



## Original Article

# Early Detection of Malignancy using Cytokeratin, HMB45 and Vimentin in OPD Patients with Marjolin's Ulcer

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## Abstract

**Objective:** To study clinico-pathological features of Marjolin's ulcer patients attending surgical clinics and to classify Marjolin's ulcer using Cytokeratin, Vimentin and HMB45 expression.

**Methods:** A cross-sectional clinical correlation study was done on 39 patients who presented to surgical OPD with clinical diagnosis of Marjolin's ulcer arising from chronic skin conditions. Histopathological evaluation and Immunohistochemistry was performed in all cases. Statistics Chi square test and statistical package for social science software (SPSS) version 23. P value <0.05 was taken as statistically significant.

**Results:** Of the total 39 cases majority of the cases were in the age group of 41-50 years (30.76%) with mean age of 47.53 years. M:F ratio was 2:1. Burn was the most common lesion (66.67%) followed by trauma (30.80%) and surgical scar (2.60%). Foot was the most common site of lesion (28.20%) followed by leg (25.64%). Mean time interval taken was 13.12 years. Shortest time interval was 6 years, whereas longest time taken was 25 years. Well differentiated Squamous cell carcinoma was the most common histology type (79.48%) followed by moderately differentiated Squamous cell Carcinoma. One case of sarcomatoid carcinoma is also present (02.56%). 25.64% of cases had lymph node metastasis. Majority of the cases were positive for cytokeratin stain (97.43%) followed by one case positive for both Cytokeratin and Vimentin (2.56%).

**Conclusion:** Burn scar transformation into malignancy was more prominent than other causes. The grade of the tumor and presence of metastasis greatly influence the prognosis of the patient. By application of immunohistochemical stains, we were able to delineate the origin of the malignancy, being epithelial, mesenchymal or melanotic.

**Keywords:** Marjolin's ulcer, Chronic Skin Conditions, Grade, Lymph Node Metastasis.

## Introduction

Marjolin's ulcer reflects malignant degeneration arising within a pre-existing cicatrix or scar.

These chronic, non healing wound, long standing scar or sinus which due to repeated process of healing and non healing and under factors, genetic

or environmental, gets transformed into malignancy and has propensity to metastasize in its course. Marjolin's ulcer is seen in all age groups, sex and races but frequently affects males more than females. These lesions are rare and most commonly found in lower extremity especially the heel and plantar region of foot. In most of the cases, the diagnosis of well differentiated Squamous cell carcinoma is made. Other malignancies that can occur are Basal Cell Carcinoma, Melanoma, Soft tissue sarcoma, combination carcinoma and other neoplasms. It is an aggressive disease that tends to spread widely in its course. Malignant changes resulting in Marjolin's ulcer are seen in burn scars, chronic venous insufficiency ulcers, pressure ulcers, vaccination sites, urinary fistulas, frostbite, snake bite, chronic osteomyelitis, pilonidal sinuses, hydradenitis suppurativa, herpes zoster, skin graft donor site, dog bite, knife wounds and gunshot wounds. The classic triad of nodule formation, induration and ulceration at the scar site, suggests the diagnosis. Any non healing chronic wound, ulcer or sinus of more than three months duration with rolled or inverted wound margins, exuberant or excessive granulation tissue, foul smelling purulence, increase in size, bleeding in contact, crusting over, epithelial pearls and pain with or without regional lymphadenopathy should immediately be brought into notice and thoroughly investigated. In the present study specimens with clinical diagnosis of non healing ulcer (Marjolin's ulcer) in the form of biopsy, excised tissue and amputated specimens with or without lymph nodes were fixed in 10% formalin, processed by routine Paraffin processing technique, 3-4  $\mu\text{m}$  sections were cut by microtome, put on a glass slide then stained by Hemotoxylin and Eosin Stain (H&E) and were studied by two experienced histopathologists. Immunohistochemistry study was done on the cut sections using Cytokeratin (for epithelial malignancy), HMB45 (for Melanoma) and Vimentin (for sarcoma).

