Electrophysical agents (EPAs) for symptom control in cancer care – what is the evidence?

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Background: Physiotherapists generally accept that electrophysical agents (EPAs) should not be applied directly over, or in the vicinity of cancerous tumours or other malignancies. The idea that EPAs are contraindicated is based upon the theoretical, but rarely proven risk of stimulating malignant cell proliferation and thus tumour growth and/or dissemination. However, a growing body of literature suggests that some electromagnetic and physical energies may be beneficial for use in the treatment of cancer-related or cancer treatment-related sequelae, and tumours.

Objectives: The aim of this narrative review was to collate information on the state of knowledge regarding the application of EPAs in some typical clinical presentations in physiotherapy cancer care; understand whether there is evidence for using EPAs in physiotherapy cancer care; and, how planning might progress to further the evidence in this field.

Major findings: Few EPAs have been specifically tested for the capacity to increase tumour growth or dissemination. Evidence exists for the use of some EPAs for symptom control and palliative management of cancer-related or cancer treatment-related symptoms and side effects.

Conclusions: Physiotherapists should reconsider the potential use of EPAs in cancer care. Further research will elucidate how best to utilize EPAs in this field of practice. Using some EPAs for tumour treatment could be considered.

Keywords: Physiotherapy, Electrophysical agents, Cancer care, Contraindications

Background

The most common treatment for patients diagnosed with cancer is some combination of surgery, chemotherapy and radiation therapy. Physiotherapists play a supportive role in cancer management, offering preventive care, functional rehabilitation and symptom control. Electrophysical agents (EPAs), such as transcutaneous electrical nerve stimulation (TENS), therapeutic ultrasound (US), and low level laser therapy (LLLT) are used by physiotherapists to reduce pain of musculoskeletal origin, to facilitate tissue healing and promote functional rehabilitation but rarely in cancer care. A number of professional organizations have developed guidelines regarding the clinical use of EPAs, e.g.[1,2] Typically, the list of recommended contraindications includes the application of electromagnetic energies directly over, or in the vicinity of tumour, or whenever a malignant condition is present. Breaches of this contraindication have the theoretical potential to result in the stimulation of malignant cell proliferation, and

thus tumour growth and/or spread. Other inadvertent outcomes include the potential to alter local concentrations of drugs, and unpredictable local reactions to the EPA due to altered cellular metabolism. Traditionally, emphasis on this contraindication has caused it to become a 'blanket rule' in physiotherapy, which results in constriction of clinical reasoning in situations where a particular EPA could provide the same beneficial physical outcomes in patients with cancer as occur in those with musculoskeletal conditions. The dilemma is to know whether, in the absence of specific evidence to the contrary, it is reasonable to apply an EPA in the presence of malignancy. Before the efficacy of EPAs can be determined, the safety of each EPA for specific types of disease, at particular stages, must first be established.

The notion that an EPA could be safe, and appropriately applied for symptom control in cancer patients should not be tested using clinical randomized control trial (RCT) methodologies. A more suitable paradigm is the one currently used by pharmaceutical companies when testing new cancer chemotherapies or pharmacological agents. That is, a continuum that includes preclinical studies of the

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effects of energies (in cell cultures to identify efficacy and in animal models to evaluate efficacy, toxicity, and safety); further testing in phase 0 (microdosing) clinical studies; small cohort phase 1 (dose-ranging) studies; then larger cohort phase 2 RCT (which could be used for identifying dose-response characteristics); and phase 3 multicentre trials. In the case of testing the safety and efficacy of EPAs for symptom control in malignancy, it would be imperative to also formulate phase 4 studies that included safety surveillance once the EPA was in common usage. Phase 4 studies are designed to detect unusual adverse effects of the EPA in the proposed application. Physiotherapists should be leading such research and formulating the research questions.

In order to understand the breadth and depth of evidence regarding the safety and efficacy of EPAs in the field of cancer care the authors searched the Scopus, MEDline, Scirus, and Cinahl databases, and the internet, for publications describing clinical applications of EPAs for the relief of signs and symptoms related to cancer. The literature includes a significant number of publications relevant to the use of EPAs in cancer care; however, the scope of this paper has been limited to the control of major symptoms or side effects of cancer and its treatment. In particular, cancer-related (malignant) pain, neuromotor control issues, chemotherapy-induced nausea, breast cancer-related lymphoedema (BCRL), and radiation/chemotherapy-induced oral mucositis. We included studies relating to both the curative and palliative management approaches. A brief discussion of the possible use of EPAs as primary cancer treatment is also included. Based on available evidence, in the following sections the authors have attempted to draw conclusions regarding the safety of EPAs in cancer settings; and provide recommendations for where further research might best be targeted.

