

Original research article

A Clinical Study of Incidence of Lymph Node Metastasis of Marjolin's Ulcer

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Abstract

Background: Marjolin's ulcer is a rare and frequently severe skin cancer that develops in chronically inflamed or injured skin, especially following burns. Marjolin's ulcers can also form from previously traumatized and scarred tissue and are present in 1% to 2% of all burn scars. The present study attempted to determine the incidence and lymph node metastasis in cases of Marjolin's ulcers reported to the Regional Cancer Center.

Methods: The study of these n=43 Marjolin's ulcer cases was carried out. After obtaining ethical clearance from the institution this study was carried out. The data is collected from patients who have undergone treatment in the form of surgery or palliative chemotherapy or conservative management. All the n=43 patients were subjected to investigations as required according to the patient. Regional lymph nodes are assessed by both clinical palpation and ultrasound of the regional lymph nodal area.

Results: In this study of n=43 cases of Marjolin's Ulcer, n=18 patients (40%) did not have clinically palpable lymph nodes whereas n=25 patients (60%) have clinically detectable regional lymph nodes. These lymph nodes were divided into clinically significant nodes (Lymph nodes > 2cms) and clinically Non-significant Lymph nodes (Lymph nodes <2cms). In this prospective study, of n=25 patients with clinically detectable lymph nodes, n=7 (16%) patients had clinically significant lymph nodes and n=18 (41%) patients did not have clinically significant palpable lymph nodes.

Conclusion: The most common etiological factor for Marjolin's ulcers was Burns. Males are more commonly affected than females. Squamous cell carcinoma is the most common variant of Marjolin's ulcer. Most of Marjolin's Ulcers are Well-differentiated cancers (90%) of cases. The incidence of lymph node metastasis in this study was 22%. Among all the factors for metastasis lymph node size is a significantly important predictor of metastasis.

Keywords: Marjolin's Ulcers, Lymph nodes, Metastasis, Squamous cell carcinoma

Introduction

Marjolin's ulcer is a rare and often aggressive cutaneous malignancy that arises in previously traumatized or chronically inflamed skin, particularly after burns. Marjolin's ulcers have a 1% to 2% incidence in all burn scars but can also develop from previously traumatized and scarred tissue of other etiologies such as chronic sinuses of osteomyelitis, post-traumatic wounds, pressure sores, and chronic fistulae and have been reported to arise in the genitalia as a complication of Fournier's gangrene. The term "Marjolin's ulcer" was named after French surgeon, Jean Nicolas Marjolin, who first described the condition in 1828. ^[1, 2] But it was Dupuytren who noted it was a malignancy. In 1923, DaCosta first coined the expression "Marjolin's ulcer" to describe malignant tumors forming over burn injuries. ^[3] The exact mechanism of the malignant transformation of Marjolin's ulcer remains unclear and controversial. Several theories including the toxin, chronic irritation, traumatic epithelial elements implantation, heredity, immunologically privileged site, co-carcinogen, ultraviolet rays, initiation and promotion, and environmental and genetic interaction theories have been reported to explain the malignant transformation. ^[4, 5] The latency period from the time of injury to the onset of malignant transformation averages 36 years. However, early arising Marjolin's ulcers have been described in the literature. Studies from western countries have shown that the average age at diagnosis is in the fifth decade of life with a range of 18-84 years, and men are three times more frequently affected than women. In Sub-Saharan Africa, Marjolin's ulcer appears to be affecting younger patients and the transition time is getting shorter over the years. ^[6] Most lesions of Marjolin's ulcer occur on the extremities (60%), with ulcers on the head and face occurring less frequently (30%) and the lowest frequency (10%) on the trunk. ^[7] Marjolin's ulcers in unusual sites such as the genitalia as a complication of Fournier's gangrene and breast skin developing in a postburn scar have also been reported. Marjolin's ulcers are very aggressive tumors that necessitate a well-thought-out treatment plan to optimize care and assure patient survival. Early diagnosis and prompt surgical intervention are mandatory in Marjolin's ulcers as they may invade vital structures. ^[5] Despite being a surface malignancy and more amenable not only to early detection but also to a potential cure, the outcome of treatment in most developing countries has been poor because the majority of these patients present late to the hospital with advanced stage. This is partly due to the paucity of local data regarding this condition and the lack of community awareness on the importance of early reporting to the hospital for early diagnosis and treatment. With this background, we in the current study tried to evaluate the incidence, management, and outcomes of treatment of Marjolin's ulcer cases presented to our Regional Cancer Institute at Hyderabad, India.