### Material and Methods

A cross-sectional clinical correlation study was done on 39 patients with clinical diagnosis of Marjolin's ulcer who presented with complaints of chronic non healing ulcer with/without palpable regional lymphadenopathy were undertaken to study histopathological and immunohistochemical pattern of the lesions that were either biopsied or resected. The specimens were fixed in 10% formalin, processed by routine Paraffin processing technique, 3-4  $\mu\text{m}$  sections were cut by microtome, put on a glass slide then stained by Hemotoxylin and Eosin Stain (H&E) and were studied by two experienced histopathologists. Immunohistochemistry study was done on the cut sections using Cytokeratin (for epithelial malignancy), HMB45 (for Melanoma), Vimentin (for sarcoma). Ethical clearance was obtained from the concerned committee of the administration to carry out the study.

### Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. The results are presented in the form of frequencies, percentages and mean  $\pm$  SD. The Chi-square test was used to compare categorical variables. The p-value < 0.05 was considered significant.

### Results

The present study was conducted with the objective to study patients of Marjolin's ulcer with histopathological and immunohistochemical evaluation. A total of 39 patients were included in the study. The following are the conclusions of the study.

- The average age of presentation was 47.53 years. Majority of patients were in the age group of 41 – 50 years (30.76%). The youngest patient was 18 years old.
- Out of a total of 39 patients, 66.67% were male and 33.33% were females and M:F ratio was 2:1.
- Burn was the most common lesion (66.67%) followed by trauma (30.80%) and surgical scar (2.60%).

- Foot was the most common site of lesion (28.20%) followed by leg (25.64%).
- Mean time interval taken was 13.12 years. Shortest time interval was 6 years, whereas longest time taken was 25 years.
- Well differentiated Squamous cell carcinoma was the most common histology type (79.48%) followed by moderately differentiated Squamous cell carcinoma (17.94%). One case of sarcomatoid carcinoma is also present (02.56%).
- Grade I was most common (79.84%) followed by grade II (17.94%) and grade III (02.56%).
- 25.64% of cases had lymph node metastasis.
- Majority of the cases were positive for cytokeratin stain (97.43%). One case was positive for Cytokeratin as well as Vimentin (2.56%).
- Majority of cases were managed by excision with split skin graft (76.92%) followed by amputation (23.07%).
- Patients with grade II and III are projected to have a bad prognosis (p=0.000 statistically significant).
- Patients with positive lymph node metastasis are projected to have bad prognosis (p=0.000 statistically significant).
- There was no association of age of patient with prognosis of the patient (p>0.05).
- There was no association of gender with prognosis of the patient (p>0.05).
- There was no association of initial skin lesion with prognosis of the patient (p>0.05).
- There was no association of lag phase with prognosis of the patient (p>0.05).
- There was no association of site of lesion with prognosis of the patient (p>0.05).

**Age**

MEAN	47.53 YEARS
RANGE	41-50 YEARS

**Gender**

M:F	2:1
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**Initial Lesion**

BURN	66.67%
TRAUMA	30.80%
SURGICAL SCAR	2.60%

**Location**

FOOT	28.20%
LEG	25.64%
KNEE	17.94%
THIGH	10.25%
ARM	10.25%
CHEST	02.56%
ELBOW	05.56%
FACE	02.56%
SCALP	02.56%

**Time Interval for Transformation into Malignancy**

MEAN	13.12 YEARS
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**Histopathology**

DIAGNOSIS	IHC	NO. OF CASES
SQUAMOUS CELL CARCINOMA	CK+	38(97.43%)
SARCOMATOID CARCINOMA	CK+, VIM+	01 (2.56%)