Cancer Pain

In its early stages malignant pain can masquerade as a common musculoskeletal condition (e.g., brain tumours may initially present as headache of cervicogenic origin). Cancer related pain differs from symptoms of musculoskeletal origin in that it is often intractable and unremitting, responding poorly to simple analgesics. Cancer pain has an insidious onset and is typically worst at rest or at night. It is most often caused by: direct compression on or traction by tumour of innervated structures (e.g., solid tumours in confined spaces such as the cranial cavity) or nerve fibres; destruction of structural integrity of tissue (e.g., bony metastases resulting in pathological fractures); or rarely, through neural infiltration. Although subject to recent criticism, cancer pain should be treated according to the World Health Organization (WHO) guidelines using the analgesic ladder.[3] Electrophysical agents may complement pharmacological agents.

Superficial warming and cooling

Generally, superficial physical agents such as heat packs for warming or ice packs for cooling are considered to be the safest, non-pharmacological options for the management of malignant pain that is unresponsive to medication, regardless of the stage of cancer. Despite a theoretical risk of disseminating malignant cells by altering local metabolism[4] the effect of warming or cooling tissues with malignancy has not been specifically tested (e.g., the effect of warming on a superficial malignant melanoma). As such, the full continuum of research starting with preclinical animal trials may be appropriate for these applications. Empirical evidence suggests that warming and cooling modalities offer only brief symptomatic effects that are not sustained beyond the period of the application. Such transient pain modulation is not unexpected given the likely mechanisms of effect of superficial warmth and cooling, and the pathophysiological basis of malignant pain. However, either agent can be beneficial when optimal pharmacological pain control is still to be achieved. Applications of warm or cool packs can provide patients with some additional control over symptoms.

Electrical stimulation

Pain that is in its early stages or poorly controlled, whether from nociceptive, neuropathic or mixed sources,[4] and pain originating from metastases to bone[5] may respond to adjuvant electrical stimulation (Table 1).[6–12]

An often-cited early paper by Avellanosa and West,[6] indicates that good short-term pain relief from TENS is possible in patients with a wide range of malignant and post-surgical conditions. The paper is instructive because it describes the gradual induction of patients to the stimulation, i.e., beginning with electrodes initially positioned on non-pathological sites and subsequently moved to the related dermatome and finally to the skin over the most painful area. The authors reported some relatively minor negative outcomes from the TENS applications, i.e., local skin reactions under electrodes, short-term exacerbation of symptoms, and one instance of cardiac arrhythmia. All untoward effects were resolved by removal and repositioning of electrodes, and there were no reports of unwanted effects on tumour growth or spread.

After a promising start, controlled research studies have not been forthcoming. No strong evidence yet exists for the efficacy of TENS for the symptomatic relief of pain (acute or chronic) in cancer patients, nor do we find any guidelines for specific parameters of dose.[13] One study reported a 60% improvement in facial pains with TENS but only in patients with low or moderate levels of pain.[14] Generally the evidence suggests that stronger amplitudes are more likely to be effective than weaker ones, and that no particular

Table 1   The use of TENS in managing cancer-related pain

Reference	Publication type or study design	Sample/number	Parameters	Results
Avellanosa and West (1982)[6]	Comparative study	60	85–180 Hz; 80 microseconds; 1–180 mA as tolerated; Application 10–14 days	Approx. 30% participants had short term pain relief
Bauer (1983)[7]	Case studies	3 patients with head and neck pain	Low amperage, low frequency alternating currents	'Extremely good results'
Jacox et al. (1994)[8]	Clinical practice guideline	4 trials	Parameters not stated	No significant difference between TENS and sham TENS
Ahmed et al. (1998)[9]	Case studies	3	4–100 Hz; 30 minutes; 3 treatments; Percutaneous: needle electrodes bilaterally at 3 spinal levels (6 channels)	Short to medium term analgesia in 2 cases
Robb et al. (2007)[10]	RCT	41 women with pain post treatment for breast cancer	Transcutaneous spinal electroanalgesia (TSE); Placebo (sham TSE)	Outcomes not significantly different to placebo
Searle et al. (2008)[11]	Pilot trial	6 patients	Single channel; 80 Hz; 200 microseconds; for 30 and 60 minutes on a strong/comfortable intensity.	Pain outcomes improved
Robb et al. (2008)[12]	Cochrane Database review; meta-analysis not possible	2 RCT (64 patients with chronic pain secondary to breast cancer)	TENS (Robb 2007) AL-TENS	No significant differences between TENS and placebo or sham