Material and Methods

This is a cross-sectional interventional study done at MNJ Institute of Oncology and Regional Cancer Centre, Hyderabad, Telangana, a tertiary referral center for the management of cancer patients in the state. The protocol for the study was approved by the Institutional Ethical committee. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language.

Inclusion Criteria

1. Patients aged 16 years and above.
2. Males and females
3. ECOG performance status 0/1.

Exclusion Criteria:

1. The poor general condition of patients unfit for surgery
2. Recurrent disease
3. Not willing to participate in the study voluntarily

The study of these n=43 Marjolin's ulcer cases was carried out. All cases of Marjolin's ulcer were presented at the outpatient department of surgical oncology. These cases were comprised of varying age groups with differing etiologies. After obtaining ethical clearance from the institution this study was carried out. The data is collected from patients who have undergone treatment in the form of surgery or palliative chemotherapy or conservative management.

All the n=43 patients have subjected investigations as required according to the patient. Regional lymph nodes are assessed by both clinical palpation and ultrasound of the regional lymph nodal area. Of n=43 patients, only n=35 patients underwent surgery and were given postoperative care. Follow-up was done at regular intervals of every 3 months during the first 12 months and every six months for the next 12 months. The remaining n=8 patients did not undergo surgery. Of these n=8 patients, n=3 patients were given palliative chemotherapy due to unresectable locally advanced disease. N=2 patients were detected with pulmonary Koch's for which antitubercular therapy was started and advised to come back after 2 weeks but patients defaulted. One patient was found to be hyperthyroid and was started on an antithyroid drug and advised to come after 6 weeks but the patient defaulted and the remaining n=2 patients denied to undergo surgery. Of the n=35 patients who underwent surgery, n=9 patients underwent Wide Excision alone, n=16 patients underwent wide excision along with regional lymph node dissection, n=6 patients underwent amputation with lymph node dissection and n=4 patients underwent amputation only.

Results

Marjolin's ulcers were reported in different age groups. The youngest age reported was 17 years and the oldest age was 65 years. The highest incidence of Marjolin's ulcer occurred in the age group of 41 years to 50 years and it corresponds to 18 cases (51.42%). Whereas only one case is reported in the age group of 10 years to 20 years. The Mean age of the cases was 46.8 years. In this study, the incidence of Marjolin's ulcer was found to be more in males than in females. N=27 male patients were diagnosed with Marjolin's ulcer whereas only 16 female patients were diagnosed. The male to female ratio is 3:2. In this study Marjolin's ulcer was diagnosed on various parts of the body but the most frequent site of incidence is the lower extremity. A total of patients were diagnosed with lower limb Marjolin's ulcer (67%). The least incidence is seen on the head and neck as only n=2 cases are recorded (4%) whereas upper extremity incidence is 16% (n=7 cases) and incidence on the trunk is 11% (n=5 cases). In this study, burns were found to be the most common causative agent causing the Marjolin's ulcer. In n=20 cases (46%) burns and thermal burns were found to be the etiologic agent. The other causative agents in the decreasing order of frequency are trauma in n=13 cases (30%), Non-healing ulcers in n=6 cases (14%), Eczema in n=2 cases (4%), osteomyelitis with multiple sinuses in n=1 case (2%) and chronic irritation and itching in 1 case (2%). In this study, the shortest latent period for the development of Marjolin's ulcer after the initial insult is 12 months and the longest latent period is reported as 60 years. The average latent period is 15.25 yrs.