**Grading**

GRADE I	79.84%
GRADE II	17.94%
GRADE III	2.56%

**Lymph Node & Metastasis**

POSITIVE	25.64%
NEGATIVE	74.36%

**Management**

WIDE EXCISION	76.92%
AMPUTATION	23.07%

Various prognostic markers were analyzed statistically

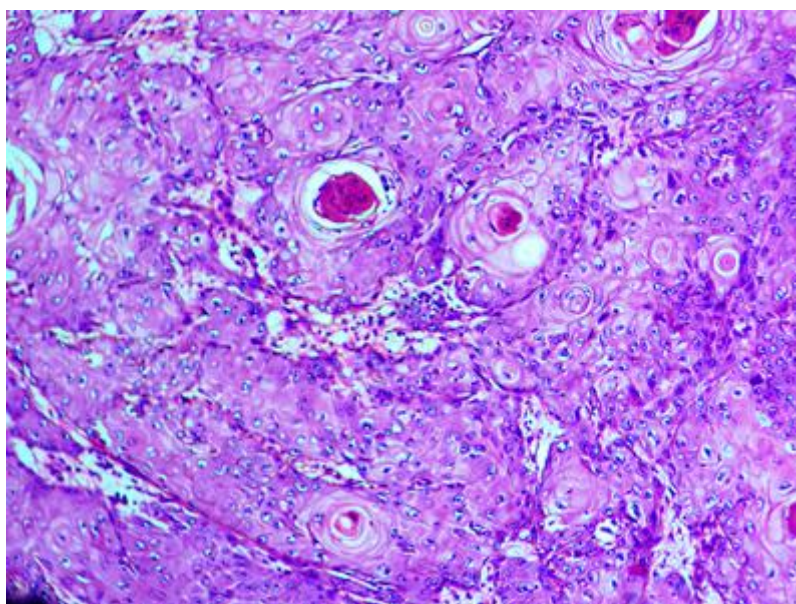
PARAMETERS	PROGNOSTICALLY SIGNIFICANT (p=<0.05)	PROGNOSTICALLY INSIGNIFICANT (p=>0.05)
AGE		✓
GENDER		✓
INITIAL LESION		✓
LOCATION		✓
TIME INTERVAL		✓
GRADING	✓	
LYMPH NODE METASTASIS	✓	

Association of grade of malignancy with prognosis of the patients

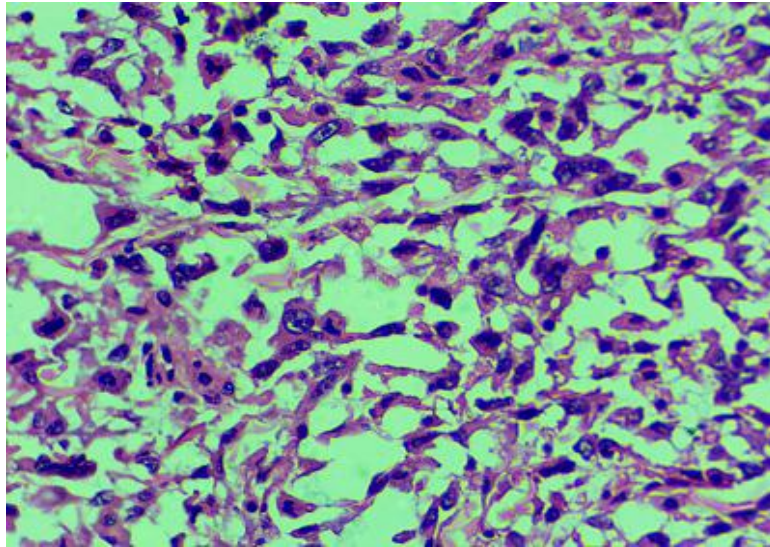
GRADE	No. OF PATIENTS (n=39)	PROGNOSIS				p-VALUE
		GOOD		BAD		
		No.	%	No.	%	
I	31	25	64.10%	06	15.38%	0.000
II	07	00	00	07	17.94%	
III	01	00	00	01	2.56%	
TOTAL	39	25	64.10%	14	35.88%	
$\chi^2$ - 20.12, df- 2, p- 0.0000425633872255081						

