MALIGNANT TRANFORMATION OF CHRONIC VENOUS LEG ULCERS: CLINICAL, PATHOGENETIC AND THERAPEUTIC ASPECTS

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Summary

Chronic venous leg ulcers (CVLUs) are a common dermatologic condition with significant morbidity, particularly in the elderly. While malignancy arising in the context of these ulcers is rare, the clinical and prognostic implications are profound. The most frequently associated skin cancer is squamous cell carcinoma (SCC), followed by basal cell carcinoma (BCC). These malignancies may either originate de novo or result from chronic inflammation and tissue damage in long-standing ulcers—a transformation classically referred to as Marjolin's ulcer. The clinical differentiation between a benign chronic ulcer and one undergoing malignant transformation is often challenging due to overlapping features. Delayed diagnosis is common, often leading to advanced-stage presentations with poor outcomes, including amputation or metastatic spread. This review provides a comprehensive overview of the pathophysiologic mechanisms involved in malignant degeneration, including the role of chronic inflammation, impaired wound healing, local immunosuppression, and molecular changes such as overexpression of matrix metalloproteinases and proto-oncogenes. It also explores diagnostic strategies, with emphasis on the role of histopathological examination and clinical red flags, as well as current therapeutic options—ranging from surgical excision to adjuvant therapies in inoperable cases. Given the potentially aggressive nature of SCC arising from CVLUs, early suspicion and timely biopsy of atypical ulcers are crucial for improving patient prognosis and quality of life.

Keywords: *chronic venous leg ulcer; squamous cell carcinoma; basal cell carcinoma; Marjolin's ulcer; malig-nant transformation; chronic inflammation; histopathology; wound healing; skin cancer.*

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Introduction

Skin cancers associated with chronic leg ulcers (CLUs) are often underrecognized and may either result from the malignant transformation of CLUs, typically evolving into squamous cell carcinoma (SCC), or develop independently and resemble CLUs. The clinical presentation of skin cancers related to CLUs can vary widely, from seemingly benign lesions to clearly exophytic growths. Marjolin's ulcer generally arises after an extended period of having a chronic leg ulcer. Consequently, guidelines and experts advocate for the biopsy of

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atypical CLUs to ensure proper diagnosis and to assess for any inappropriate clinical changes.

In this review we aimed to bring to light information regarding the possibility of malignant degeneration in chronic venous ulcers, given the widespread occurrence of this condition.

Malignant degeneration of chronic venous ulcers is infrequent. Some examples from the literature reflect the rarity of this complication, in the study conducted by Fischerman et al [3], on 6500 patients with chronic venous ulcers, only one case with malignant degeneration was detected. Also, in the study conducted by Nobl, one patient out of 200 was diagnosed with skin carcinoma [4].

It is very important to state that many ulcerated skin tumors can mimic a venous ulcer and vice versa. A rigorous clinical evaluation is necessary and when we are in front of a patient with chronic venous insufficiency (CVI) C6 CEAP stage with ulcers that do not respond to conventional therapies, we must consider the possibility of malignant degeneration, considering the aggressive evolution of these types of tumors, the vast majority being diagnosed late, leading to an unfavorable prognosis, with the risk of amputation of the affected limb or the risk of systemic dissemination [5].

Epidemiology

The prevalence of skin tumors arising on chronic venous ulcers is unknown. In terms of histological subtype, the most common is squamous cell carcinoma, in second place being basal cell carcinoma. In the study conducted by Combemae et al, which included the largest series of skin carcinomas arising on chronic venous ulcer, 97,6 % (83 out of 85) were SCC and 2,4% were BCC. Cases of malignant melanoma, lymphoma or sarcoma developed on chronic venous ulcers have also been reported [5,6].

Pathophysiology of Chronic Ulcers

The Malignant Potential and Pathogenetic Mechanisms in Chronic Ulcers

There are several hypotheses regarding the mechanism of malignant transformation in chronic leg ulcers, but the exact aetiology remains controversial and poorly understood [7,8].