Clinical Incidence of Lymph nodes: In this study of n=43 cases of Marjolin's Ulcer, n=18 patients (40%) did not have clinically palpable lymph nodes whereas n=25 patients (60%) have clinically detectable regional lymph nodes. These lymph nodes were divided into clinically significant nodes (Lymph nodes > 2cms) and clinically Non-significant Lymph nodes (Lymph nodes <2cms). In this prospective study, of n=25 patients with clinically detectable lymph nodes, n=7 (16%) patients had clinically significant lymph nodes and n=18 (41%) patients did not have clinically significant palpable lymph nodes.

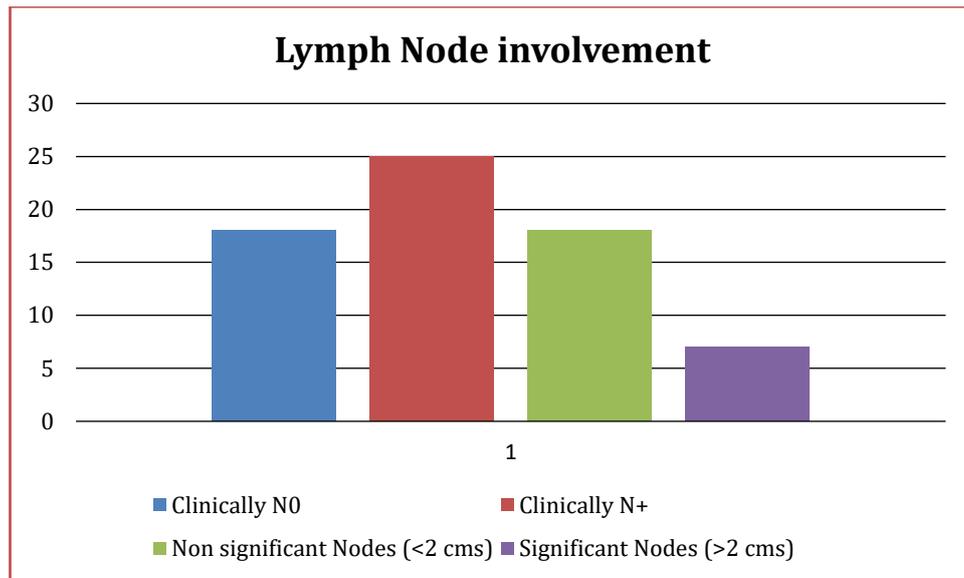


Figure 1: clinical Involvement of lymph nodes in the cases of study

In this study of n=43 patients with Marjolin’s Ulcer, only n=35 patients underwent surgery. Of these n=35 patients, n=25 patients underwent Wide excision (72%) and n=10 patients underwent the procedure in the form of Amputation or Disarticulation due to advanced disease (28%).

Wide Excision (25), only wide excision in n=9 patients, wide excision with lymph node dissection in n=16 patients. 72% Amputation/Disarticulation (n=10), amputation and lymph node dissection in 6 patients, amputation only in n=4 patients 28%. The total number of patients who underwent lymph node dissection was n=22. Among n=22 patients, pathologically positive nodes were n=7. Pathologically node positivity is noted in 31.8% of patients.

