Transcutaneous Electrical Stimulation, Interferential Current and Photobiomodulation May Lead to the Recurrence of Breast Cancer in Rats?

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Estimulação Elétrica Transcutânea, Corrente Interferencial e Fotobiomodulação podem levar à Recorrência do Câncer de Mama em Ratas?

¿La Estimulación Eléctrica Transcutánea, la Corriente Interferencial y la Fotobiomodulación pueden Provocar la Recurrencia del Cáncer de Mama en Ratas?

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ABSTRACT

Introduction: Transcutaneous electrical nerve stimulation (TENS), interferential current therapy (IFC) and photobiomodulation therapy (PBMT) have been used in the management of cancer-related pain in adults. However, there are still some controversy regarding the effects of this therapy on tumor cells that may remain after cancer treatment. **Objective:** To evaluate the risk of recurrence of breast cancer in rats when using TENS, IFC or PBMT. **Method:** An experimental, randomized, controlled and cross-sectional study. With 90 days of age, 7,12-dimetylbenz(a)anthracene (7,12-DMBA) was administered to rats by gastric gavage to induce mammary cancer. After 120 days the mammary glands of the rats belonging to the group with mammary cancer were removed. **Results:** 39 female Sprague-Dawley rats were studied: 9 rats without induction of mammary carcinoma; 9 rats with induction of mammary carcinoma and without surgery; 9 rats with induction of mammary carcinoma with surgery and placebo application of TENS, IFC, PBMT; 9 rats with induction of mammary carcinoma, surgery and the application of TENS, IFC and PBMT. **Conclusion:** This study demonstrated that there was local recurrence of tumors in rats that were stimulated with TENS or IFC, however no evidence of local recurrence with PBMT.
Key words: transcutaneous electric nerve stimulation; electric stimulation therapy; low-level light therapy; physical therapy modalities; breast neoplasms.

RESUMO

Introdução: Estimulação elétrica nervosa transcutânea (TENS), corrente interferencial (IFC) e fotobiomodulação (PBMT) são usadas no tratamento da dor relacionada ao câncer em adultos. No entanto, ainda existem algumas controvérsias sobre os efeitos dessa terapia nas células tumorais que podem permanecer após o tratamento do câncer. **Objetivo:** Avaliar o risco de recorrência de câncer de mama em ratos ao usar TENS, IFC ou PBMT. **Método:** Estudo experimental, randomizado, controlado e transversal. Com 90 dias de idade, 7,12-dimetilbenz(a)antraceno (7,12-DMBA) foi administrado em ratos por gavagem gástrica para induzir câncer mamário. Após 120 dias, as glândulas mamárias das ratas pertencentes ao grupo com câncer mamário foram retiradas. **Resultados:** Foram estudados 39 ratos-fêmeas Sprague-Dawley: nove ratos sem indução de carcinoma mamário; nove ratos com indução de carcinoma mamário e sem cirurgia; nove ratos com indução de carcinoma mamário com cirurgia e placebo, aplicação de TENS, IFC, PBMT; nove ratos com indução de carcinoma mamário, cirurgia e aplicação de TENS, IFC e PBMT. **Conclusão:** Este estudo demonstrou que houve recorrência local de tumores em ratos que foram estimulados com TENS ou IFC, no entanto, nenhuma evidência de recorrência local com PBMT.
Palavras-chave: estimulação elétrica nervosa transcutânea; terapia por estimulação elétrica; terapia com luz de baixa intensidade; modalidades de fisioterapia; neoplasias da mama.