Arons et al proposed a progression from acanthosis, an increased thickness of the prickle cell layer of skin, to basal cell hyperplasia and atypia, then pseudoepitheliomatous hyperplasia, and eventually epidermoid carcinoma [9].

Gan et al proposed that infection stimulated dormant neoplastic cells to develop into cutaneous malignancy [8].

Fleming et al surmised that local deposition of toxins released from chronically inflamed tissue would induce malignant mutation of cells [10].

Both Arons et al and Fleming et al proposed that repetitive mechanical deposition of epidermal cells into the dermal layer would cause a foreign body reaction and cellular alteration resulting in a granulomatous degeneration similar to the development of an inclusion cyst literature [9,10].

In comparison to healthy skin or acute wounds, Ouahes et al. found that chronic wounds had enhanced expression levels of proto-oncogenes, which are known to be responsible for cellular proliferation [11].

Giving all the above, the most important risk factors presumed to be responsible of this process include: exposure to cytotoxic byproducts of chronic inflammation, an impaired mitotic cycle and epidermal implantation resulting in a dermal foreign body reaction [8].

In regard to the mitotic cycle, Ch'ng et al delineated the role of peri-wound mast cells as catalysts for malignant development. These agents interrupt the normal cutaneous cell cycle, and protease release can also cause stromal disruption that allows endothelial migration of cancerous cells. Mast cell mediators (fibroblast growth factor-2 and interleukin-8) stimulate mitosis of dormant malignant cells. Mast cells stimulate the necessary angiogenesis for tumor cells to rise in healthy tissues [12].

This microenvironment perpetuates a persistent degradation of extracellular matrix proteins. (TNF) α and β, in addition to PDGF, raise mitosis rate and stimulate extracellular matrix production. To acquire complete wound healing, is necessary an increase of inhibitors of MMP (TIMP1, TIMP-2) [13,14,15].

It is well known that in chronic leg ulcers, wound healing is affected because of an imbalance of regeneration and degeneration of the extracellular matrix. This vicious circle is maintained by an intrinsic dysfunction of the granulocytes with the disturbed release of growth factors. This phenomenon induces the decrease of platelet derived growth factor (PDGF) levels and an increase of matrix-metalloproteinases (MMP) level. Persistently high levels of MMP lead to the chronicity of a wound [16].

This prolonged inflammatory reaction, is further caused by bacterial contamination and repetitive painless tissue damaging. Immigrated granulocytes stimulated by bacterial endotoxins, fragments of extracellular matrix and cellular detritus secrete a mixture of cytokines and growth factors. In particular, TNFα and interleukin 1β (IL 1β) lead to sustained chronic inflammation. In this (micro)environment of chronic inflammation, stimulated mitosis, degradation and regeneration of extracellular matrix lies the cornerstone of abnormal cell proliferation. Therefore, inflammation is a key driver in development of cancer in chronic wounds. This is emphasized by several studies reporting small but significant lower risk of SCC in people taking nonsteroidal anti-inflammatory drugs, e.g., aspirin or ibuprofen [17,18].

The most critical phase in wound healing is the reepithelialisation, when keratinocytes initiate hyperproliferation and migration on the wound bed. Alterations in keratinocytes during re-epithelialization are rather similar to those that occur during cancer initiation and metastasis, with the crucial difference being that the hyperproliferative behaviour is (normally) self-limiting in case of wound repair [19].

Potentially direct carcinogenic effects of toxins generated by necrotic tissue are highlighted, along with the imbalance of cytokines in the microenvironment of chronic wounds. Additionally, it is believed that areas of chronic scar tissue lose immunologically active cells, such as dendritic cells. Malignant cells escape immune detection and become more aggressive and prone to metastasis [20].