Association of lymph node metastasis with prognosis of the patients

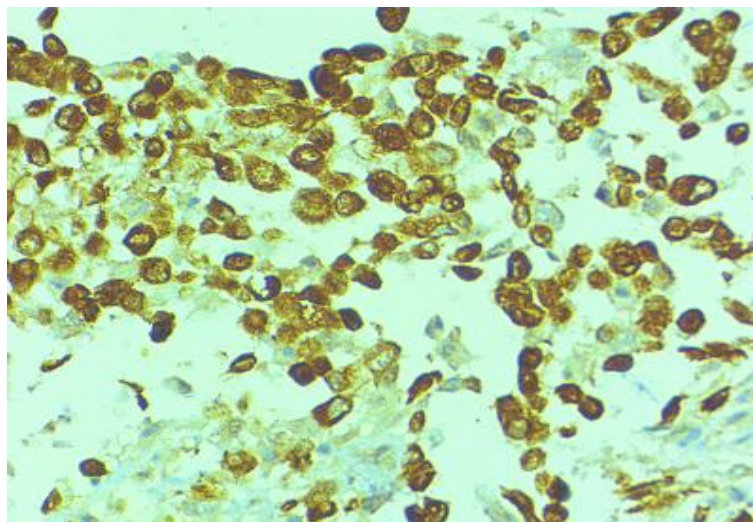
LYMPH NODE METASTASIS	No. OF PATIENTS (n=39)	PROGNOSIS				p-VALUE
		GOOD		BAD		
		No.	%	No.	%	
POSITIVE	10	00	00	10	25.64%	0.000
NEGATIVE	29	25	64.10%	04	10.25%	
TOTAL	39	25	64.10%	14	35.89%	
$\chi^2$ value- 19.43, df-1, p-0.0000104204275648979						



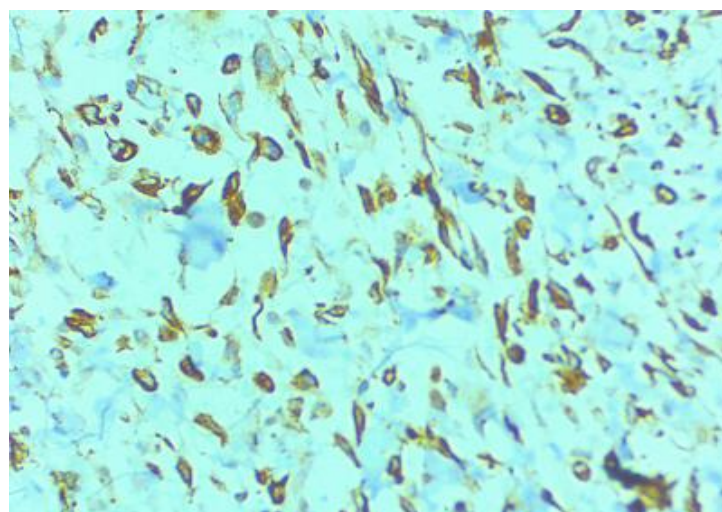
Microphotograph of Marjolin's Ulcer Showing Well Differentiated Squamous Cell Carcinoma (H&E 10x)



**Microphotograph of Marjolin's Ulcer Showing Sarcomatoid Features in poorly Differentiated Squamous Cell Carcinoma (H&E 40x)**



**Microphotograph of Marjolin's Ulcer Showing Poorly Differentiated Squamous Cell Carcinoma with Grade Iii Immunoreactivity with Cytokeratin (40x)**



**Microphotograph of Marjolin's Ulcer Showing Grade Ii Immunoreactivity with Vimentin (Sarcomatoid Areas in Poorly Differentiated Squamous Cell Carcinoma 40x)**

## Discussion

Marjolin's ulcers, actually a misnomer, are non-healing chronic conditions of skin with malignant transformation. Contrary to what was formerly indicated, Marjolin's ulcer no longer refers to malignant neoplasms secondary to burns but include any condition leading to chronic ulcer without healing following burns, trauma, surgical scar, vascular insufficiency, venous stasis, radiation, osteomyelitis, nodular leprosy, pressure, diabetes, bites, vaccination and hemoglobinopathies. These conditions may lead to breach in cutaneous continuity which does not heal with proper epithelisation and with ensuing mutations, transform into malignancy. The exact mechanism by which chronic ulcers undergo transformation is yet unknown but many theories have been put forward. It is seen that most frequent predisposing lesion of Marjolin ulcer was post burn scars that healed slowly without skin grafting<sup>[1]</sup>.

According to Virchow's theory, due to chronic irritation and repeated injury on same tissue incomplete healing takes place and regenerating epithelium is unstable. This unstable epithelium under repeated actions of irritation and regeneration eventually undergoes mutation and malignant change<sup>[2]</sup>.

