CHAPTER 13

8-YEAR OBSERVATIONAL STUDY ON NATUROPATHIC TREATMENT WITH MODULATED ELECTROHYPERTHERMIA (MEHT): A SINGLE-CENTRE EXPERIENCE

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Abstract

There is a considerable amount of research supporting the use of hyperthermia a treatment in oncology, and on the use of naturopathic treatment methods to complement therapy. This investigation examines survival outcomes in cases of advanced, metastatic solid tumor entities in patients with distant disease and a poor prognosis. Our objective is to present the findings of our complex integrative treatment from the past 8 years within an integrative naturopathic oncology setting.

Locoregional hyperthermia was applied in complementary protocols using the modulated electrohyperthermia (mEHT) device, the Oncotherm EHY-2000+. The mEHT method has been integrated with conventional treatment, studied alongside various adjuvant treatments for many solid tumor cancer types.

An examination of the data from the past 8 years is provided, showing the synergy between the naturopathic oncology and hyperthermia methods. mEHT has been administered to hundreds of patients with over 35 cancer types over the past 8 years in our center. Data elements include patient statistics, cancer group & type, treatment(s) used, adverse events, overall survival (OS), diagnostic imaging & blood test results.

mEHT is a safe treatment with very few adverse events or side effects, allowing patients to maintain a high quality of life. Moreover, our initial data indicates that the addition of this therapy into an integrative oncology setting provides benefits to PFS and OS, as well as to QoL.

Introduction

Life is based on energetically open systems, where environmental conditions determine their equilibrium. Living systems are controlled by complex mechanisms, always trying to maintain homeostasis [1]. Malignant disease breaks this dynamic equilibrium. Using a naturopathic oncology (NPO) approach to reestablish healthy homeostasis [2] is increasingly playing a role in the treatment of cancer. The NPO approach provides the effective and safe use of natural and supportive therapies combined with standard of care [3]. The aim is to provide the best possible outcomes for patients while improving quality of life, supporting recovery, and managing the adverse effects of conventional treatments. NPO further teaches patients how lifestyle factors can improve quality of life and reduce the risk of recurrence. In doing so, NPO can also manage comorbidities and chronic symptoms like diabetes, hypertension, autoimmune reactions, allergies, anxiety, and depression. The NPO approach treats the person as a whole, similar to the traditional far-east medical principles. It is also based on up-to-date knowledge, and includes addressing lifestyle factors like diet and exercise alongside natural medicines, herbal extracts, and phytochemicals. With this ideology, there is strong potential for the use of an integrative approach in cancer therapy [4], including the psycho-spiritual well-being of patients in terminal cases [5], [6].

Hyperthermia (HT) in oncology has a long-standing history, having roots in ancient medicine [7] going back more than two thousand years [8], much like the roots of naturopathic medicine. The benefits of HT shown in experimental and clinical studies [9], [10], [11] support wide application of the method in many advanced malignant diseases [12]. HT is increasingly used as a complementary therapy to conventional cancer-treatments.

In addition to its benefit as an adjunctive therapy there is also evidence to support its use as a monotherapy. Classical HT as monotherapy has been applied when no other treatments were available, [13], and used for palliative care because of its selectivity towards tumor cells [14], [15] while maintaining a low side effect profile. In an extended study, localized HT alone has been used for the treatment of cancer recurrences in which previously administered conventional therapies have failed [16]. The results of the combined therapies (when it was applicable) was found to be more effective [17].

The physiological and molecular framework of tumor cells differs from healthy cells leaving malignant cells more sensitive to the damaging effects of higher temperatures when compared to healthy tissue [18]. The potential benefits of HT as complementary to standard of care are promising. This, combined with the knowledge that the therapy appears to be safe and does not contribute to additional treatment related toxicity [19] lends itself to be a promising treatment in cancer care.

HT has a multitude of complex actions against cancer. Its effects on reshaping vascularization are especially notable. Solid tumors and their healthy environment react first with vasodilatation, increasing the blood-flow in the heated tissues [20], [21]. However, once over a tumor-specific temperature threshold, this turns to vascular contraction [22] within the solid tumors, while in the healthy tissue the vasodilatation continues in an accelerated way [23], [24] Multiple cellular changes are also seen, as HT causes changes in lipid-protein interactions [25] and can denature proteins [26]. These changes in blood-flow are crucial for the chemosensitizing benefits found when combined with conventional pharmaceutical agents delivered to the tumor via the bloodstream. Higher local temperature vasodilates peri-tumoral arteries, increasing microcirculation in the heated volume, thus enhancing the efficacy of conventional chemotherapies [27]. Based on this

blood-flow increase the synergy between HT and many chemotherapies is well-established [28], [29]. HT has been shown to accelerate the primary mode of action of various chemotherapy drugs including alkylating agents, inducing protein and DNA damage, and enhancing the production of oxygen free radicals [30], [31], [32], [33], [34]. Several drugs including melphalan, nitrogen mustards, anthracyclines, cyclophosphamide, nitrosoureas, bleomycin, and mitomycin [35], [36] have shown clinical improvement when combined with HT.