frequency is more effective than any other within the low frequency range (1–120 Hz).[15] The presence of the placebo effect with TENS is widely acknowledged in the literature, as are the positive effects that can occur when a patient is empowered with active control of some of the parameters, e.g., stimulation intensity, duration and number of sessions, and electrode positioning.[16] There may be additional benefits for the patients' quality of life from complementary treatments, such as TENS, within the special environment of palliative care.[16]

Nowhere in the current body of literature is there a discussion of the risk of dissemination of cancerous cells by exogenous electrical currents. Possible reasons for the hiatus could be: in published papers the selection criteria excluded patients where the electrical currents' potential for dissemination was high; the anticipated short-term benefits of pain relief and improved quality of life were assumed to outweigh the longer term risk of spread of the disease; and with no tools for measuring dissemination effects the possibility for harm from this source remains theoretical.

Given the extent of its use, it is important to identify safety and efficacy factors related to electrical stimulation in the management of cancer pain. In the absence of definitive information on optimal treatment parameters, and without specific knowledge of the effects of electrical stimulation on malignant cells, it appears that judicious use of this modality needs the consideration of a number of factors. These factors include a thorough understanding of the malignancy (including tumour classification/stage); an understanding of the extent of the electric 'field' between and around electrodes; and the potential to stimulate malignant cells *in vivo*. Without a clear

understanding of these factors, it continues to be reasonable to limit the use of TENS to the palliative stage only, as a means of symptom control.

The principle aim of treatment during the palliative stage of cancer care is to maintain or improve quality of life, 'through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'.[17] Where conventional methods of pain relief are inadequate, or where alternative methods are being trialled, it would be appropriate to trial TENS to reduce pain symptoms, or to manage pain (in conjunction with pharmacological agents). In this setting phase 1 or phase 2 research should elucidate the effectiveness of different stimulation parameters, and the influence of the site of electrode position. From the literature reviewed, on balance, compared with other medical interventions, and given that the usual safety precautions are applied, our opinion is that low amplitude TENS is safe for the palliative management of cancer pain.

Application of TENS in the curative stage (particularly if the success of cancer treatment has not yet been established) potentially places a patient at risk. In this setting research related to safety and efficacy trials should aim to establish a clear progression from preclinical through to phase 4 studies, with the first stage being an understanding of the effects of electrical current on a variety of malignant cells.

Management of Side Effects of Cancer and Cancer Treatment

Although there are a significant number of potential side effects from cancer and its treatment, the authors have limited the following discussion to those that are most commonly seen clinically.

Table 2 The use of TENS in managing cancer-related nausea and vomiting

Reference	Publication type or study design	Sample/number	Parameters	Results
Dundee *et al.* (1991)[23]	Comparative and crossover	100 patients with inadequately controlled chemotherapy induced nausea	15 Hz, 5 minutes every 2 hours (self-administered) including over acupuncture point P6 (Neiguan)	75% effective reduction of symptoms
Gadsby and Franks (1997)[24]	Double blinded randomized controlled trial	15 patients with nausea and vomiting in palliative care	3 Hz, 200 milliseconds; 30 minutes applications, 5 days; 4 cm^2 surface electrode connecting P6 to Li4	No significant effect
Ezzo *et al.* (2005)[20]	Review	11 trials $n=1247$	Electro-acupuncture	Reduced severity of chemotherapy induced nausea and vomiting ($P=0.04$)