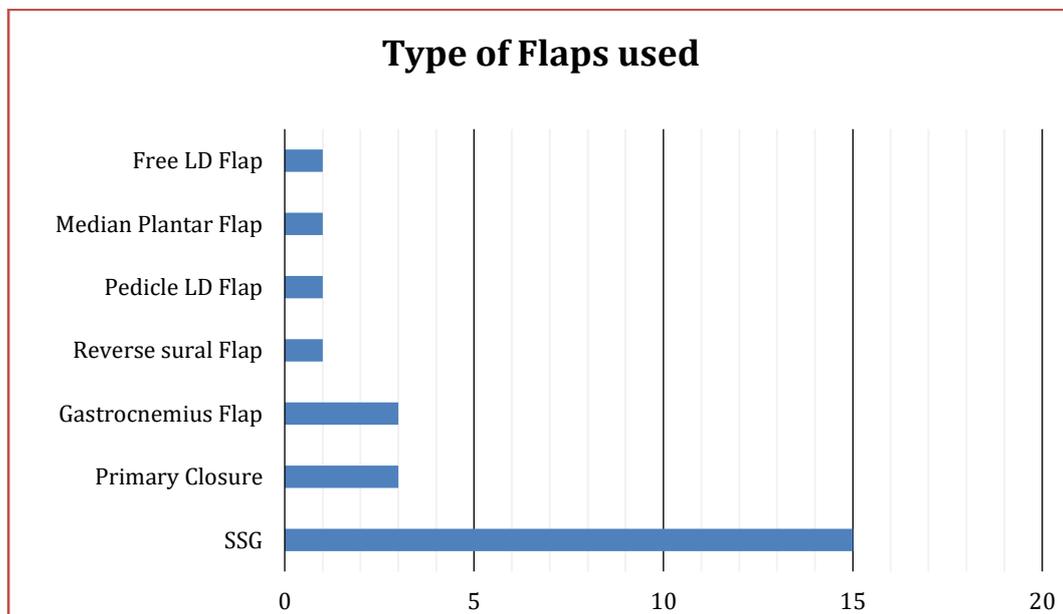


Figure 2: Type of flaps used for wound closure in the cases of study

In the present study, tumor thickness was evaluated for its significance for the development of lymph nodes. The minimum thickness of the tumor recorded is 1cm and the maximum thickness of the tumor recorded is 7cm. Of n=7 patients with positive lymph nodal incidence

n=3 patients were having tumor thickness in the range of 1cm to 2cm and another n=3 patients were found to have tumor thickness in the range of 2.1 cm to 4cm and one patient had a tumor thickness of more than 4cm. In our study tumor thickness was not found to be a significant predictive factor for lymph node metastasis with a p-value of 0.695(not significant) depicted in table 1.

Table 1: Tumor thickness and metastasis

Variable	Metastasis (n=7)	No metastasis (n=25)	Significance of difference
Mean Tumor thickness \pm SD (Range) In cm	2.74 \pm 1.67 (1-6)	2.45 \pm 1.76 (0-7)	t=0.396; p=0.695 (NS)

Latent Period: In our study, an average latent period of 15.25 yrs was recorded to develop Marjolin's Ulcer from the initial insult. The shortest interval is 12 months and the longest interval is 60 years. In our study, the latent period was not significantly associated with the prediction of lymph node metastasis in Marjolin's ulcer with a p-value of 0.718 (not significant) depicted in table 2.

Table 2: Correlation between latent period and metastasis

Variable	Metastasis (n=7)	No metastasis (n=25)	Significance of difference
Mean latent period \pm SD (Range) in years	12.93 \pm 9.07 (1.5-30.0)	14.42 \pm 9.68 (1.0-30.0)	t=0.365; p=0.718 (NS)

Depth of Invasion: In this study of n=32 patients with Marjolin's ulcer who were operated on, and in n=3 patients' tumor was involved up to dermis, in n=13 patient's tumor was involved up to superficial cutis, in n=11 patients' tumor was involving up to muscle and in n=5 patients' bone was involved. None of the patients out of n=3 patients in whom tumor was involved up to dermis had positive lymph nodes. Out of n=13 patients in whom tumor was involved up to superficial cutis, n=3 patients had positive lymph nodes, out of n=11 patients in whom tumor was involved up to muscle n=2 patients had positive lymph nodes and out of n=5 patients in whom bone was involved n=2 patients positive lymph nodes. In our present study, the level of invasion is not found to be a significant predictive factor for the development of lymph node metastasis as the p-value is 0.085 (not significant) depicted in table 3.

Table 3: Extent of Involvement and metastasis

Variable	Metastasis (n=7)	No metastasis (n=25)
Bony involvement	2 (28.6%)	3 (12.0%)
Up to muscles	2 (28.6%)	9 (36.0%)
Up to subcutaneous dermis	0	10 (40.0%)
Superficial dermis	3 (42.9%)	3 (12.0%)

$\chi^2=6.626$; p=0.085 (NS)

Degree of differentiation: In our study of n=32 patients, n=29 patients were found with well-differentiated squamous cell carcinoma whereas n=3 patients were found with moderately differentiated squamous cell carcinoma. None of the patients were detected with poorly differentiated squamous cell carcinoma. All the n=7 patients who were found to have positive

lymph nodes had well-differentiated squamous cell carcinoma only. None of the patients had moderately or poorly differentiated carcinoma. In our study degree of differentiation was evaluated to find out the correlation with the development of lymph nodes and we found that degree of differentiation was not a significant predictive factor for the development of lymph nodes as the p-value is 0.336 (not significant) depicted in table 4.

