Malignant wound management in advanced illness: new insights

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Purpose of review
This article describes why this review is timely and relevant. To report on the recent research, which advances our understanding and practice of palliative wound care (wound-related pain and symptom management or wound palliation).

Recent findings
This article describes the main themes in the literature covered by the article. The main themes include the problem of malodour and the palliative management of cutaneous and subcutaneous malignancy of skin and nonskin origins. The findings from an international survey of measures to combat wound malodour are reported, which indicate that malodour is one of the most distressing and difficult to manage symptoms associated with malignant wounds. A relatively novel palliative treatment for cutaneous malignancy, electrochemotherapy, is outlined, together with the growing evidence supporting its use.

Summary
This article describes the implications of the findings for clinical practice or research. The findings of the wound malodour survey indicate that approaches to managing malodour are wide ranging, but ineffective. Collaborate research and development is needed with industry into interventions to combat malodour, which are based on the causal agents. The growing evidence of the effectiveness of electrochemotherapy, as an uncomplicated palliative treatment and method of managing symptoms, offers palliative care clinicians a means of managing the otherwise relentless progression of cutaneous malignancy.

Keywords
electrochemotherapy, fungating malignant wounds, wound malodour

INTRODUCTION
Patients with advanced illness have been defined by Maida et al. [1] as individuals with incurable illness (cancer and noncancer) whose life-expectancy is generally less than 6 months (p. 1). Patients with advanced illness represent the cohort within healthcare with the highest overall prevalence of wound-related issues. Paradigms that describe the potential goals of care as well as potential outcomes, in this clinical context, have been graphically depicted by Maida et al. in 2009 and 2012 [2,3**]. Despite the pervasive opinion that dying patients cannot experience wound healing, recent prospective studies, carried out in a Canadian regional Palliative Care programme, show that marginal levels of complete healing may occur when patients are given time-limited trials of wound healing therapies, together with high levels of wound maintenance, though not in the case of malignant wounds [1,3**].

Clinical interventions and outcomes for wound management in advanced illness are focussed on symptom management and local wound management strategies to prevent deterioration and maintain personal dignity [4].

Specifically for this review, fungating malignant wounds are a particular type of wound that arises in advanced and uncontrolled cancer through cutaneous and subcutaneous infiltration by skin and nonskin cancers. The scale of the problem of these wounds in global population terms is unknown; however the often quoted estimates, based on small-scale surveys, range between 5 and 17% [1,5***].
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KEY POINTS

- Malignant wounds and the symptoms arising, such as bleeding, exudate and malodour, continue to pose enormous challenges to patients and carers.
- Whilst pain is a subjective symptom, it is routinely measured by clinicians, whereas malodour is not.
- A range of topical and environmental agents used to combat malodour are reported by clinicians; however, low levels of efficacy are also reported.
- Emergence of a new palliative treatment, electrochemotherapy, offers a means of controlling what is otherwise a relentlessly progressive and visible advancement of malignant tumour growth through the skin.

This review focusses on the new insights into the scale of the problem of malodour and a relatively novel palliative treatment for cutaneous malignancy, electrochemotherapy. Studies are drawn, selectively, from the research conducted in Europe, where the authors are working towards the development of clinical guidelines for palliative wound care. These include an international survey on wound malodour providing evidence of the lack of efficacy of current strategies to combat malodour, and the significance of the problem from the viewpoint of clinicians [12**]. In addition, standard operating procedures and evidence to support the use of electrochemotherapy for tumour volume reduction and symptom management are included [13**,14**].

Overall, this review reinforces the significance of malignant wounds, the limitations in current approaches to combating malodour, together with a promising treatment to palliate malignant wounds and control troublesome symptoms, such as bleeding. Further collaborative research and development are urgently needed into interventions that are effective in reducing the physical burden of these wounds and ameliorating their psychosocial impact.

