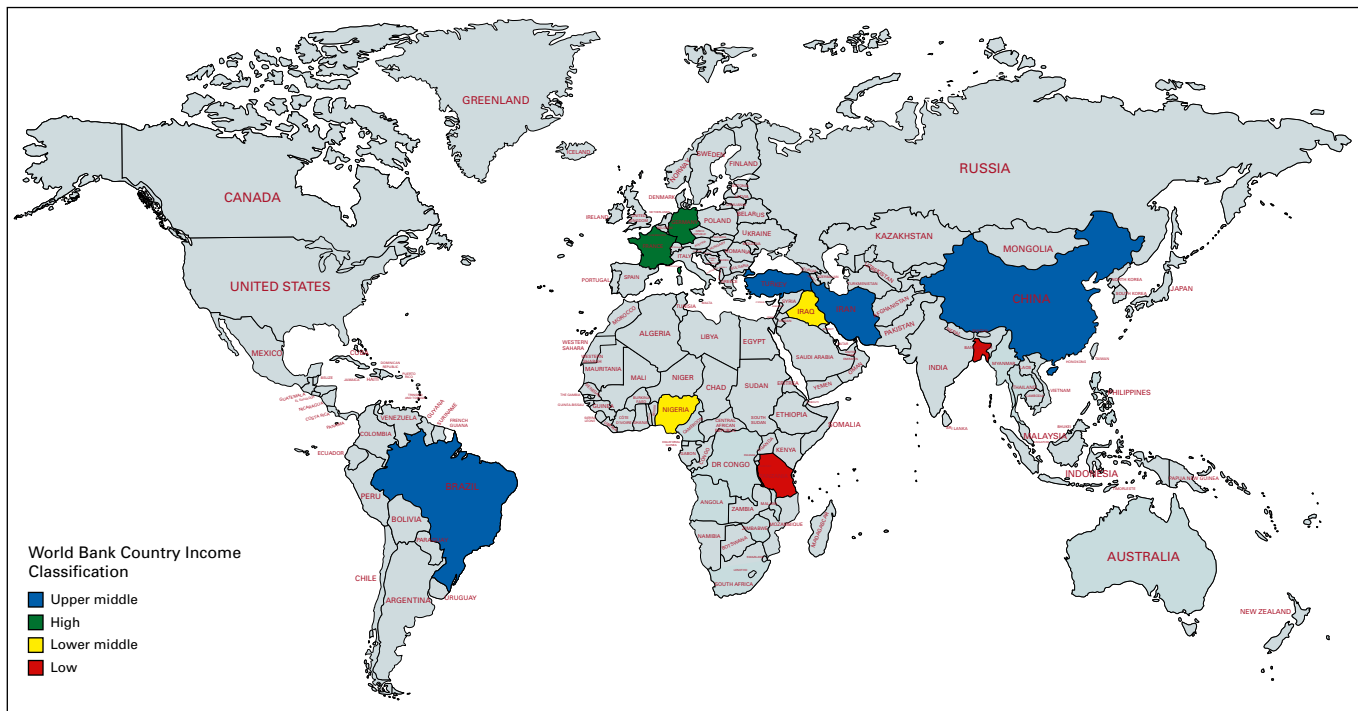
**TABLE 1.** Primary Treatment of Marjolin's Ulcer