Chronic leg ulcers as well as non-ulcerated skin may present similar risk factors, for example, the influence of sunlight, found especially in women. In response to UV-B radiation exposure, mast cells degranulate, resulting in neuropeptide and protease release into the surrounding tissues, as a defence mechanism [21]; the excess of proteases, if they cannot be controlled by specific inhibitors, affects the homeostasis of the skin, therefore the ability to regulate inflammation, immune response, chemotaxis, cytokine expression, vascular function, tissue repair and apoptosis will be completely altered [22].

Reduction of immune defence, as often observed in diabetic patients, can also favour malignant transformation [23].

Another important risk factor is venous stasis also considered an inducer of malignant transformation, especially for the long-lasting non-healing leg ulcers. In these cases, the malignant change in VLU is directly related with the duration of the ulcer [24].

The multiple faces of the Malignant Venous Ulcers

Primary malignant ulcer or secondary malignancy?

The criteria for differentiating primary tumors from secondary ones are not clear, most studies are based on the history of patients with advanced CVI with long-term ulcerations [25,26].

In the study conducted by Silverman et al, the primary malignancies were the lesions that debuted less than 3 years prior to the biopsy [25].

Lidell K suggested that skin changes caused by venous stasis should be present for at least 2-3 years to determine malignant degeneration [26].

In the study led by Yang et al, 75% of the patients with venous ulcers responded to conventional therapy in a time interval between 3-6 months, which is why the biopsies were limited only to cases of recurrent chronic ulcers that did not respond to conventional therapies after that time interval and in those that presented characteristics that might suggest malignancy (irregular nodular appearance of the ulcer surface, raised or rolled edge, firm surrounding skin with lipodermatosclerosis or

raised granulation tissue in an area of the ulcer base). Malignant ulcerations had a latency period for development between 20 weeks and 7.2 years [27]. In other studies, the latency period was between 11 and 75 years, with an average of 30 to 35 years [28-30]. Cases of acute Marjolin ulcer have also been reported in the literature, 6 weeks after injury [31]. The younger the patient, the longer the latency period for malignant degeneration [32].

Scuamocellular Carcinoma in Chronic Ulcers

Squamous cell carcinoma is the most common histopathological form of skin malig-nancy that can occur in the context of venous ulcers [25,33]

In the study led by Baldursson et al: from a total of 10,913 patients with CVI, 23 cases of sSCC were diagnosed, of which 17 were categorized as secondary malignancies. On this basis, it was concluded that the risk of malignant degeneration in this category of patients is 5 times higher than in the general population [33].

In the study led by Silverman et al in 14 cases of SCC located in the lower limbs, 4 patients had a history of advanced CVI [25].

Basocellular Carcinoma in Chronic Ulcers

Although basal cell carcinoma is the most common nonmelanoma skin tumor, its association with chronic venous ulcer is rare [34].

Most of the BCC cases reported in the literature are based on patients with a medical history of chronic venous ulcers that do not respond properly to topical treatments, subsequently presenting clinical characteristics suggestive of malignancy (increase in size, elevated anfractuous margins, the presence of an abnormal hyperkeratotic granulation tissue, bleeding, pain) [24,34,35].

Other Types of Tumours in Chronic Ulcers

Angiosarcoma is a very aggressive form of cancer which likewise can be associated with chronic venous ulcers [36].

The majority of cases of lower leg ulcerating malignant melanoma reported in the literature involve acrolentiginous melanoma that was incorrectly diagnosed as diabetic foot ulcers. On the other hand, malignant melanoma has frequently been reported to occur on chronic scars, supporting the theory that it can develop in open wounds over time [37].

In a case study, Gan et al. describe how a chronic heel pressure ulcer gave rise to a malignant melanoma. Since the ulcer had been present for 18 years prior to the tumor's discovery, a malignant transformation into melanoma might be assumed even if no prior histological examinations of the ulcer have been disclosed. Such modest growth would be highly unusual for a malignant melanoma [38].

There has been reported in literature only one case of pigmented malignant melanoma developed on a chronic venous ulcer, but given the rarity of this association it was probably a chance occurance [39].