Nausea and vomiting

Stimulation of the acupuncture point known as Neiguam or Pericardium 6 (P6) can reduce sensations of nausea and emesis. Electrical stimulation of P6 has been trialled in patients with symptoms either directly related to the disease or secondary to chemotherapy treatments,[18–22] however the studies lacked rigour and the strength of the evidence is poor (Table 2).[20,23,24]

Most papers report that needle acupuncture was more effective than acupuncture-like TENS or manual pressures on the point.[23,24] The style of stimulation depends upon the availability of a trained professional required for dry needling versus the convenience and relative safety of self-applied methods, e.g., electronic wristbands. Authors agree that the clinical efficacy of exogenous stimulation must be weighed against the cost and availability of newer antiemetic medications and that responses to the TENS type treatments may have been affected by patient perceptions of issues regarding drug interactions, tolerance, and quantity of prescribed medications. Phase 1 research studies would appear to be appropriate for this area of practice.

Muscle weakness and dysfunction

With the increasing interest in applications of neuro-muscular electrical stimulation (NMES) for rehabilitation after stroke,[25] it is not surprising to find trials reporting good results for retardation or remediation of gait impairments, breathlessness and for urinary incontinence, in studies investigating the potential benefits of NMES for neuromotor indices of quality of life of cancer patients (Table 3).[26–29] Indices of protein catabolism, quadriceps muscle strength and endurance, and functional gait respond to NMES in a small number of cases and controlled trials.[26–28] However, post-prostatectomy patients with urinary incontinence appear not to gain real benefits from NMES, with or without biofeedback.[30–33]

Other researchers have shown improvement in dysphagia when NMES was applied to the throats of patients following radiation therapy for squamous cell carcinoma of the head and neck.[29] The improvements may have been related to reductions in xerostomia (dry mouth) associated with radiotherapy treatment. In a recent Cochrane review[34] of three RCT (comprising 50 chronic obstructive pulmonary

Table 3 The use of TENS in managing cancer-related muscle weakness and dysfunction

Reference	Publication type or study design	Sample/number	Parameters	Results
McDuffie and Morgan (2005)[29]	Retrospective review	12 questionnaires	4–30 mA; 80–100 microseconds; 3 sessions per week for 4–8 weeks. Four electrodes placed along anterior neck over pharyngeal muscles	Improved xerostomia and dysphagia in all subjects
Crevenna *et al.* (2006)[28]	Case study	47-year-old female with advanced lung cancer and metastatic disease	Combined with passive exercises 5 times per week for 4 weeks	Improved 6-minute walk distance, timed 'up-and-go', SF-36 quality of life scale
Strasser *et al.* (2009)[26]	Assessor blinded controlled trial	26 people after major abdominal surgery for cancer	50 Hz; 250 microseconds; 8 seconds on 4 seconds off; for 30 minutes, for 4 consecutive days starting day 1 post-op at maximum tolerable intensity for quadriceps muscle contraction; control was contralateral thigh (same parameters; intensity gentle tingling)	Positive effects on protein catabolism ($P=0.008$) and reduction of muscle degradation ($P=0.029$)
Maddocks *et al.* (2007)[27]	Randomized controlled pilot study	16 patients with cachexia due to lung cancer	50 Hz; 0–120 mA; duty cycle 11–25%; delivered over 1 hour to the quadriceps for 4 weeks	Non-significant increases in quads muscle strength and exercise endurance

disease patients), NMES (ranging from 15 to 30 minutes to quadriceps muscles; 3–5 times per week for 4–6 weeks) resulted in improvements in ratings of perceived exertion and shuttle walk test, and decreased dyspnoea in patients in advanced stages of malignant and non-malignant disease. Although a meta-analysis was not possible, the RCT were considered of high quality.

For the authors' views on the appropriateness and need for research in the field of NMES for motor control factors in cancer care, the reader is referred to the previous section on electrical stimulation for cancer pain.

Breast cancer-related lymphoedema (BCRL)

Lymphoedema of the upper limb is a side effect of the surgical management of breast cancer, or of radiation damage to the lymphatic system. Less commonly, lower limb lymphoedema occurs following surgery for gynaecological cancers, or other pelvic cancers, in females and males. This discussion is limited to BCRL for which there is no definitive cure. Physical treatment includes patient education and self-management strategies, compression bandages and sleeves, manual lymphatic drainage, massage and range of motion exercises (alone or in combination). Recently laser phototherapy and ultrasound have been trialled for BCRL. Lymphoedema research is hampered by the absence of a gold standard outcome measure hence definitive conclusions regarding interventions are difficult to make.