Table 4: Degree of differentiation and metastasis in the cases of the study

Variable	Metastasis (n=7)	No metastasis (n=25)	Significance of difference
Moderately Differentiated	0 (0%)	3 (12.0%)	$\chi^2=0.927$; p=0.336 (NS)
Well-differentiated	7 (100%)	22 (88.0%)	

Peritumoral Lymphocytic Infiltration: In our study, out of n=32 patients who were operated on and evaluated for lymph nodes, n=9 patients had low (+) infiltration of lymphocytes, n=22 patients had moderate (++) infiltration of lymphocytes and only one patient had high (+++) peritumoral lymphocytic infiltration. Peritumoral Lymphocytic infiltration was evaluated for, whether it is a significant predictive factor for lymph node positivity or not. In our study, we found that this factor is not a significant predictive factor for the development of lymph node metastasis as the p-value is 0.437 (not significant).

Table 5: Peritumoral Lymphocytic Infiltration and metastasis

PM lymphocytic infiltration	Metastasis (n=7)	No metastasis (n=25)	Significance of difference
Low	1 (14.3%)	9 (36.0%)	$\chi^2=1.656$; p=0.437 (NS)
Moderate	6 (85.7%)	15 (60%)	
High	0 (0%)	1 (4.0%)	

Perineural Invasion: In this prospective study of n=32 patients, with n=7 patients having positive lymph nodes, none of the patients had a perineural invasion. Perineural invasion was studied in our study to find out whether it has any significant predictive value in lymph nodal positivity. We found that perineural invasion is not a significant predictive factor for the development of positive lymph nodes.

Etiological Factors: In our study, various etiological factors like burns, trauma, non-healing ulcers, chronic itching and irritation, eczema, and chronic osteomyelitis were studied for, whether they have any predictive value in developing lymph node metastasis. Of n=7 patients who developed lymph node metastasis n=3 patients developed Marjolin's ulcer due to the previous history of burns at the same site, n=2 patients developed due to trauma, and n=2 patients developed due to other etiological factors. In our study etiological factors did not find to be a significant predictive factor for the development of lymph node metastasis as the p-value is 0.825 (not significant).

Table 6: Etiological factors and metastasis

Etiology	Metastasis (n=7)	No metastasis (n=25)	Significance of difference
Burns	3 (42.9%)	10 (40.0%)	$\chi^2=0.385$; p=0.825 (NS)
Trauma	2 (28.6%)	10 (40.0%)	
Others	2 (28.6%)	5 (20.0%)	

In our study of n=32 patients, clinical lymph nodes detected were divided into significant nodes which are more than 2 cm in size, and clinically non-significant which are less than 2cm in size. In our study, all the n=7 patients who had positive lymph nodes were found to have clinically significant lymph nodes preoperatively. Clinically significant lymph nodes were evaluated in our study for, whether they have any significant predictive value in the development of lymph node metastasis and we found in our study that this factor has a significant predictive value in the development of lymph node metastasis p value was <0.001 (significant).