Friedwald and Rouse came up with the 'co-carcinogenic theory' which proposed an 'initiator phase' and a 'promoter phase' in the development of Marjolin ulcer<sup>[3]</sup>. A carcinogenic stimulus, known as the 'initiator' acts on previously exposed area converting the existing normal cells into dormant neoplastic cells. These dormant cells when acted upon by a carcinogen or a 'promoter' are activated and get converted into uncontrolled actively dividing neoplastic cells. The 'initiator' and the 'promoter' acting alone are not sufficient enough to bring about the development of malignancy. By this theory, a burn may act as an "initiator," while actinic radiation or some other carcinogenic stimulus acting on the burn scar acts as the "promoter".

Ewing depicted a set of criteria to establish the relationship between trauma and development of cancer<sup>[2]</sup>. These criteria are as follows:

- The cancer must arise within the boundaries of the scar or wound.
- Incontrovertible evidence of trauma or the pre-existing ulcer as evidenced by the wound or scar.
- The absence of any precursory or similar neoplasm on the site of the trauma/wound prior to the development of the cancer.
- The histologic variety of the cancer must be compatible with the tissues found in the site of the trauma or scar/wound
- The interval time between the trauma/ulcer and the onset of the cancer must be appropriate. A period of one month has been proposed as the minimum acceptable time between the trauma/ulcer and the onset of the cancer.

These criteria are equally relevant in modern times as a relationship between cancers and pre-existing chronic condition must be established to make a diagnosis of Marjolin ulcer.

## Molecular Pathology

Genetic mechanisms involving HLADR4<sup>[4]</sup>, mutation in p53<sup>[4]</sup> and loss of function mutation in Fas gene mutation in death domain and ligand-binding domain of Fas gene plays an important role in the pathogenesis of burn scar related SCC.

It is well recognized now that deregulation in division of cells and failure of apoptosis results in survival of genetically transformed cells playing an important part in pathogenesis of tumors and Fas-Fas ligand (FasL) system has been recognized as a major pathway for the induction of apoptosis in cells and tissues<sup>[5]</sup>. As such it can be implicated that Fas gene mutation is involved in the development and progression of tumors.

It is suggested that although morphological features are same, SCC in burn scar is more aggressive in nature and carries a poorer prognosis from conventional SCC, and as such the underlying molecular mechanism in the

development of these two entities has to be different.

In a study by Sug Hyung Lee et al, which aimed at exploring genetic basis of Conventional SCC (CSCC) and Burn scar SCC (BSCC) analyzed somatic mutation of Fas gene in these tumors. They detected 3 mis-sense mutations in Fas gene in 3 of 21 patients of BSCC (14.3%), whereas no mutation was seen in Fas gene in 50 patients of CSCC by PCR based mutational analysis of Fas gene. The somatic mutations in BSCC were in FasL binding domain, another in transmembrane domain and other in death domain. Thus molecular mutation of fas, to an extent, promotes neoplastic alteration<sup>[6]</sup>.

None of the theories mentioned above are confident enough in explaining the exact mechanisms involved in pathogenesis of Marjolin's ulcer and so it can only be asserted that multifactorial events and combination of theories best explain the steps paving the way for development of Marjolin's ulcers.

In our study on 39 patients, the **mean age** of patients at diagnosis was about **47.53 years** with an **age range** of **18-72 years**. This can be attributed to people being more physically active in their work in this age group. This is in concordance with the study conducted by Chun Yuan Huang et al<sup>[7]</sup> on 11 patients of burn scar carcinoma, where mean age at diagnosis was 47 years with a range of about 22-63 years and also in another study by Soo Bong Hahn et al<sup>[8]</sup> on 19 patients of Marjolin's ulcer, the mean age group was 50 years and the age range was 25-72 years. It has been observed that younger the patient at the time of injury, the longer the time it takes to undergo the malignant degeneration<sup>[9]</sup>. Latest studies in Africa reveals, that mean age of patient with Marjolin ulcer is lowering and appears to be affecting younger patient over the year 12 to 22 and also the transition time from initial insult to malignant transformation is also getting shorter<sup>[10]</sup>. In the present study, the association of age at diagnosis with prognosis has been shown to be statistically insignificant (**p=0.093**).

In our study, the **M: F** ratio came out to be **2:1** similar to study by Ursula Ochenduszkiewicz et al<sup>[11]</sup> and Vasu Reddy Challa et al<sup>[11]</sup> where M: F ratio was 2:1 and 2.5:1 respectively. Lack of education and ignorance led to mismanagement of the patient and ultimate devastation. Men are more prone to physical injuries owing to exposure to more physically challenging work environment in the rural areas whereas women face negligence and given less importance to their health. As such a simple physical injury such as a burn or trauma (as in our study) or anything, persisting over a period of time, due to ignorance, gets converted into malignancy.