Author	Country (World Bank Classification)	Earliest Case Report Date	Cohort	Cohort With Treatment Information	Excision	Amputation	Radiotherapy (no surgery/chemotherapy)	Chemotherapy (no surgery/radiotherapy)	No Treatment
				O <sup>a</sup>	NR	NR	NR	NR	NR
Sadegh Fazeli <sup>15</sup>	Iran (UM)	1995-1999	83	0 <sup>a</sup>	NR	NR	NR	NR	NR
Combemale <sup>13</sup>	France (H)	1995-1999	80	51	12	29	3	1	6
Smith <sup>6</sup>	Brazil (UM)	1995-1999	21	21	0	19	0	0	2
Shahla <sup>17</sup>	Iran (UM)	1995-1999	19	19	0	19	0	0	0
Karasoy Yesilada <sup>9</sup>	Turkey (UM)	1995-1999	34	34	28	6	0	0	0
Aydođdu <sup>7</sup>	Turkey (UM)	1995-1999	15	15	12	0	3 <sup>b</sup>	0	0
Oruç <sup>14</sup>	Turkey (UM)	2000-2004	63	63	63	0	0	0	0
Kadir <sup>16</sup>	Iraq (LM)	2000-2004	48	47	44	3	0	0	0
Tahir <sup>11</sup>	Nigeria (LM)	2000-2004	36	32	18	9	NR	NR	5
Chalya <sup>8</sup>	Tanzania (L)	2000-2004	56	48	42	6	NR	NR	NR
Shen <sup>12</sup>	China (UM)	2000-2004	51	43	28	13	1	0	1
Das <sup>3</sup>	Bangladesh (L)	2000-2004	46	46	45	1	NR	0	0
Yu <sup>1</sup>	China (UM)	2005-2010	17	17	17	0	NR	0	0
Reich-Schupke <sup>10</sup>	Germany (H)	2005-2010	30	29	23	6	NR	NR	NR
<b>Total</b>			<b>599</b>	<b>465</b>	<b>332</b>	<b>111</b>	<b>7</b>	<b>1</b>	<b>14</b>

Abbreviations: H, high income; L, low income; LM, lower-middle income; NR, not reported; UM, upper-middle income.

<sup>a</sup>All patients underwent surgery. No additional details were provided.

<sup>b</sup>One patient received radiotherapy and chemotherapy.



**FIG 2.** Countries reporting Marjolin's ulcer in identified case series. Reporting countries are colored light blue. Eight of ten were low-income or middle-income countries.

342 patients). The median rate reported in the 7 series was 5% (range, 0% for Germany and China to 27% for Tanzania).

### Treatment Modalities

Surgery was the primary modality of therapy in all series (Table 1). For the 465 patients with treatment information, surgical excision was used in 71% ( $n = 332$ ), followed by amputation in 24% ( $n = 111$ ), primary radiotherapy in 2%, and chemotherapy in  $< 1\%$ . Three percent of patients did not receive active treatment; 58% of surgery patients received amputation in earlier series (1995-1999 earliest report), compared with 12% for later series (2000-2010 earliest report;  $P < .001$ ).

In some cases, radiotherapy was used in addition to other treatments. For example, Karasoy Yesilada et al<sup>9</sup> used adjuvant radiotherapy in 18 of 34 cases. In total, of 465 patients with treatment information, 41 patients received radiotherapy as part of their primary management, though only 7 received it without surgery. Three series reported radiotherapy use without quantifying the number of cases.<sup>1,3,8</sup> Reported indications were for inoperable tumors, advanced cases, and postoperative radiotherapy. Chemotherapy was rarely used as part of initial management, with only 9 receiving it as part of their primary management and only 1 patient receiving chemotherapy alone.

### Outcomes

All but 2 series reported on cancer outcomes. These outcomes varied.<sup>10,15</sup> Seven series reported on mortality; 7, on local recurrence; and 4, on distant recurrence. No series

reported Kaplan-Meier survival statistics. Only 2 series reported lymph node recurrence, and the 4 reported nodal recurrences were accompanied by local ( $n = 2$ ) or distant ( $n = 2$ ) metastasis.<sup>3,12</sup> Outcome reporting was heterogeneous in terms of number of endpoints, chosen endpoints, and length of follow-up, making meta-analysis inappropriate (Table 3).

Mortality ranged from 7% to 73%, though intensity of follow-up was usually unclear. Duration of follow-up was summarized as mean or median in only 3 series (all results, between 2 and 3 years). Mortality rates for these 3 series were 12%, 24%, and 37%.<sup>1,12,13</sup> Mortality by stage was provided by 1 series, with a rate of 27% (11 of 41 patients) for stage I and a rate of 80% (8 of 10 patients) for lymph node and/or visceral metastasis.<sup>13</sup> There was a pattern of worse reported mortality in earlier series (1995-1999), with a range of 37%-73%, compared with later series (2000-2010; range, 7%-24%). Results were not pooled, given the limited information on follow-up.