CURRENT DEVELOPMENTS IN MALODOUR MANAGEMENT

The impact of malodorous wounds on patients, carers and healthcare professionals is profound [15*]. The causative agents in malodour have historically been attributed to devitalized tissue and a mixture of volatile agents produced by aerobic and anaerobic bacteria, together with a mixture of amines and diamines such as cadaverine and putrescine that are produced by the metabolic processes of other proteolytic bacteria [16]. More recently, in an investigation of the volatile substances emitted from fungating malignant wounds, dimethyl trisulfide (DMTS) was identified as the causal agent of the characteristic malodour from these wounds [17,18]. This finding provides a sound base from which malodour combating agents can be developed. Without this, clinicians are working in an area of uncertainty and the picture that emerges from the research literature is one of a significant number of products being tried, with scant evidence of efficacy for any of them.

A systematic review of the evidence to support the use of topical agents generally for the management of fungating malignant wounds, including metronidazole for the control of malodour, found weak evidence from one small trial to support the use of a topical cytostatic agent (miltefosine) applied to superficial fungating breast lesions (smaller than 1 cm) previously treated with radiotherapy, surgery,
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hormonal therapy or chemotherapy for their breast cancer, to slow disease progression. With regard to other agents, they found insufficient evidence to guide the clinical practice in relation to symptom management or improving the quality of life [19].

Another systematic review focussed on the topical agents for the management of malodour in fungating malignant wounds and identified 11 interventions [20]. Some evidence was found to support the use of metronidazole gel and a saline-based dressing, together with activated carbon dressings and a turmeric ointment. Other interventions reviewed included topical arsenic trioxide, essential oils, green tea extract, hydrogel polymer dressings, antiseptic solutions, hydrogels and debridement enzymes (pp. 1073–1074). Overall, this review reports that few high-quality studies were found to guide the topical treatment of malodour in fungating malignant wounds. The key limitations of the studies reviewed included a lack of controlled clinical and randomized trials, small sample sizes, and the absence of instruments or scales to measure malodour.

Overall, there is no consensus or guideline to manage this distressing symptom [15∗]. As a starting point to the development of palliative wound care guidelines, a survey was undertaken to determine, from an international perspective, those measures that clinicians currently use to assess and manage malodorous wounds.

In all, 1444 clinicians from a range of disciplines and specialities across 36 countries participated. Results revealed a lack of strategies to assess and manage malodour as only 12% currently assess malodour, yet 83% report this as being a major problem for both the patient and caregiver. A total of 3671 words were suggested to describe malodour and seemed to represent repulsion to malodour with words such as ‘offensive, pungent, foul, putrid, rotten’ being amongst the most commonly cited.

The most frequently applied dressing(s) were charcoal and metronidazole, yet, only 30% report these as being ‘very effective’. In total 74% of participants combine a range of dressings and topical agents in an attempt to manage malodour, but cite these as being only ‘somewhat effective’. Eight percent of respondents currently use aromatherapy oils to the wound bed, of which lemon grass, lavender and tea tree oil are the most common with a reported level of efficacy ranging from 20 to 38%. A large range of environmental agents are being employed, of which, commercial deodorizers are the most popular. Other items such as oil burners and cat litter are frequently reported. Again, the reported level of efficacy was low at 14–27%.

The greatest challenge that respondents encounter in the overall management of wounds, in particular malignant fungating wounds, was malodour 80%; pain 70%; exudate management 70%; bleeding and difficulties with fitting the dressing to the wound. The greatest difficulties reported by their patients were malodour 83%; social concerns 70%; pain and containment of exudate 68%, followed by emotional distress 65% [12∗] (Gethin et al., in preparation).

According to patients and healthcare professionals, internationally, malodour remains the most distressing aspect of a wound. Malodour was cited by all as the worst or one of the worst aspects of the wound and yet there appears to be no real attempt to assess it, as shown by only 12% reportedly assessing the symptom (of which 50% used words rather than a tool). Discussions of the results with clinicians suggest malodour is seen to be subjective and unmeasurable, yet we assess pain and cannot actually measure it. People evidently struggle to manage this distressing symptom and resort to a range of measures, to the wound, and in the patient’s environment to manage it with low levels of efficacy. Words used to describe malodour display a level of repulsion to it. Could it be that clinicians avoid it rather than assessing and managing the problem? Given the enormous psychological impact of wounds and malodour, there is an urgent need for further research and guidelines in this area.