When suspicion of a malignant tumor in a chronic scar arises, additional rare tumour entities must be taken into account for diagnostic purposes, including Merkel cell carcinoma, lymphoma, Kaposi's sarcoma, leiomyosarcoma, or malignant fibrous histiocytoma [40-43].

Diagnosis in Malignant Ulcers

Anamnestic Diagnosis Criteria

For the moment, there is currently no agreed standard or clinical *guidelines* for the identification of MU, but in the past decade, considerable efforts have been made on overcoming this problem [44,45].

In this purpose, Ju Tian et al, has proposed in a recent study a concise algorithm, meant to speed up the *diagnostic* process and reduce errors. The diagram indicates the importance of recognizing the risk factors, the atypical features and establish whether is mandatory to perform a biopsy or adopt a watch-and-wait approach [46].

In a similar way, Catherine N Tchanque-Fossuo et al, suggested a flowchart for the management of venous leg ulcers, pointing out the importance of an available step-by step diagnostic and treatment guide [47].

There is consensus in the literature that tissue biopsy is the gold standard in order to obtain *diagnostic certainty* of MU [48].

However, as clinicians, the most important aspect when starting to investigate an ulcer, is an inquiry into the patient's detailed general history, followed by a thorough and systematic clinical examination. The aim is to achieve a complete, correct and early diagnosis, in order to avoid unnecessary investigations or treatments, that in most of the cases leads to underdiagnosis [49,50].

As a general rule, it is most useful to outlook for a back-to-basics concept. Patient anamnesis, when *performed* correctly, can bring to the surface important details that otherwise might be overlooked [51]. For example, it can identify important risk factors such as history of burns, venous disease, diabetes, deep vein thrombosis, trauma/surgical procedures, obesity, multiple pregnancies, intermittent claudication, chronic osteomyelitis, radiation induced wounds, pressure ulcers [5,52,53].

Clinical Diagnosis Criteria

A well conducted clinical examination of an ulcer has to start by describing the site, size and shape of the wound, colour of the base, shape of the border, depth of the ulcer and structure of the discharge [54].

When the ulcer takes a long time to heal and the patient relapses, it should be assumed that the ulcer is malignant, especially if the secretions increase, smell bad, or are likely to contain blood [54].

The "BBEDDS" mnemonic is a very helpful and succinct method for inspecting, characterizing, and differentiating an ulcer [55]:

- **B** - Basics – site, size, shape;
- **B** - Base – colour (red, pink, white, black);
- **E** - Edge: (Flat, sloping (venous); Punched-out (arterial/neuropathic); arterial = pain, neuropathic = no pain; Under-mined (pressure sores); Rolled edge (basal cell carcinoma); Everted edge (squamous cell carcinoma);
- **D** - Depth – measure height (mm);
- **D** - Discharge – serous (clear), blood, purulent;
- **S** - Surroundings – skin changes, colour, scars;

The presence of the following characteristics should prompt a suspicion of cancerous ulcers:

Atypical location

Non-malignant ulcers, such as venous stasis, arterial, or neuropathic ulcers, are well-described, and it's important to be aware with the typical anatomical places where these wounds usually originate in order to spot anomalies. In the gaiter region of the lower leg (from the malleoli to the mid-calf), venous ulcers are frequently encountered; Typically, bony prominences are where the ischemic or neuropathic ulcers develop, while calf ulcers are not frequently associated with vascular pathology and should raise suspicion for vasculitic, infectious, or malignant aetiologies [56,57].

However, because of their potential to develop into malignancy, chronic venous stasis ulcers in the gaiter region that are resistant to routine therapies should be further examined for malignancy [58].

Atypical appearance

In addition to its location, an ulcer's appearance offers crucial clinical hints about its genesis. Long-standing ulcers with abnormally elevated or rolled wound edges, changes in shape or size, and abundant granulation tissue in the ulcer base with or without expansion beyond the ulcer margins are suggestive of malignancy [56,59].