RESUMEN

Introducción: Estimulación nerviosa eléctrica transcutánea (TENS), interferencial corriente (IFC) y la terapia de fotobiomodulación (PBMT) en el tratamiento del dolor relacionado con el cáncer en adultos. Sin embargo, todavía quedan algunas controversias sobre los efectos de esta terapia en las células tumorales que pueden permanecer después del tratamiento del cáncer. **Objetivo:** Evaluar el riesgo de recurrencia del cáncer de mama en ratos cuando se usa TENS, IFC o PBMT. **Método:** Estudio experimental, aleatorizado, controlado y transversal. Con 90 días de edad, se administró 7,12-dimetilbenz(a)antraceno (7,12-DMBA) a ratos por sonda gástrica para inducir cáncer de mama. Después de 120 días, las glándulas mamarias de las ratas pertenecientes al grupo con cáncer de mama fueron extraídas. **Resultados:** Se estudiaron 39 ratos-hembras Sprague-Dawley: nueve ratos sin inducción de carcinoma de mama; nueve ratos con inducción de carcinoma mamario y sin cirugía; nueve ratos con inducción de carcinoma mamario con cirugía y placebo aplicación de TENS, IFC, PBMT; nueve ratos con inducción de carcinoma mamario, cirugía y la aplicación de TENS, IFC y PBMT. **Conclusión:** Este estudio demostró que hubo recurrencia local de tumores en ratos que fueron estimulados con TENS o IFC, sin embargo, no hay evidencia de recurrencia local con PBMT.
Palabras clave: estimulación eléctrica transcutánea del nervio; terapia por estimulación eléctrica; terapia por luz de baja intensidad; modalidades de fisioterapia; neoplasias de la mama.

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INTRODUCTION

When it comes to cancer survivors, pain is a common problem, mainly in breast cancer, and in the first few years after the treatment. Cancer treatments, in general, have the potential to cause pain and the life expectancy of those patients is 10 years which is a longtime using medication. Hence, the use of non-pharmacological therapies appears to be necessary[1].

Transcutaneous electrical nerve stimulation (TENS) is a safe and non-invasive modality for pain treatment. Although studies about its use in the cancer population are controversial[2], it is generally not recommended or contraindicated for patients with active cancer[3]. The effect of TENS on blood flow remains unresolved. Few studies have evaluated its use in specific cancer populations. As tumor growth is angiogenesis and blood flow dependent the effect of TENS on blood flow in the cancer population is controversial[4].

Interferential current therapy (IFC) is a common electrotherapeutic modality broadly used to treat pain[5]. It not only reduces pain by stimulating thick nerve fibers, but it can also normalize neurovegetative balance and, in consequence, cushion the orthosympathetic system, facilitating muscle relaxation and increased circulation, which also contributes for pain relief[6]. IFC can be more useful than TENS since it is meant to penetrate deeply into the skin, while it causes minor discomfort to the user[7]. However, the clinical impact of interferential currents on cancer patient remains controversial and no studies evaluating the safe use of IFC in cancer patients have been published[8].

Photobiomodulation therapy (PBMT) has been used successfully to reduce oral mucositis[9], chemotherapy-induced peripheral neuropathy[10], breast cancer related lymphedema[11], radiodermitis[12], wound healing and post-surgical pain syndrome[13] however it is still controversial about the effects on tumor cells that may remain after cancer treatment. As tumor cells or premalignant cells could be irradiated unintentionally with PBMT during the treatment of cancer-related complications, the parameters of the effects of its irradiation on tumor cells is a very important issue and has been the focus of previous studies[14].

In vivo studies are essential for studying disease development and should be the main tool for studying the tumor cells' behavior. The complexity of the multicellular environment of the disease in progress makes it difficult to predict tumor behavior and cell culture studies alone don't assess tumor responses properly[15].

The aim of this study is to analyze the effect of low and high frequency TENS, IFC and 830 nm PBMT in the appearance of local recurrence of breast cancer in rats.

METHOD

Sample

Experimental, randomized, controlled and cross-sectional study submitted and approved by the Ethics Committee of Animal Use (number 003/2016) of "*Centro Universitário das Faculdadades Associdas de Ensino*" – UNIFAE. The animals were randomly assigned to each group. The experiment was conducted in UNIFAE. The animals were allocated individually per cage. The technician who accompanied the experiment remained blind to the interventions performed.