Mohammad Sadegh Fazeli et al<sup>[12]</sup> in his study of 83 cases on chronic skin lesions observed that Marjolin ulcer developed on burn (87.9%), osteomyelitis (2.4%), radiation (2.4%), electrical burn (1.2%), surgical scar (2.4%), pemphigus (1.2%), bite (1.2%) and bed sore (1.2%). As being seen in the literature as well as in our study too, burn scar transformation into malignancy was more prominent than other causes accounting for about **66.67%** of the cases. In a review by Kowal-Vern and Criswell<sup>[13]</sup>, the major risk factor for the development of post burn neoplasm have been healing by secondary intention, non healing wounds and fragile scars that ulcerated and easily got traumatized. Though, burn is the most common initial lesion leading to malignancy, it was found to be statistically insignificant (**p=0.20**).

The lag phase i.e., the time interval between initial lesion to malignancy has been pointed out to be very crucial in progression to malignancy<sup>[14]</sup>. 'Acute' Marjolin ulcers have also been seen within one year of burn scar, which is rare, and have been diagnosed as early as 6 weeks after injury<sup>[15]</sup>. Urszula Ochenduszkiewicz<sup>[11]</sup> et al in their study on 449 patients with malignant neoplasm arising in scars, the time interval for transformation into malignancy was 36 years whereas in a study by Maria G Onesti et al<sup>[16]</sup> on 13 patients with chronic ulcers the mean time interval was 9 years. In our study, the **mean time**

**interval is 13.12 years.** The impact of lag phase on the outcome of the disease has not shown to be statistically significant (**p=0.36**) in the study. This result may be due to the fact that the duration of our study was only one year.

Anatomic location seemed to play a role in the metastatic potential of the tumor. Those lesions of the lower extremities are at a higher risk than other locations. Lower extremity was the most common area of presentation of lesion in our study in which **foot** was the **most common site (30%)**. Similar pattern was found in study conducted by Mohammad Sadegh Fazeli et al (2013) (n=83) where foot was the most common site of presentation (49.4%). Treves and Pack in 1930 estimated incidence figure according to site of origin which were 38% in lower extremity, 22% in upper extremities, 30% head and face and 10% trunk<sup>[4]</sup>. Novick et al<sup>[2]</sup>, in a review of 46 patients from M.D. Anderson Hospital, reported a metastatic rate from lower extremity lesions that were twice as high as rates in any other part of the body. It has also been observed in some studies that Marjolin's ulcer have been shown to behave differently, depending on their location. SCC arising on burn scar is mostly localized on extremities (60%) spread along the flexion creases with reduced blood supply and increased trauma than on head and face (30%) followed by that on trunk (10%). The association of site of lesion with prognosis of the disease has not shown to be statistically significant (**p=0.44**).

Histological variation includes well differentiated Squamous cell carcinoma (SCC) (most common) followed by differentiation not reported SCC, moderately differentiated SCC, Basal Cell carcinoma, poorly differentiated SCC, Verrucous carcinoma, mucoepidermoid carcinoma, Melanoma<sup>[17]</sup>, Soft tissue sarcoma (malignant fibrohistiocytic sarcoma, leiomyosarcoma, dermatofibroma protuberans, fibrosarcoma, liposarcoma) has been reported<sup>[13]</sup>. Squamous cell carcinoma is most commonly seen in burn scar where as Basal cell carcinoma is most common in radiation burns<sup>[2]</sup>. Basal cell carcinoma rarely

occurs in lower extremities and is mainly limited to face neck and scalp area. Among the soft tissue tumors, **fibrosarcoma** is the most **common type** of sarcoma in the **scar** due to precursor cells of fibrosarcoma (fibroblasts) exist in abundance in the skin scar tissue<sup>[18]</sup>. Malignant fibrous **histiocytoma** is the most common **soft tissue sarcoma**<sup>[19]</sup>. Occasionally mixed histology variant is also seen like a mix of basal cell carcinoma and squamous cell carcinoma (basosquamous variant)<sup>[2]</sup> and a mixed variant of squamous cells and melanoma have also been reported within the same lesion. **Squamous cell carcinoma** was the most common histopathological diagnosis in the present study (**97.78%**). Thomas Giblin et al (1964) and Mohammad Sadegh Fazeli et al (2013) in their study had histological diagnosis of squamous cell carcinoma in 85.71% and 81.9% of the patients respectively.