Local recurrence in 7 reporting series ranged from 6% to 67% (Table 3). Two series reported on outcomes after local recurrence.<sup>7,16</sup> All 24 patients in these 2 series with local recurrence died of cancer. Distant recurrence ranged from 0% to 12% in 4 reporting series (Table 3).

### DISCUSSION

Marjolin's ulcer is an aggressive skin malignancy that occurs after a chronic nonhealing wound. We observed that it is often found in an advanced state, with a propensity for

**TABLE 2.** Clinical and Pathologic Lymph Node Involvement for Marjolin's Ulcer

Author	Country (World Bank Country Classification) <sup>a</sup>	Earliest Case Report Date	Clinical Node Positive	Pathologic Node Positive	Total Patient Population
Sadegh Fazell <sup>15</sup>	Iran (UM)	1995-1999	43	NR	62
Combemale <sup>13</sup>	France (H)	1995-1999	35	7	80
Smith <sup>6</sup>	Brazil (UM)	1995-1999	6	1	21
Shahla <sup>17</sup>	Iran (UM)	1995-1999	1	NR	19
Karasoy Yesilada <sup>9</sup>	Turkey (UM)	1995-1999	10	4	34
Oruç <sup>14</sup>	Turkey (UM)	2000-2004	12	4	63
Tahir <sup>11</sup>	Nigeria (LM)	2000-2004	12	NR	36
Chalya <sup>8</sup>	Tanzania (L)	2000-2004	18	NR	56
Shen <sup>12</sup>	China (UM)	2000-2004	3	8	43
Das <sup>3</sup>	Bangladesh (L)	2000-2004	12	0	46
Yu <sup>1</sup>	China (UM)	2005-2010	1	0	17
Reich-Schupke <sup>10</sup>	Germany (H)	2005-2010	0	0	30
Total			153	24	507

Abbreviations: H, high income; L, low income; LM, lower-middle income; NR, not reported; UM, upper-middle income.

<sup>a</sup>World Bank Country Income Classifications<sup>5</sup> for 2010, accessed July 4, 2019: low income (L), ≤ \$1,005; lower-middle income (LM), \$1,006-\$3,975; upper-middle income (UM), \$3,976-\$12,275; high income (H), > \$12,275.

**TABLE 3.** Recurrence and Mortality Outcomes for Marjolin's Ulcer

Author	Country (World Bank Country Classification)	Earliest Case Report Date	Mortality	Local Recurrence	Distant Recurrence	Overall/Any-Site Recurrence	Other Recurrence or Mortality Outcome
Sadegh Fazelj <sup>15</sup>	Iran (UM)	1995-1999	NR	NR	NR	NR	NR
Combemale <sup>13</sup>	France (H)	1995-1999	37% (19/51); mean follow-up, 2.3 years	NR	NR	NR	Mortality: 27% (11/41) for stage I, 80% for nodal and/or visceral metastasis (8/10); cause of death not specified
Smith <sup>6</sup>	Brazil (UM)	1995-1999	42% (8/19) died of any cause, 21% (4/19) died of cancer, 2 were lost to follow-up (refused surgery); length of follow-up not provided	NR	NR	NR	Death or recurrence in 42% (8/19); length of follow-up not stated
Shahla <sup>17</sup>	Iran (UM)	1995-1999	NR	NR	NR	No recurrence or metastasis with mean 4-year follow-up	NR
Karasoy Yesilada <sup>9</sup>	Turkey (UM)	1995-1999	NR	6% (2/34)	NR	17% (10 years of follow-up)	NR
Aydođdu <sup>7</sup>	Turkey (UM)	1995-1999	73% (11/15, within 8-20 months)	67% (8/12)	NR	67% (8/12)	100% (8/8) local recurrences died of cancer; mean survival, 13.3 months
Oruç <sup>14</sup>	Turkey (UM)	2000-2004	NR	14% (9/63)	3% (2/63)	NR	NR
Kadir <sup>16</sup>	Iraq (LM)	2000-2004	NR	33% (16/48)	NR	NR	100% (16/16) of local recurrences died of cancer
Tahir <sup>11</sup>	Nigeria (LM)	2000-2004	8% (3/36; follow-up, 3-36 months)	NR	6% (2/36)	17% (6/36)	NR
Chalya <sup>8</sup>	Tanzania (L)	2000-2004	7% (All documented deaths appeared to have occurred during first admission.)	NR	NR	NR	NR
Shen <sup>12</sup>	China (UM)	2000-2004	12% (5/43; median follow-up, 2 years; range, 1-8 years)	7% (3/43)	12% (5/43)	12% (5/43)	Nodal recurrence in 2/43, accompanied by lung metastasis in both cases
Das <sup>3</sup>	Bangladesh (L)	2000-2004	NR	13% (6/46, with 2 also nodal recurrence)	0% (0/46)	13% (6/46; within 6 months)	NR
Yu <sup>1</sup>	China (UM)	2005-2010	24% (4/17; all within 1 year, all of cancer; mean follow-up, 2.9 years; range, 1-6 years)	6% (1/17)	NR	NR	One patient developed a new separate primary.
Reich-Schupke <sup>10</sup>	Germany (H)	2005-2010	NR	NR	NR	NR	NR