This study included 39 Sprague - Dawley rats distributed in five groups. The sample size was suggested by the Ethics Committee of Animal Use.

Groups

- GROUP A: 9 rats without breast cancer induction.
- GROUP B: 9 rats with induction of mammary carcinoma and without surgery.
- GROUP C: 9 rats with induction of mammary carcinoma with surgery and with the application of placebo TENS (TENS-D, n=3), IFC (IFC-D, n=3), PBMT (PBMT-D, n=3).
- GROUP D: 9 rats with induction of breast carcinoma, with surgery and with the application of high frequency TENS (TENS-D, n=3), IFC (IFC-D, n=3), PBMT (PBMT-D, n=3).
- GROUP E: 3 rats with induction of breast carcinoma, with surgery and with the application of low frequency TENS.

Breast carcinomas were induced with 90 days of life in the rats of groups B, C, D and E. After 120 days, the rats of groups C, D and E underwent surgery to remove the tumors. Three weeks later (after 141 day), the interventions were carried out for ten consecutive days, except on weekends. All rats were followed up for one year.

All rats were fed with purine for rodents and water *ad libitum* in photoperiodic cycles of 12 hrs light and 12 hrs dark at 22 °C, ± 2 °C. Breast carcinoma was induced through a single dose of 20 mg of 7.12 dimethylbenz (a) anthracene given intragastrically by gavage in rats of groups B, C, D and E.

Stimulation protocols

1. Transcutaneous Electrical Nerve Stimulation (TENS),

Electrostimulation was applied with adhesive electrodes of 1 cm in diameter placed around the surgical scar. The parameter used for high-frequency TENS

(Neurolinguística Ibrmaed®, 2000 generation) was 100 Hz/100 μs and for low frequency 2 Hz/200 μs. Pulses were squared, symmetrical, balanced and biphasic. Both parameters were administered for 30 minutes each, below the motor threshold for 10 consecutive days, except on weekends. The tumors were referred for histopathological analysis after surgery.

2. Interferential Current Therapy (IFC)

Electrostimulation was applied with adhesive electrodes 1cm in diameter placed around the surgical scar. The parameter used for the IFC (Neurovector Ibramed®, shapphire line) was bipolar continuous mode, 4khz, 100 Hz, 55 sweep frequency (Hz), 20 minutes/ below the motor threshold/10 consecutive days, except on weekends. After surgery, the tumors were referred for histopathological analysis.

3. Photobiomodulation Therapy (PBMT)

After tumorectomy with surgical safety margin, rats of group D were stimulated at the site of surgery by PBMT (Laserpulse, Ibramed®) GaAlAs, 2J/cm², 4 seconds per point, 830Nm, continuous mode, for 10 consecutive days, except on weekends.

Material collection

The C, D and E rat groups were anesthetized with 5% ketamine (5 mg/kg) intraperitoneally and submitted for tumor removal (lumpectomy). Antibiotic therapy was administered 10 minutes before surgery (Amoxicillin 150 mg/kg) and dipyrone (150 to 600 mg/kg) for 2 to 4 hours per half of subcutaneous injection.

After the lumpectomy, TENS, IFC or PBMT stimulated D and E rat groups at the site of surgery.

Histological analysis

The original hematoxylin and eosin slides were retrieved by 2 experimented pathologists to reclassify the breast tumors according to the current histopathologic criteria[16]. All specimens had been previously formalin-fixed and paraffin-embedded. Deparaffinized 4-5μm sections of the blocks were rehydrated and H&E stained according to routine staining procedures. All H&E-stained slides were reviewed by at least 2 observers (surgical pathologists). The pathologists were blinded. They evaluated 10 high power fields (HPF) of each slide and the interpretation results were released by consensus.