Malodor, uneven wound boundaries, and escalating pain intensity are additional, less specific indicators of malignant ulcers [60].

Histopathological Diagnostic

Most authors recommend performing multiple biopsies on different areas of the ulcer to escape the risk of false-negative single biopsies. Sometimes, dysplastic changes occur only in one edge of the ulcer, which should not be missed by biopsy. A minimum of two biopsies, taken from different areas of the wound, ideally the wound edge and wound bed, should be performed [49,61,62].

Biopsies can either be in the form of a punch biopsy (3-4 mm), shave biopsy or deep wedge-shaped incisional biopsy. Nevertheless, some authors still consider this procedure a high risk in

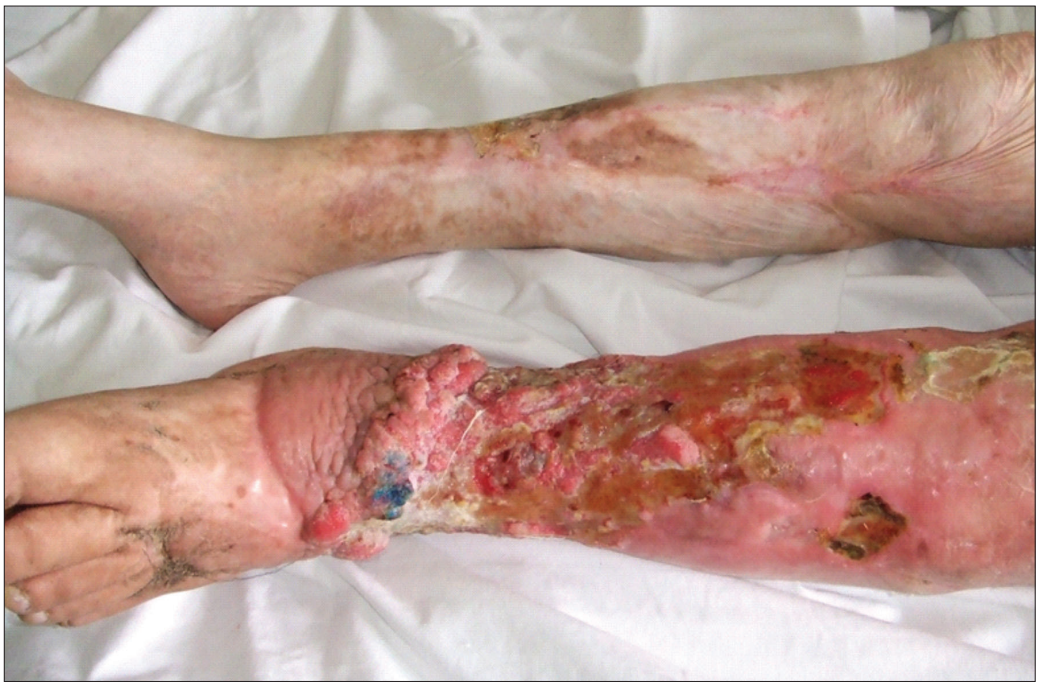

Figure 1. Well-differentiated squamous cell carcinoma arising in a chronic venous ulcer on the anteromedial aspect of the left lower limb in a patient with recurrent venous ulcer, unresponsive to conventional therapies with several red flag signs: irregular raised growth located on the lower edge, irregular nodular appearance of the ulcer surface, firm surrounding skin with lipodermatosclerosis (case report of the C.F Iași Clinical Hospital's Dermatology Clinic, with considerations D.E. Brănișteanu).

patients affected by leg ulcers (LUs) and prefer reserving it for selected cases [63].

The subsequent steps after histologic confirmation of malignancy include tumor staging. Computed tomography (CT) scan and MRI may provide the degree of soft tissue involvement; however, these are not required for diagnosis [29].