Therapeutic ultrasound

Little is known about the effectiveness of ultrasound for BCRL. Only one study on the subject was located. The researchers compared US given to 50 BCRL patients, with standardized compression pump treatments provided to 100 other women with the condition.[35] The US application was different to usual musculoskeletal style of treatment in which the transducer emits low levels of temporal and spatially averaged energy. Instead, ten stationary transducers were positioned over acupuncture points that had been used previously in experiments of low level laser for lymphoedema. The transducers emitted a peak power of 2 W/cm^2 at 3 MHz. The treatment program consisted of 2 cycles of 10 sessions, each session lasting for 30 minutes. The US mode was pulsed but the duty cycle was not specified. The study found that, at 4-month follow-up, the US group had reductions in circumferential limb size that were not statistically different from the compression pump group and did not persist at 12 months. However the patients who received US reported some advantages of the therapy e.g., relatively softer limb tension, lower levels of musculoskeletal pain and discomfort, and a satisfaction that they had avoided the need to wear a compression sleeve.

Electrical stimulation

Very few papers describe the external use of electrical stimulation in humans with lymphoedema. In 1991, Bertelli *et al.*[36] described an RCT comparing elastic sleeves worn for 6 months with sleeves plus electrical stimulation. There were no significant differences between groups for reductions of limb girth. More recently a dedicated electrical stimulation device (Bodyflow™; Bodyflow International, Collingwood, Victoria, Australia) has been developed with the intention to stimulate the smooth muscle pump within the active anatomical units of the lymphatic system (the lymphangion). Research in animals supports neuromuscular stimulation of smooth muscle fibres with low amplitude, low frequency (1.5 Hz) currents, however published clinical trials with this device are few and low powered. Piller *et al.*[37] describe the use of low frequency electrical stimulation in conjunction with compression garments for lymphoedema of the lower limbs. The study was low powered, mainly because patients had difficulty complying with the need to wear compression garments and electrodes concurrently. With regard to safety, treatments to the lower limb may be less problematic than applications to proximal regions of the upper limb when consideration is given to the potential for unsafe electrical stimulation of the autonomic neural plexes. Preclinical through to phase 1 research may explicate some of the issues related to the application of electrical stimulation for lymphoedema.

Low level laser therapy

The earliest example of using LLLT to influence the lymphatic system is the work of Lievens[38] who examined the effect of helium–neon (HeNe) and gallium arsenide (GaAs) laser (904 nm) on lymph vessels and healing after surgically-inducing wounds in mice. Thelander and Piller[39] raised awareness of laser phototherapy as a clinical treatment strategy for BCRL in a report of 11 subjects with the condition (participants acted as their own controls). Using a scanning laser with HeNe and infrared wavelengths (2–4 J/cm^2) they recorded 19.3% average reduction in lymphoedema at the end of treatment; and a 26% average reduction in BCRL at 6-month follow-up.

Three studies[40–42] evaluated the efficacy of LLLT alone or in combination with pneumatic compression and/or exercise. In a double blind, placebo-controlled, randomized, single crossover trial,[40] a significant number of participants did not benefit from LLLT, although improvement in 31% of participants is benefit that may not have been gained by other means. In general, studies in this field are characterized by low participant numbers and disparate intervention parameters yet each study reports benefits from LLLT for outcomes of tissue softening, arm volume, limb circumference and pain when

compared to control and/or placebo group participants. Follow-up measures in these studies suggest maintenance of the improvement in outcomes. Despite increasing interest, evidence remains limited, and disparate methodological designs make it difficult to decide which LLLT parameters are most effective in the management of BCRL.

Despite encouraging reports of benefit from LLLT in cases of BCRL, little regard has been paid to its safety in the (possible) presence of malignant cells. The potential for stimulating growth or spread of malignant cells using LLLT is poorly understood. Mikhailov et al.[43] examined recurrence rates in 41 patients with BCRL who developed post-operative complications and were subsequently treated with LLLT. Specific details of the treatments and patient groups are unclear. However, 87% and 77.7% of patients with Stage II and Stage III breast cancer respectively, treated with LLLT had no disease recurrence over a 10-year follow-up period. Although the cohort numbers are small, the figures compare with known data[44] suggesting that the addition of laser phototherapy has no effect on survival or disease recurrence.