The histopathological findings were: the histological type and degree of differentiation of the tumor, the tumor size, vascular invasion, breast skin involvement, the tumor multifocality, the distal organ and regional lymph node metastases, and the pathologic stage and molecular subtypes (anticipating the prognosis and predictive markers of therapeutic response).

All applicable international, national, and institutional guidelines for the care and use of animals have been followed[17]. All the procedures conducted in studies involving animals complied with the institution's ethical standards where the studies were conducted or the current practice.

RESULTS

In group A the rats had no sign of breast cancer during their one year of follow up. The rats in group B developed breast cancer since they were not treated. All of them had consumptive syndrome and died because of the cancer prior to the follow up period of one year. All the rats in group C showed no sign of local recurrence of breast cancer. In group D, all the rats submitted to the surgical procedure and the application of high frequency TENS and IFC presented local recurrence of breast cancer. In group E, 33% of the rats submitted to the surgical procedure and the application of low frequency TENS presented local recurrence of breast cancer.

After the application of PBMT, the rats of group A had no sign of breast cancer during one year of follow up. The rats in group B developed breast cancer and as they were not treated, all of them had consumptive syndrome and died because of the cancer before one year of follow up. All the rats in group C showed no sign of local breast cancer recurrence and the same happened with the rats in group D after one year of follow up showing no influence of PBMT on breast cancer local recurrence. Rats of groups A, C and D had no weight loss [Chart 1].

Rats of groups A and C had no weight loss. Rats of groups D and E had weight loss proportional to their local recurrence of breast cancer growth with TENS and IFC stimulation.

After the histopathologic analysis, all the tumors were classified as invasive malignant epithelial neoplasms[16] as follows: invasive mixed adenocarcinoma with tubular areas, papillary areas, and cribriform areas. The tumor exhibited clinical criteria (weakened, emaciated rats with large tumor volumes, infiltrating neighboring structures, skin ulcerations and faster growth); macroscopic criteria (friable consistency, areas suggestive of necrosis and hemorrhage); and histopathological criteria: necrosis, atypia, mitosis atypical and infiltration in adjacent tissues (skeletal musculature, adjacent skin, and adipose tissue).

DISCUSSION

This study showed that the use of low and high frequency TENS and IFC increased the local recurrence

Chart 1. Signs of breast cancer during one year of follow up per group of rats according to protocols TENS, IFC and PBMT

Groups	Group description	TENS	IFC	PBMT
			One year of follow up	
A	Rats without breast cancer induction	No sign of breast cancer	No sign of breast cancer	No sign of breast cancer
B	Rats with induction of mammary carcinoma and without surgery	Developed breast cancer without treatment and died before their one year follow up	Developed breast cancer without treatment and died before their one year follow up	Developed breast cancer without treatment and died before their one year follow up
C	Rats with induction of mammary carcinoma with surgery and with the application of placebo TENS	No sign of local breast cancer	No sign of local breast cancer	No sign of local breast cancer
D	Rats with induction of breast carcinoma, with surgery and with the application of high frequency TENS or IFC or PBMT	Presented local recurrence of breast cancer	Presented local recurrence of breast cancer	No sign of local breast cancer
E	Rats with induction of breast carcinoma, with surgery and with the application of low frequency TENS	Presented local recurrence of breast cancer (33%)		

Captions: TENS = Transcutaneous Electrical Nerve Stimulation; IFC = Interferential Current Therapy; PBMT = Photobiomodulation Therapy.

of breast cancer in rats after they had their breast cancer surgically removed. On the other side, no influences of PBMT were noticed in the appearance of local recurrence.

TENS is used as a targeted therapy, a low-cost non-pharmacological intervention for the treatment of acute and chronic pain conditions. It delivers alternating currents via cutaneous electrodes positioned near the area of pain[18]. Both high and low frequency TENS have been shown to provide analgesia specifically when applied at a strong, non-painful intensity and high frequency TENS may be more effective for individuals taking opioids[18].