Clinical examination of regional lymph node basins is necessary. The regional lymph nodes can be staged clinically or radiologically. Further, if a diagnosis of MU is made and the patient is clinically node-negative, a sentinel lymph node biopsy is a reasonable consideration. Because of the high rate of MU metastasis, a distant metastatic workup with a positron emission tomography scan, chest CT scan, abdominal ultrasound, and brain CT scan should be obtained [64,65].

Immunohistochemistry

Immunohistochemistry aimed at detecting metalloproteinase expression seems to be able to facilitate the differentiation of malignant and non-malignant wounds. In a small study with 9 SCC patients, the authors suggested that epithelial expression of MMP-7, MMP-12, and MMP-13 provided a diagnostic clue for distinguishing SCCs from non-malignant wounds [66].

Differential Diagnosis (DDx)

Considering the clinical aspect and the possibility of malignant degeneration of the venous ulcer, the diagnoses that we must consider are: venous, arterial or mixed ulcer, squamous cell carcinoma, basal cell carcinoma, angiosarcoma, Merkel cell carcinoma, lymphoma, Kaposi's sarcoma, leiomyosarcoma, malignant fibrous histiocytoma and pyoderma gangrenosum [67].

Treatment Options in Malignant Ulcers

Surgical Treatment

Surgery is the primary modality of therapy for malignant ulcers. A wide array of non-

surgical treatment modalities has entered in clinical practice over the years, but surgical excision remains the first line of therapy for high-risk lesions. Surgical treatment includes standard excision, histologically controlled excision, known as Mohs micrographic surgery (MMS), curettage and electrodessication (C&E) [68].

For BCCs, non-surgical treatment methods include cryotherapy, topical therapy(eg Imiquimod), photodynamic therapy or radiation therapy [69].

For CSCs, topical and photodynamic therapies are not recommended, mostly due to lack of available data. It is generally accepted that the majority of cSCCs are successfully treated with standard treatment modalities, such as surgical excision [70].

On the other hand, there is a subset of tumors that have a higher risk of local recurrence, perineural dissemination, and even nodal or distant metastasis, especially in immunocompromised people [71].

Recurrence rate, function preservation, patient expectations, and potential side effects must all be taken into account while deciding on the best treatment strategy [72].

For high-risk lesions larger than 2 cm in clinical diameter or with higher histologic grade, at least 6-mm margins were required to achieve 95% clearance rates [73].

The NCCN guidelines recommend 4- to 6-mm clinical margins for routine excision of low-risk cSCC [74].

Non Surgical Treatment

In the case of low risk tumors, nonsurgical therapies may be considered when surgical therapy is not feasible or desired with the understanding that the cure rate may be inferior [75].

Photodynamic therapy (PDT) is a two-part procedure that involves applying a photosensitizer topically, usually 5-aminolevulinic acid or methylaminolevulinate, and then incubating for one to several hours under light irradiation, usually with a blue, red, or broadband light source [76].

The effectiveness of PDT or laser therapy in the treatment of cSCC is not currently supported by the data that are now available. PDT may be used as an adjuvant modality in combination with curettage and surgery for invasive cSCC in high-risk patients like solid organ transplant recipients (SOTRs), and it may be used to spare tissue, according to limited case report and case series data. However, the precise contribution of PDT to observed outcomes in such combination approaches is unknown. PDT can be utilized in numerous sessions when combined with surgery [77-79].

At this time, the data provided do not support the use of topical treatments in the treatment of cSCC. Few case reports and two short case series have been published, examining the use of topical imiquimod or 5-fluorouracil (5-FU) for cSCC (excluding SCC in situ) [75].

Primary radiation therapy can be used in specific circumstances where surgery is not feasible, is not advised, or is not desired by the patient even though surgery is still the first-line and most effective treatment for cSCC. With the understanding that the cure rates may be reduced, primary or adjuvant radiation therapy is a useful treatment choice for some patients with cSCC, resulting in good tumor control and cosmesis. Radiation therapy may be more effective on cancers that are thinner and smaller [80-82].