Wide excision with a split skin graft is the most popular choice of management of the cutaneous malignancy followed by amputation. In our study, about **76.92%** of the patients underwent wide **excision** and about **23.07%** of patients had amputation. Similar pattern of management of the patients were seen in studies conducted by Maria G Onesti et al<sup>[16]</sup> and Chun Yuan Huang et al<sup>[7]</sup> with wide excision as the popular choice for management. Study conducted by Soo Bong Hahn et al where 19 patients were taken up, amputation was preferred (52.63%) followed by wide excision (42.10%) and radiotherapy was also given (15.78%).

Of great importance are the grade of the tumor and metastasis to local lymph nodes and that turned out to have a high statistically significant value in our study (**p=0.000**). The presence of metastasis and grade of the tumor greatly influence the prognosis of the patient. Grade of tumor greatly determine the prognosis and outcome of disease. Grade I tumor are the most common tumors which are less likely to spread and was slower, if it did spread whereas Grade II (moderately differentiated) and Grade III (poorly differentiated) Marjolin's ulcer tends to recur and



metastasize to the regional lymph nodes. In our study, about **79.48% of cases** had **grade I** tumor, **17.94%** had **grade II** tumor and **2.56%** had **grade III** tumor. Similar observations were made by Soo Bong Hahn et al<sup>[8]</sup> on 19 patients with Marjolin's ulcer, where about 94.73% of patients had grade I tumor, and 5.26% had grade III tumor. Most of the lesions are well differentiated by nature, but due to its aggressiveness, Marjolin's ulcer carries a poor prognosis. Compared to other causes of squamous cell carcinomas (CSCC), metastasis occur in up to **3% of cases**, whereas metastases in malignancies due to Marjolin's ulcer are found in up to **27% of patients**<sup>[20]</sup>. The 5-year survival rate after metastasis is 43% to 58%<sup>[21]</sup>. As such the earlier the malignancy is diagnosed, before it has changed its grade and has metastasized, the more proper is the management and fairer is the prognosis. In our study, about **25.64%** of patients had **lymph node metastases**. Similar results were seen in studies conducted by Julius Smith et al (2001) and Vasu Reddy Challa et al (2014) where palpable lymph node was found to be in 30% and 35.71% respectively with SCC metastasis. A highly statistically significant value was obtained while observing the impact of lymph node metastasis on the prognosis of the patient (**p=0.000**). Thus early detection of the cancer is very important for proper management of the patient.

Further, on application of immunohistochemical stains, we were able to delineate the origin of the malignancy, being epithelial, mesenchymal or melanotic where **97.43%** of cases were positive for Cytokeratin and one case stained positive for cytokeratin as well as Vimentin (**02.56%**).

### Conclusion

To conclude, time plays a very crucial role in defining the course of Marjolin's ulcer so any chronic wound or ulcer persisting for more than three months should be given great attention and is to be inspected at regular intervals and if possible biopsied. Marjolin's ulcers are highly aggressive malignancies and therefore early

detection and aggressive management of the patient results in good prognosis saving the patient's life and reducing the emotional burden on the patient's family.

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ORIGINAL SKIN LESION	HISTOLOGY OF MALIGNANT TRANSFORMATION	IHC
TRAUMA	MIXED	CK, VI,
BURN	WD SCC	CK
TRAUMA	WD SCC	CK
Sx FILARIA	WD SCC	CK
BURN	WD SCC	CK
TRAUMA	WDSCC	CK
BURN	MD SCC	CK
TRAUMA	WD SCC	CK
BURN	MD SCC	CK
BURN	WD SCC	CK
BURN	WD SCC	CK
BURN	MD SCC	CK
BURN	WD SCC	CK
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TRAUMA	WD SCC	CK
BURN	MD SCC	CK
BURN	WD SCC	CK