It is one of the main therapeutic electrical currents used to influence and modulate pain in the nerve conduction process and acts as a liberator of endogenous opioids. Although TENS is predominantly used for the symptomatic relief of pain in clinical practice, it has been increasingly used as an antiemetic and to restore blood flow in ischemic tissue and wounds[19].

In the literature review, arguments that tried to explain how TENS can act as adjuvant in the control of cancer pain were found. In despite of reports encouraging its use as a therapeutic method for pain relief caused by cancer, it is not still a consensus[20] among authors.

There is insufficient scientific evidence to determine whether TENS can be used to treat pain in cancer patients and if its use is effective. Salim and Nigim[21] have shown that there is no significant pain relief. On the other hand, some authors support the use of TENS.

TENS was reported to stimulate the peripheral nerves and induce the release of the substance P (an 11 amino acid peptide) from the sensory nerve endings triggering vasodilation. Calcitonin gene-related peptide was also claimed to be related to TENS stimulation. An increase in blood flow patterns with this treatment resembled what was achieved by calcitonin gene-related peptide administration rather than the inhibition of vasoconstriction. When applied at the sensory threshold, it increased blood flow by alteration of the sympathetic vasomotor activity. On the other hand, whether applied at the motor threshold level it is thought to promote blood flow as a result of the increased metabolic demand in the contracting muscle[4].

Possibly there are several reasons contributing for the restricted utilization of TENS, including some concerns about the potential acceleration of metastatic cancer[20] limited knowledge or resources for applying

TENS. Possibly, the compassionate use of TENS in life-limiting situations may be more effective as opposed to nonterminal situations where risk of reoccurrence of cancer is present[22].

Until now, there is poor evidence to decide whether TENS should be used in adults with cancer-related pain[23]. Previous studies concluded that TENS, along with a range of other interventions, but acknowledged that scarce data are unable to support this[24]. Moreover, two other studies have shown little evidence that TENS is better than placebo in treating women with chronic pain following breast cancer treatment[25].

This therapeutic modality modifies the cardiovascular system responses, causing vasodilation, increased blood flow, and decreased peripheral vascular resistance, heart rate and systemic arterial blood pressure, all of which are associated with modulating the autonomic balance. Therefore, some studies have focused on the application of TENS tools in the treatment of other clinical conditions, such as those involving the alteration of systemic arterial pressure, as noticed for hypertension and diabetes[26].

The effect of TENS in the cancer population is controversial. Tumor growth is highly dependent on angiogenesis and blood flow; therefore, with blood flow affecting oxygen and nutrient supply to tumors, attention must be paid to the use of TENS[27].

Recent studies indicate that the high blood flow at the TENS stimulus site is the result of increased muscle activity and that the high frequency, or low frequency of the TENS below the motor threshold has no clinically significant effect on blood flow[28]. In the present study, it was evident the increased blood flow in the postoperative scar.

Another study suggested that TENS may encourage metastasis by increased blood flow from a stimulated muscle contraction or by stimulation-induced angiogenesis thereby encouraging tumor growth or spread[24]. Nevertheless, neuromuscular electrical stimulation does not promote the growth of underlying tumor in head and neck cancer[29].

However, in 2010, the journal Physiotherapy Canada recognized as one of the leading scientific journals of physiotherapy, published the results of a research by Houghton et al.[30] entitled "*Electrophysical Agents, Contraindications and Precautions: An Evidence-Based Approach to Clinical Decision Making in Physical Therapy*" consisting of recommendations for the use of electrophysical agents in a variety of conditions or in specific areas of the body. According to this research, they recommended not using TENS as a treatment option if there is any presence of malignancy or on any part or regions of the body where suspected or confirmed malignancy exists, since TENS may stimulate growth and promote the spread of cancer cells and the angiogenic effects may provoke the spread of tumors. Bone is a common metastatic site for many types of cancer; the analgesic effects of TENS may mask pain as well as the early signs of metastatic disease as concluded in this study[30].