CURRENT DEVELOPMENTS IN PALLIATIVE TREATMENT: ELECTROCHEMOTHERAPY

An emerging technology, electrochemotherapy, is aimed at treating and palliating primary skin cancers and melanoma, and cutaneous and subcutaneous metastases of nonskin origins. Electrochemotherapy is an antitumour therapy in which a nonpermeant (i.e. bleomycin) or poorly permeant (i.e. cisplatin) chemotherapy drug is administered followed by local application of electroporation pulses [21]. There is mounting evidence of the efficacy of electrochemotherapy in terms of tumour volume reduction and symptom management, for example, bleeding and exudate. In terms of symptom control, clinicians using electrochemotherapy have observed a ‘vascular lock’, which has a local effect on bleeding, oedema, exudate and malodour. Standard operating procedures have also been developed and validated, and used in studies after the 2006 publication, which enables comparisons between different study findings [22–24].

Electrochemotherapy appears to be effective with minimal and transient side effects, and in patients who are refractive to conventional
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treatments. Treatment can be given in a single session over one to hours and in out-patient clinics, which is convenient and also cost-effective. It is reported to be accepted by patients and there is the ability to retreat if the tumour recurs [25, 26].

The first systematic review and meta-analysis of electrochemotherapy, comprising 44 studies and 1894 tumours, is now published [27]. Local effectiveness of a single session of electrochemotherapy was estimated as complete response (CR) and objective response of 59.4 and 84.1%, respectively. The authors report significantly improved tumour response rates (≤50%) with electrochemotherapy than with chemotherapy alone. The overall effectiveness of electrochemotherapy was reported to be significantly higher after the introduction of standard operating procedures (CR 61.1% and objective response 77.4% versus CR 59.7% and objective response 87.8%, respectively).

In addition to these findings, the review by Mali et al. provides new insights into the responses by tumour histology. Prior to this review, it was reported that the responses were regardless of tumour cause; this review indicates that melanomas are less responsive than carcinomas or sarcomas (p. 10). In addition, basal cell carcinomas were more responsive than squamous cell carcinomas. The authors consider that this may be because of the more extensive size of squamous cell carcinomas, which may require more than one treatment.

With regard to unresectable melanomas that were also refractory to other antitumour treatments, Möller et al. [28] reviewed current treatments and found significant limitations to a range of treatments, including cryosurgery, carbon dioxide laser ablation and immunomodulation. They concluded that electrochemotherapy is a therapeutic option for otherwise untractable melanomas and cite an objective response of 80–90%.

Matthiessen et al. [26] conducted the first systematic investigation into large, metastatic, cutaneous recurrence amongst a cohort of breast cancer patients for whom no further treatment was possible. Seventeen previously heavily treated patients were given electrochemotherapy. Twelve of these were evaluable. Using clinical examination, a CR was observed in one patient and a partial response (PR) in another. Stable disease was observed in nine patients and progressive disease (PD) in one patient. Interestingly, positron emission tomography (PET) scans and computed tomography (CT) scans showed higher objective response rates than on clinical examination. For example, tumour volume measurement on CT scan showed a reduction greater than 50% in four patients, seven had a less than a 50% reduction and one patient was not evaluable on CT (p. 716).

Matthiessen et al. also report a reduction in the following symptoms: exude and bleeding (pp. 718–719). Six of the twelve patients reported a reduction of exude and four of the twelve reported less bleeding. With regard to malodour, five reported a reduction, three reported no change, whereas three patients reported an increase in the problem. Seven patients reported posttreatment pain of a neuropathic nature, which the authors speculate may be because of the previously heavily treated areas. Overall, Matthiessen et al. advocate that electrochemotherapy is a modest intervention that can be quickly learned by experienced clinicians, and can benefit patients who otherwise face relentlessly progressive and visible disease.