In an attempt to address the safety question, one of the authors (LL) has investigated whether laser irradiation has the capacity to promote cancer cell growth and the dose-response characteristics of laser in malignant cells in culture.[45,46] Utilizing three common laser wavelengths (780, 830, and 904 nm) and a range of doses,[46] the results in human mammary epithelial and human breast cancer cells (adenocarcinoma and ductal carcinoma) demonstrate that one line of mammary epithelial cells proliferated significantly after exposure to a range of doses at 780 and 904 nm. A second line of mammary epithelial cells and a ductal carcinoma cell line showed negligible effects with one exposure from all wavelengths. Human breast adenocarcinoma cells irradiated with 780 nm laser demonstrated an increasing dose response relationship after one exposure, yet a decreasing dose response relationship after three exposures. When irradiated with 904 nm laser, the same cells demonstrated a decreasing dose response relationship after two and three exposures. In these studies, laser did not malignantly transform cells confirming that low intensity laser is not a carcinogen.

The next step should be to translate the findings into preclinical animal models before a more systematic investigation of wavelengths and doses in clinical settings. Research of safety and efficacy issues must progress from preclinical through to phase 4 studies before the use of laser for this indication can be assured.

Oral mucositis

Oral mucositis is an inflammatory reaction to radiotherapy or chemotherapy applied in a range of cancers across the continuum of cancer care (through curative to palliative stages). The reported incidence of oral mucositis ranges from 36 to 100%.[47] Therefore a measure to prevent or manage cancer treatment-induced oral mucositis would have significant benefits for patient quality of life, and on resultant costs related to bed days and length of hospital stay.

Ciais et al.[47] were the first to publish a case series describing the use and potential benefit of LLLT for oral mucositis caused by cancer treatment. Subsequently, a range of authors has investigated the efficacy of LLLT for oral mucositis in well-designed prospective, blinded and controlled trials (Table 4).[47–60]

The majority of reports demonstrate significant improvement in a range of indicators including pain, severity, erythema, oedema, ulceration and atrophy. The results are not unexpected based on existing knowledge of the healing response of soft tissues to laser phototherapy.[61] The outcomes of the research listed in Table 4 clearly demonstrate that laser phototherapy using wavelengths in the visible range of the electromagnetic spectrum (e.g., HeNe, 632.8 nm) and in a fluence range less than 2.5 J/cm^2, has significant potential in the prevention or management of cancer-related oral mucositis (and perhaps mucositis in other parts of the body).

Despite the evidence supporting its potential use, there remains the unknown factor of what effect the laser irradiation of mucous membranes may have on cancer cells in the immediate vicinity. It is worth noting that after an initial surge in research investigating the treatment, some are now questioning the safety of applying LLLT in close association with cancer.[62] Research related to safety and efficacy trials should be undertaken before the use of laser for this indication becomes more widespread, e.g., phase 1 and phase 2 testing for dose-response effects in palliative patient samples.

Potential of EPAs for Cancer Treatment

It is interesting to note that electromagnetic energies (such as magnetic fields) are being investigated to treat cancer cell lines albeit in experimental models, e.g. Subo et al.[63] Should physiotherapists and research colleagues be taking another perspective of these developments?

Therapeutic ultrasound

Therapeutic ultrasound applications are absolutely contraindicated directly over cancerous lesions or where a tumour or malignancy is suspected.[64] Ultrasound has been shown to stimulate tumour growth and dissemination,[65] whether or not the output mode of the device is continuous or pulsed[66] and is therefore considered contraindicated.