In addition, the TENS parameters are variable, according to the intensity, frequency, pulse duration, electrode placement, and application time. In relation to the cardiovascular system, the pulse frequency seems to present different hemodynamic responses, generally applied at low (<10 Hz) or high (>50 Hz) frequencies. The application of acute TENS at low frequencies (2 and 4 Hz) produced a local increase in muscle and coetaneous blood flow. On the other hand, at high frequencies (80 and 110 Hz), these changes were unnoticed. Nonetheless, the high frequency (80 Hz) promoted vasodilation, reduced systemic blood pressure, and improved sympathetic-vagal balance during exercise[30]. The parameters of pulse frequency intensity are adjustable and linked to the effectiveness of TENS.

Despite the fact that the safety of the use of TENS in oncological patients is not entirely clear and there is no consensus in the literature, the present study demonstrated a higher rate of recurrence of breast cancer after the use of TENS.

There are scarce studies investigating the mechanisms of analgesic action of IFC, but the most quoted theory to explain the modulation of the pain by IFC is the gate control theory similar to TENS. The theory suggests that stimulation of afferent fibers of large diameter (Aβ) promotes the activation of local inhibitory circuits of the dorsal horn of the spinal cord and in consequence, prevents pain impulses carried by small-diameter fibers (C and Aδ) from reaching the upper centers[30].

Investigators have reported IFC effects as increased blood flow on account of its impact on parasympathetic nerve fibers and induced-muscle contractions electrical stimulation that result in better venous and lymphatic return. These currents can also be applied to accelerate the healing of wounds and bone fractures, improving cell function, and increasing cell proliferation. It seems that the IFC chain alters the concentration of intracellular enzymes and other molecules that are important in varied metabolic processes[5].

IFC uses two different intermediate frequencies (1001-10,000 Hz) of alternating currents in the painful area. The two medium-frequency currents come together, thereby creating a stream with a lower frequency (1-1000 Hz) or beats per second (bps). It has been purported to relieve pain and to increase blood flow to the tissues, acting as a counter-irritant stimulus[6].

Studies with animal models indicate that the IFC while increasing angiogenesis, improves tissue perfusion and, therefore, reduces swelling. Its use expands regional blood perfusion and diminishes ischemic pain. Electrical stimulation can lead to physiological suppression of sympathetic fibers of small arterioles in the muscle belly, reducing sympathetic tonus, and thereby, augmenting local blood flow. This mechanism has been suggested as the main cause of expanded tissue oxygen. IFC may provide an increment of local circulation and a decrease in interstitial edema as a result of stimulatory and pumping effects[31].

Rats submitted to IFC and TENS therapy after cancer removal had a higher rate of breast cancer local recurrence. However, no sign of local breast cancer recurrence with PBMT application was detected.

Unlike electrical currents, photobiomodulation emits light, and the light absorption is made possible by the chromophores (photoacceptors) located in the mitochondrial inner membrane. In 2014, the North American Association for Laser Therapy and the World Association for Laser Therapy defined PBMT as the "therapeutic use of light absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic, biological reactions through photochemical or photophysical events, leading to physiological changes"[32]. The proliferative cellular response to PBMT is believed to be the result of a change in the redox state of mitochondrial redox couples, which in turn regulates a number of signaling pathways and transcription factors that are involved in cell proliferation, growth, and motility. PBMT is able to increased expression of genes related to protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, antioxidant enzymes. Stem cells and progenitor cells appear to be particularly susceptible to PBMT[33].

The effect of PBMT is based on the capacity to modulate various metabolic processes by converting the laser light energy input through biochemical and photophysical processes that transform the laser light into energy useful to cells. The energy interacts with the cells and creates a myriad of positive functions such as accelerated wound healing, pain relief, regeneration, and immune enhancement[34]. There are multiple biological actions of PBMT in experimentally induced models of inflammation such as changes in biochemical markers of inflammation and effects on neural structures that are damaged by compression or inflammation[35].