Abbreviations: H, high income; L, low income; LM, lower-middle income; NR, not reported; UM, upper-middle income.

lymph node metastasis and distant metastasis, and with substantial mortality. Reported cases are most often from LMICs. To tailor treatment, careful staging with cross sectional imaging is important, and careful consideration of the relevant draining nodal basin(s) should be undertaken on exam.

A minority of series reported the use of cross-sectional imaging. We hypothesize that this reflects the lack of use of such imaging in many resource-limited settings. The available data on the clinical occurrence of lymph node metastasis and distant metastasis at diagnosis suggest that there may be more cases with occult metastasis that are clinically undetected. Cross-sectional imaging, such as computed tomography or magnetic resonance scans, would help better define the clinical extent of disease at diagnosis. Biopsy of suspicious lymphadenopathy appears important. We observed that only 28% of patients undergoing biopsy and/or dissection for clinically involved nodes had pathologic involvement (24 of 85 patients). The occurrence of lymphadenopathy without pathologic involvement may relate to the chronic nature of the wound preceding the development of malignancy. For cases without clinical evidence of lymph node metastasis, the role of sentinel lymph node biopsy is not well defined. In adequately resourced settings, additional investigation of the utility of sentinel node biopsy in Marjolin's ulcer would be worthwhile.

Surgery forms the backbone of treatment of Marjolin's ulcer. We observed increasing use of excision, rather than amputation, over time. Whether this relates to improvements in resource availability among the identified series, a change in philosophy of local management, or a change in the extent of disease over time is unclear. We note the importance of both clinical examination and imaging in determining the extent of disease when a more radical local procedure is undertaken. As noted, there was a sizeable risk of both lymph node metastasis and distant metastasis in the identified series.

There may be opportunities for prevention and early detection of Marjolin's ulcer, especially in LMICs. We note the divergence in injury mechanism between LMIC (predominantly burns) and high-income country reports (all venous ulcers). The predominance of burn injury may point to the need for optimizing initial wound management. Because of the lack of patient and system resources, deep wounds may be allowed to heal by secondary intention rather than getting proper medical care and skin grafting.<sup>3,8</sup> The latency period in all series was lengthy (median, 28 years), though it was longer in LMICs (median, 29 years) than in high-income countries (median, 22 years). Though the difference may relate to differences in disease factors or patient factors, this difference in latency period raises the question as to whether substantial improvements in early detection of Marjolin's ulcer may be possible in LMICs. Increased access to public health education, transportation, and lower-cost interventions might allow more patients to be treated earlier; to avoid the notable and often

severe morbidity of chronic wounds; and, probably in some cases, to avoid development of Marjolin's ulcer.