Recently however, the attention of researchers has been drawn to the potential of low intensity ultrasound, and its bio-effects, as an agent of active treatment for cancer. Cavitations caused by low

Table 4 The application of LLLT in managing cancer-related oral mucositis

Reference	Study design	Participants/number	Laser parameters*	Results
Ciais *et al.* (1992)[47]	Descriptive case series (retrospective, non-randomized study)	Variety of patients receiving combination chemotherapy: *n*=67	HeNe 632.8 nm, cw, 25 mW; 0.75 J/cm^2, total 54 J	Reduction in: time to healing and incidence of oral complications
Pourreau-Schneider *et al.* (1992)[48]	Retrospective case review	Patients undergoing combination chemotherapy for a variety of cancers; laser: *n*=16; no laser: *n*=20; prophylactic laser: *n*=23	632 nm laser, 25 mW	Time to resolution of mucositis was faster in both laser treated groups. Severity and incidence of mucositis lower in prophylactic laser group
Franquin *et al.* (1994)[49]	Randomized phase II study	Autologous BMT patients: *n*=24; two groups (daily active laser; and sham control)	632 nm, cw, 60 mW, 1.5 J/cm^2	Significant decrease ($P<0.01$) of incidence, severity and the duration of mucositis
Schubert *et al.* (1994)[50]	Non-blinded open phase I/II pilot study with comparison to an historical disease and treatment matched control group	Patients undergoing BMT chemotherapy: *n*=13	GaAs (*n*=6) or HeNe (*n*=7), once a day for 3 weeks	Mean oral pain scores and oral mucositis index improved in patients who received laser compared to controls
Barasch *et al.* (1995)[51]	Prospective, double-blind, controlled study (split-mouth design)	BMT patients undergoing chemotherapy and XRT: *n*=20 completions	HeNe 632.8 nm, cw, 25 mW, 1 J/cm^2, 0.8 cm^2 aperture, 40-second exposures, daily for 5 days	Oral mucositis index ($P<0.005$) and VAS pain ($P=0.027$) significantly better on treated side
Cowen *et al.* (1997)[52]	Prospective, double-blind randomized study	Patients undergoing BMT: *n*=30 completions	HeNe 632.8 nm, cw, 60 mW, 1.5 J/cm^2, total=54 J/session, 0.8 cm^2 aperture, 40-second exposures, daily for 5 days	Maximum intensity ($P=0.04$) and severity ($P=0.01$) of oral mucositis, use of morphine ($P=0.05$), saliva production ($P=0.005$) and ability to swallow ($P=0.01$) significantly reduced in laser group
Bensadoun *et al.* (1999)[53]	Multicentre phase III, double-blind, randomized study; laser versus sham laser	Patients with carcinoma of the oropharynx, hypopharynx and oral cavity treated by external radiotherapy: *n*=28 completions	HeNe 632.8 nm, cw, 60 and 25 mW, 2 J/cm^2, 1.2 mm spot size, 33 seconds per point to 9 points, daily for 5 days each week for 7 weeks	Mean intensity ($P=0.01$) and grading of mucositis ($P=0.001$) and pain ($P=0.025$), pain intensity ($P=0.001$) and ability to swallow ($P=0.01$) significantly better in laser group
Migliorati *et al.* (2001)[54]	Pilot trial in series	Patients requiring BMT for variety of haematological and solid tumours: *n*=11	GaAlAs 780 nm, 60 mW, 2 J/cm^2, daily for 10 days	Equivocal results
Wong and Wilder-Smith (2002)[55]	Pilot study	Patients undergoing chemotherapy for variety of cancers and with prior history of oral mucositis: *n*=15	830 nm, cw, 45–50 mW, 0.7–0.8 J/cm^2, total 50–60 J, 24 h prior to commencement of chemotherapy and weekly thereafter	11 of 15 patients had no mucositis and of remainder, one had high grade (severe) and others had low grade mucositis. No change in measured intraoral perfusion ($P<0.05$)
Nes and Posso (2005)[56]	Case series (patients as own controls)	Patients with cancer undergoing chemotherapy resulting in oral mucositis: *n*=13	AsGaAl 830 nm, 250 mW, 35 J/cm^2, spot diameter 0.60 mm, daily for 5 days	Significantly lower pain scores ($P=0.007$) after laser treatment compared to pre-laser scores
Maiya *et al.* (2006)[57]	Prospective, assessor-blinded randomized controlled clinical trial	Cancer of oral cavity undergoing XRT: *n*=50 completions	HeNe 632.8 nm, 10 mW, 1.8 J/cm^2 delivered over 3 minutes.	Mean pain ranking ($P<0.001$) and pain scores ($P<0.001$), and mucositis grade (severity) ($P<0.001$) significantly reduced in laser group
Cruz *et al.* (2007)[58]	Prospective, randomized clinical trial	Paediatric patients with solid or haematological malignancies: *n*=60; completions: control *n*=31 versus laser *n*=29	780 nm, cw, 60 mW, 4 J/cm^2, 5 consecutive days	Incidence ($P=0.649$) and severity ($P=0.234$) of oral mucositis was similar in both groups
Jaguar *et al.* (2007)[59]	Comparative group study	Patients undergoing BMT; total *n*=49 (laser *n*=24 versus historical control *n*=25	660 nm, cw, 10 mW, 2.5 J/cm^2, 10 seconds per point.	Significantly delayed onset of mucositis ($P=0.01$). Duration of pain ($P=0.04$) and requirement for morphine ($P=0.07$) was significantly less in laser group. Grading of mucositis was unchanged between groups.