PBMT, approved by the USA Federal Drug Administration in 2007, has been used in the treatment of postmastectomy lymphedema since 1995 in countries other than the USA. At the cellular level, PBMT is reported to stimulate fibroblasts, macrophages, and lymphocytes under physiologic stress or in pathologic conditions[36]. The 830nm PBMT showed favorable results in reducing limb volume[37] and is used in the clinical treatment of breast cancer-related lymphoedema, despite limited safety information[34].

PBMT has been reported to induce angiogenesis in several experimental models of animals treated. Various types of cells can have their proliferation levels increased by PBMT. It appears that stem cells are particularly sensitive to light. It induces the activity of stem cells demonstrated by increased migration, differentiation, proliferation, and cell viability, as well as by the activation of protein expression[38].

With such well-documented effects on cell proliferation, PBMT faces opposition when light is clinically applied to body sites that present tumor cells or lesions with metastatic potential, mainly because the literature is still contradictory about this issue. For example, the fluence of 30 J cm–2 (1.2 J) did not influence cell viability following exposure to 2.5 Gy but a significant increase on viability occurred on day 4 in cells exposed to 10 Gy. These results indicate that the stress level caused by ionizing radiation may be an important factor when measuring PBMT cellular response to low light fluences[39].

Additionally, Crous and Abrahamse[40] indicate the possible detrimental effect that PBMT may have when used as a biostimulatory therapy on the underlying tissue lung cancer stem cells when considering the proliferation and viability induced using visible wavelengths.

Because PBMT has been shown to increase blood flow and cellular energy production, it has been hypothesized that laser could have a carcinogenic influence on tissues. There is an *in vivo* study of Frigo et al.[41] that showed high irradiance and high dose of PBMT increased tumor volume and blood vessels on melanoma. *In vitro* studies showed no adverse effects, some of them reporting increased phagocytic and chemotactic activity of leukocytes while noticing no acceleration of tumor cell reproduction[42].

The use of PBMT has brought concerns regarding many adverse effects occurring during chemoradiotherapy/radiotherapy in cancer patients. When a malignant solid tumor or a potentially malignant region is irradiated with low-dose laser irradiation, it may be stimulated to undergo malignant transformation with negative effects, such as proliferation of tumor cells or promotion of metastasis[43]. To address these concerns, Sonis et al.[44] carried out a review of the literature on the possibility of an impact on tumor growth or proliferation, the risk of local invasion or metastases, a negative effect on a tumor's treatment response, and whether local application of PBMT could have effects distant from the targeted site.

Brandão et al.[45] suggest that PBMT is not capable of promoting mutagenesis in clonally related dormant tumor cells, because no evidence of malignant transformation of potentially malignant lesions was identified in the regional sites during the sessions. It did not impact the incidence of local-regional or distant control and survival outcomes in oral cancer patients. Therefore, until it is established that PBMT does not negatively affect established cancers, the North American Association for PBMT states that it is contraindicated[39].

Limitations of the present study are the lack of sample size calculation, statistical analysis, and blinding of researchers during interventions. It is suggested that research on the safety of the use of electrophysical agents be conducted in oncology to support the use in human beings.

CONCLUSION

In the present study, rats submitted to TENS or IFC therapy after cancer removal had a higher rate of local breast cancer recurrence. Based on these results, TENS and IFC should not be used in patients with breast cancer unless studies in humans show these therapies hold no influence on breast cancer recurrence. TENS and IFC should be used cautiously in the cancer population when curative intent is being attempted. In contrast, PBMT does not have the potential to generate heat in the cellular metabolic process with the parameterization used in the present study. As well as electric stimulation, the PBMT should only be considered safe in human application if human studies do not show an influence of this resource on cancer recurrence.

CONTRIBUTIONS

All the authors contributed substantially for the study conception/design, collection, analysis and/or interpretation of the data, wording and critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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