Cryosurgery should only be considered for low-risk lesions when more effective therapies are contraindicated or unfeasible due to the absence of histologic margin control with this procedure and the known potential for subclinical expansion of cSCC [75].

Prognostic factors and follow-up

As in all malignant pathologies, the prognosis depends on the histological type, histological differentiation grade, the stage of the disease, the involvement of regional lymph nodes and the presence of distant metastases. [25]

According to Baldurson [83] the most important prognostic factor in the case of these malignancies would be the degree of histological differentiation, in his study and that of other authors [25] the mortality in the case of GIII tumors was 100%, GII 60% and GI 0%.

It is important to state that SCC developed on chronic venous ulcers is much more aggressive and metastasizes much earlier than primary SCC [84]. Contrary to SCC, the prognosis of BCC arising on chronic venous ulcer is favourable [25].

Conclusions and discussions

Malignant degeneration of chronic venous ulcers is infrequent. The most common skin tumor that can develop on a chronic venous ulcer is squamous cell carcinoma, in second place being basal cell carcinoma [3-5].

There are several hypotheses regarding the mechanism of malignant transformation in chronic ulcers, but the exact aetiology remains controversial and poorly understood [7,8].

It is very important to state that many ulcerated skin tumors can mimic a venous ulcer and vice versa. Therefore, the most important aspect when starting to investigate a venous ulcer that do not respond to conventional therapies, is an inquiry into the patient's detailed general history, followed by a thorough and systematic clinical examination. The aim is to achieve a complete, correct and early diagnosis, considering the aggressive evolution of these types of tumors, the vast majority being diagnosed late, leading to an unfavorable prognosis, with the risk of amputation of the affected limb or the risk of systemic dissemination [5,49,50].

The criteria for differentiating primary tumors from secondary ones are not clear, most studies are based on the history of patients with advanced CVI with long-term ulcerations that do not respond to conventional therapies [25,26].

According to the literature, squamous cell carcinoma and basal cell carcinoma have to be included in diagnostic considerations when suspicion of a malignant tumour in a chronic venous ulcer arouses. Other rare tumour entities, such as angiosarcoma or malignant melanoma could be considered [5,6,36,39].

A well conducted clinical examination of an ulcer has to start by describing the site, size and shape of the wound, colour of the base, shape of the border, depth of the ulcer and structure of the discharge [54].

There is consensus in the literature that tissue biopsy is the gold standard in order to obtain *diagnostic certainty* of MU. Most authors recommend performing multiple biopsies on different areas of the ulcer to escape the risk of false-negative single biopsies. Nevertheless, some authors still consider this procedure a high risk in patients affected by leg ulcers (LUs) and prefer reserving it for selected cases (recurrent chronic ulcers that did not respond to conventional therapies or the presence of characteristics that might suggest malignancy (irregular nodular appearance of the ulcer surface, raised or rolled edge, firm surrounding skin with lipodermatosclerosis or raised granulation tissue in an area of the ulcer base) [49,62].

The subsequent steps after histologic confirmation of malignancy include tumor staging, which can be made clinically or radiologically for the lymph node invasion and for the distant metastases, PET scan and CT should be considered [64,65].

Surgery is the primary modality of therapy for malignant ulcers. A wide array of non-surgical treatment modalities have entered in clinical practice over the years (PDT-in cSCC, topical therapies-in BCC, radiation therapy- used in special situations in which surgery is not feasible, contraindicated, or not preferred by the patient, or cryotherapy- only for low-risk lesions, when more effective therapies are contraindicated or impractical), but surgical excision remains the first line of therapy for high-risk lesions [71].

As in all malignant pathologies, the prognosis depends on the histological type, histological differentiation grade, the stage of the disease, the involvement of regional lymph nodes and the presence of distant metastases. [25]

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Conflict of interest
NONE DECLARED

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