The role of radiotherapy and systemic therapy for Marjolin's ulcer remains unclear. Local control is important for this condition. In the 2 series reporting outcomes after local recurrence, all patients died.<sup>7,16</sup> However, there was insufficient data in the identified series to evaluate the safety and efficacy of adjuvant radiotherapy after excision. This may relate to limitations in resources and access to these treatments. It also may relate to a justifiable hesitancy to radiate a poorly vascularized chronic wound site, even after surgical excision. Response rates to radiotherapy for gross disease are also unclear, according to the series we found. We found that areas of involvement with Marjolin's ulcer are often quite large. Though the relationship of size and outcome with radiotherapy is unknown for Marjolin's ulcer, larger lesion size and/or advanced disease for cutaneous SCC and other advanced skin cancers is associated with lower control rates with radiotherapy.<sup>18-20</sup> For example, in a series of 88 patients with clinical T4 nonmelanoma skin cancers treated with radical radiotherapy, the local control was only 53% at 5 years; 44% of lesions treated were SCC, and 12% were basosquamous.<sup>18</sup> Another series of patients with advanced head and neck skin SCC were treated with concurrent chemoradiation.<sup>20</sup> Eleven patients had disease > 5 cm. Only approximately half of the evaluable patients (10 of 19 patients) achieved a complete response with this aggressive approach.

The role of systemic therapy for Marjolin's ulcer is not defined in the literature, and its use is quite scattered. The benefit of concurrent systemic therapy with radiotherapy is unclear, as is the potential use of systemic therapy (and/or radiotherapy) as a neoadjuvant treatment to facilitate surgical removal. The potential benefits of immunotherapy also require investigation. Cemiplimab is now approved for advanced and metastatic cutaneous SCC. In a phase II study of 59 patients with metastatic cutaneous SCC, a response rate of 47% was observed.<sup>21</sup> The applicability to Marjolin's ulcer is not clear.

Our study provides, to our knowledge, the largest analysis of contemporary patients with Marjolin's ulcer, with data on 599 patients. For the first time, to our knowledge, an international perspective is provided, comparing reports from LMICs and high-income countries.

There are limitations. Available case series often had incomplete data. There was a lack of well-defined follow-up over an extended period, and there was variable reporting of outcomes. Thus, data were not analyzed via Kaplan-Meier statistics. There was probably only limited use of cross-sectional imaging for staging and follow-up, meaning that our estimates of disease extent at diagnosis, and recurrence rates, are likely to be underestimates of actual rates. There are also probably differences in extent of disease between cases seen in referral centers and cases that were never referred to a specialty center. Our systematic review was limited to English only. Limitations



excepted, this review provides valuable insights into elements of diagnosis, treatment, and outcome of this disease. It also emphasizes the importance of rigorously conducted clinical case series and registry studies for rare diseases.

Marjolin's ulcer is a cutaneous malignancy with a notable risk of lymph node metastasis and distant metastasis, suggesting the need for cross-sectional radiologic staging. The optimal

role of radiotherapy and systemic therapy requires additional investigation. In identified case series, patients are most often from LMICs, where medical resources can be limited. The injury causing the chronic wound is most often a burn injury, and the wound usually has been present for decades before the diagnosis of Marjolin's ulcer. There may be opportunities for prevention and early detection.

## AFFILIATIONS

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## EQUAL CONTRIBUTION

M.A.A. and M.Y. contributed equally as co-primary authors.

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**Conception and design:** All authors

**Collection and assembly of data:** All authors

**Data analysis and interpretation:** All authors

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Agree to be accountable for all aspects of the work:** All authors

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

The screenshot shows the Ovid search interface. At the top, there is a navigation bar with 'Search', 'Journals', 'Books', 'Multimedia', 'My Workspace', and 'EBP Tools'. Below this is a 'Search History (7)' section with a 'View Saved' link. The search history is presented as a table with columns for '#', 'Searches', 'Results', 'Type', 'Actions', and 'Annotations'. The search steps are as follows:

#	Searches	Results	Type	Actions	Annotations
1	(marjolin or "scar neoplasm" or "scar cancer" or "chronic ulcer").mp.	1990	Advanced	Display Results More	
2	limit 1 to english language	1394	Advanced	Display Results More	
3	limit 2 to human	952	Advanced	Display Results More	
4	limit 3 to yr="2000 -Current"	657	Advanced	Display Results More	
5	"case report".mp.	2696227	Advanced	Display Results More	
6	4 not 5	437	Advanced	Display Results More	

FIG A1. Search strategy for modern series of Marjolin's ulcer.