From a palliative wound care perspective, electrochemotherapy appears to offer patients and clinicians a standardized means of containing and preventing the devastating advancement of cutaneous and subcutaneous metastases of skin and nonskin origins, experienced by patients and carers [7–9, 11].

CONCLUSION

The relentless progression of malignant wounds and their associated symptoms have for too long remain unchanged with patients and carers reporting malodour, exude leakage and bleeding as causing significant distress. Complex, chronic wounds in advanced illness require advanced thinking to aid the quality of life. Systematic methods of multidisciplinary assessment of patients’ experiences and clinical problems are needed together with effective management strategies, whilst acknowledging the highly individual presentation of complex chronic wounds, and patient and carer experience. This review has highlighted how an emerging technology, electrochemotherapy, can reduce tumour volume and palliate symptoms. Clear evidence of the significance of the problem of malodour has been presented, together with a range of topical and environmental agents used to combat the malodour, with scant evidence of efficacy. Additional collaborative research is needed to develop effective strategies of combating malodour. As the evidence builds for the efficacy and clinical and cost-effectiveness of interventions, they can be integrated into clinical guidelines to support, in a meaningful way, clinical practice and care.

Acknowledgements

None.
Conflicts of interest

The authors report no conflicts of interest.

Georgia Gethin has been supported by a small grant from the Wound Management Association of Ireland for the Malodour survey.

For the remaining authors, none were declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


This study aimed to determine from an international audience current practices in the management of wound malodour. An online survey tool (www.surveymonkey.com) was developed and assessed for construct validity, translated into Spanish, Italian and German and pilot tested. The final survey was distributed amongst international wound care and oncology nursing groups. In all, 1,444 clinicians from a range of disciplines and specialties across 36 countries participated. Results revealed a lack of knowledge and strategies to assess and manage malodour.


In this review, the role of electrochemotherapy in advanced melanoma is reviewed together with the potential to combine electrochemotherapy with biological response modifiers and immunotherapeutic compounds. The authors conclude that electrochemotherapy has shown to be effective and clinically well tolerated in the local control of primary and metastatic solid tumours of disseminated superficial melanoma. Few data on the role of immunologic response in electrochemotherapy-treated patients have been reported. However, the authors further conclude that protocols combining electrochemotherapy with biological response modifiers (interleukin-2 and interferon) and immunotherapeutic compounds should be further explored in animal and human cancer models.


This review highlights the profound problem of wound malodour. Malodour is cited as one of the most distressing symptoms of these wounds, is a complex phenomenon with multiple potential causes, and may signify infection or necrosis. Malodour can cause depression, social isolation, nausea, anorexia and, in some individuals, a gagging or vomiting reflex. This article explores in detail the causes of malodour and current management strategies, with particular reference to palliative care wounds.


25. Matthiessen LW, Johannessen H, Hendel HW, et al. Electrochemotherapy for large cutaneous recurrence of breast cancer: A phase II clinical trial. Acta Oncol 2012; 51:713–721. This is the first systematic investigation of electrochemotherapy for larger cutaneous recurrences of breast cancer. A phase II trial was conducted in patients with cutaneous recurrences where no further treatment options were available. The primary endpoint was objective response evaluated by clinical examination. Symptomatic relief included decreasing exudates, malodour, and bleeding. Treatment was well tolerated; the main side-effect was posttreatment pain. The authors conclude that this first phase II study indicates that clinical examination is a promising treatment alternative for cutaneous recurrences of breast cancer.


The purpose of this systematic review was to consolidate the current knowledge about clinical effectiveness of electrochemotherapy, a local therapy for cutaneous and subcutaneous tumours, and to investigate the differences in effectiveness of electrochemotherapy with respect to tumour type, chemotherapeutic drug, and route of drug administration. In total, 44 studies involving 1894 tumours were included in the review. The results of this review shed new light on effectiveness of electrochemotherapy and the authors propose that it can be used for prediction of tumour response to electrochemotherapy with respect to various treatment conditions and should be taken into account for further refinement of electrochemotherapy protocols.