Table 4 Continued

Reference	Study design	Participants/number	Laser parameters*	Results
Arora *et al.* (2008)[60]	Single centre, prospective, controlled group comparison study	Newly diagnosed primary oral cancer: *n*=24 completions (11 laser and 13 controls)	HeNe 632.8 nm, 10 Hz scanning, 10 mW, 1.8 J/cm^2 for 5 minutes daily over 8 days	Pain significantly decreased in laser group compared to control (*P*=0.033); significantly lower mucositis grading in laser group across all weeks (e.g., week 1: *P*=0.004; week 7: *P*=0.045)

Notes: *Order of presentation of parameters where supplied: wavelength, continuous or pulsed wave, power, fluence, total energy, diode aperture size, number of exposures/treatment, treatment frequency and duration.
BMT, bone marrow transplant; XRT, radiation therapy; HeNe, helium–neon; cw, continuous wave; GaAs, gallium arsenide; GaAlAs, gallium–aluminium–arsenide; AsGaAl, arsenide–gallium–aluminium; VAS, Visual Analogue Scale.

intensity ultrasound may enhance the actions of chemotherapeutic drugs and the transfer of genetic material.[67] Reviewers describe a range of changes to cell structure, from reversible permeation through degrees of damage to cell death, and effects on function, such as proliferation, migration and synthesis, that all depend directly on US dose (amplitude, frequency and time of application).[68] Animal studies have demonstrated that, compared to their healthy neighbours, the cells of cancers and mildly hyperthermic or chemically sensitized tissues have a lower threshold for apoptosis and lysis when exposed to low amplitude ultrasound.[69] Other authors, noting the augmentation of the destructive effects of ultrasound with even small increases in tissue temperature (e.g., from baseline to 40°C) suggested that the effects of ultrasonic imaging in febrile patients be investigated.[70] For the same reason therapeutic applications of ultrasound should be avoided in patients with fever until safe dosages have been established, perhaps in pre-clinical animal studies.

Microwave thermotherapy
In a phase 2 dose-escalation study of 25 patients, Vargas and colleagues[71] utilized the thermal effects of focused microwave energy to induce pathologic necrosis in early stage breast cancer tumours. Treatment tolerance was excellent and all patients underwent tumour excision on average 17 days after thermotherapy. Two cases demonstrated complete tumour ablation and in the remainder, the extent of tumour necrosis ranged from 25 to 90% depending on the dose applied. Side effects were noted in particular at higher doses and included short-lived erythema, reports of mild to severe pain, oedema and three reports of skin thermal burns.

Low level laser therapy
The findings of Powell *et al.*[46] noted earlier, raise the possibility that repeated laser treatment may have a protective effect or even an inhibitory effect on malignant cell proliferation. Santana-Blank[72] had previously suggested that laser therapy be considered as a potential treatment for cancer. The preclinical laboratory evidence supports this possibility (e.g.[45,46])

and the potential deserves greater attention in animal studies.

Conclusion
There is sufficient evidence to suggest that certain EPAs have a role in the management of the sequelae of cancer and cancer treatment, and perhaps directly for particular cancers. There is a need for further study that, like pharmaceutical industry research, systematically investigates the effect of EPAs on malignant cells in culture (across a range of dosing parameters) and in animal models (using dosing parameters established as 'safe' in cell culture studies), and later in phase 1 and 2 clinical trials to establish safety and efficacy. Suitable models for such testing are imperative with the possibility that such models could then be used to test the effects of a range of EPAs in malignant conditions.

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