Discussion

Marjolin's ulcer is defined as a tumor arising from a chronic wound, scar, or chronic inflammation. Various studies indicate that Marjolin's ulcers make up 1.2% of all skin cancers. [7-10] The Mean age of the cases was 46.8 years which is lower than the age reported in western countries. Studies in Africa have reported that the mean age of patients with Marjolin's ulcers is lowering and appears to be affecting younger patients over the years. It also appears that the transition time is getting shorter. [11] Marjolin's ulcers in general, develop in younger patients amongst sub-Saharan patients than in those reported from other regions. [11] The male-to-female ratio in this study was 3:2. The two-fold increase in the number of males with Marjolin's ulcers compared to females in the present study is similar to what was reported in other studies. [12-14] Male preponderance in the present study may be due to their increased susceptibility to trauma which, if poorly managed, these lesions have been reported to undergo malignant transformation. Marjolin ulcers generally occur in regions of previous deep burn that healed slowly without skin grafting. Burn scar carcinoma has a propensity for the extremities, specifically to flexion creases of the extremities, where blood supply is decreased and vulnerability to trauma is increased. Marjolin's ulcers have also been reported following other traumatic injuries, leg ulceration, chronic sinuses of osteomyelitis, pressure sores, and discoid lupus erythematosus Two variants of Marjolin's ulcer have been described; an acute form, in which cancer occurs within one year of the injury, and a chronic form in which malignant changes are more than one year from the date of injury. The chronic form is more frequent and malignancy tends to develop slowly, with an average a latency period of 36 years. [15, 16] It has been observed that the latency period is inversely proportional to the patient's age. The reason for this phenomenon is unknown. In keeping with other studies, the lower limb was the most frequent site for Marjolin's ulcers. The anatomical locations reported by Arons et al., [17] Lawrence et al., [18], and Novick et al., [8] show that the average distribution of Marjolin ulcers is 40% in the lower extremity, 30% in the head, and face, 20% in the upper extremity, and 10% in the trunk area.

Marjolin's ulcers have been reported to have an aggressive course and a much greater tendency to metastasize than other types of skin cancer, which makes early diagnosis imperative. In the present study, 60% of patients had lymph nodal presentation at the time of diagnosis and pathologically 31.8% have lymph nodal disease, the rate which is higher than that reported in other studies like K Vern et al., [19] study. High lymph node incidence in our study is because most patients in the present study present late when the disease is already in advanced stages. In developing countries like ours, especially in rural areas with poor living conditions most patients are already in advanced stages of disease at the time of diagnosis of Marjolin's ulcer, which has been proven both in the present study and in literature. [20, 21] In the present study, more than 80% of patients presented late with a large tumor > 2 cm in diameter. Late presentation is common in most developing countries as a result of poverty, ignorance, and poor referral systems in a relatively expensive health care system devoid of meaningful health insurance. [11] Financial problems and delayed referral to tertiary health care facilities were the

most common reasons for late presentation in the present study. Treatment modalities of Marjolin's ulcers include wide local excision, block dissection of the regional nodes, and amputation in advanced lesions of limbs. Wide local excision (surgical margin of at least 2 cm), together with skin grafting primarily or primarily delayed, is usually considered appropriate in the treatment of Marjolin's ulcers. ^[21, 22] Adequate surgical resection is most important to prevent local recurrence and a margin of 2-5 cm has been advocated. ^[11, 22] Frozen sections have been reported to be used for intraoperative diagnosis and evaluation of surgical excision safety margins. However, like in most developing countries, frozen sections are not performed in our center partly because of the lack of facilities for performing frozen sections. Amputation is indicated when wide local excision is not possible due to deep invasion, bone or joint involvement, infection, or hemorrhage, or when excision would cause major functional disability. Regional lymph node dissection is indicated when nodes are clinically palpable. Size of the lesion, thickness of the tumor, latent period, depth of invasion, etiological agent, degree of differentiation, peritumoral infiltration of lymphocytes, and perineural invasion did not have any significant value in predicting the lymph node metastasis. In agreement with other studies, Ochenduszkiewicz U, et al., ^[21] wide excision was commonly done surgical procedure performed in the present study in 25.7% patients' wide excision with lymph node dissection done in 45% patients quite high when compared to other studies amputation with lymph node dissection done in 17% patients only amputation done in 11% patients.

Conclusion

Within the limitations of the current study, it was found that the most common etiological factor is Burns. Males are more commonly affected than females. Squamous cell carcinoma is the most common variant of Marjolin's ulcer. Most of Marjolin's Ulcers are Well-differentiated cancers (90%) of cases. The incidence of lymph node metastasis in this study was 22%. Among all the factors for metastasis lymph node size is a significantly important predictor of metastasis.

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