HT is a catalyst for hyperthermic drugs [37] and local HT increases target specificity of the treatments while at the same time reducing systemic side effects [38], [39]. In cases where the toxicity of chemotherapy has become the limiting factor, low-dose chemotherapy may be used [40], [41] with HT promotion. This is a promising combination with low-dose metronomic chemotherapy for example [42]. Heat accelerates the metabolic rate and activates the dormant cells in G0 phase, making it possible to kill these cells by concomitant therapy.

Increased microcirculation from HT sensitizes the effect of ionizing radiation [43] and complements cell-cycle arrest [44] together with the suppression of DNA-dependent protein-kinase (DNA-PK) [45]. Excellent summaries of clinical results with radio-thermotherapy have already been published [46], [47].

In respect to surgery, HT can be considered to shrink tumors pre-operatively. In the setting of an inoperable tumor, HT may be used to make surgical interventions possible [48]. Postoperatively HT may be used to prevent metastatic dissemination and relapses of the tumor [49].

Heat shock protein (HSP)-promoter gene therapy is improved with HT by inducing local HSP production and by enhancing the local rate of release from liposomes [50]; it was also found helpful in the double suicide gene transfer into prostate carcinoma cells [51], and successful combination has shown synergistic effects of HT with HSP-promoter mediated gene therapy in cases of patients with advanced breast cancer [52]. This combination therapy was highly selective for mammary carcinoma cells. Heat-induced gene expression could be an excellent tool in targeted cancer gene therapy [53]. Combinations of HT with hormone [54], enzyme [55], photodynamic [56], gene [57], immune- [58] and other supportive-therapies [59] are well described in the medical literature.

T lymphocytes (helper and killer T-cells) have specific affinity for tumor cells through the recognition of major histocompatibility complexes (MHC I) bound to tumor antigens. Cancer cells have the capability to down-regulate MHC I, leading to decreased susceptibility to T-cell mediated destruction [60]. The action of natural killer (NK) cells which target MHC deficient cells is essential in this evasive process [60], [61] HT increases NK cell activity [62] and combats this protective antitumor mechanism [60, [63], [64].

Two HT methods are used in integrative therapy: the immunogenic modulated electrohyperthermia (mEHT), [65], and the immune-stimulating fever-range whole-body hyperthermia (fWBHT) [66], [67]. Both have been added to integrative medical approaches as adjuvant treatment of various cancer types. The heat-stress induced chaperones are the basis of the known tumor-specific vaccination effects of mEHT [68], [69].

Numerous widely accepted and proven protocols exist for different tumor entities, acting both locally (like most of radiotherapies) or systemically (like with most pharmaceutical products). While these therapies are largely successful, they may be limited by toxicity and adverse effects. When patients develop distant metastases, prognosis drastically worsens [70] and the standard of care treatments typically fail. Distant spread of solid tumors turns the patient's treatment into palliative care. The lack of success with conventional therapies in advanced metastatic cases requires a change of the treatment paradigm.

One should keep in mind that malignancy is a systemic process, and the medical task is not only to eliminate the visible tumors, but to address the expected non-visualized micrometastases. Our task in oncology is complex and needs personalized thinking to heal the suffering patient, or at least increase their quality of life in the palliative setting. The obvious solution is to enhance the patient's innate ability to fight against the disease. The missing piece for oncologic therapy could be the patient's own self-healing mechanisms, recognized by the new paradigm of immuno-oncology, where the patient's own immune system is augmented to treat the disease. In this new approach, the patient is an integral part of the therapy. Naturopathic medicine uses the best of conventional medicine together with natural medicines, diets, and lifestyle changes, and the use of HT.

HT as a physical method can support curative intent by re-sensitizing and enhancing the effect of previously refractive therapies. There is a considerable amount of research supporting the use of HT as an adjuvant treatment in oncology. The success of HT is shown in many clinical trials, but still lacks wide acceptance among the medical profession. mEHT is a further advancement over conventional HT [71]. The concept of mEHT is the selective deep heating of malignant cells [72]. It uses electric field technology for selection.

More recently the electromagnetic-based HT applications have become much more actively studied for cancer treatment [73], [74], [75]. A distinguishing feature of malignant cells is their ability to metabolize more intensively than healthy cells, using anaerobic glycolysis, a less complex metabolism than the mitochondrial Krebs-cycle; to support rapid proliferation with sufficient amounts of ATP [76]. The high metabolic rate produces a high concentration of ionic species (metabolites and waste) in the microenvironment, which specially conducts radiofrequency (RF) current. Another distinguishing feature of malignant cells is their isolated (autonomic) behavior. These cells break their intercellular junctions [77] and bonds [78]. Despite the detriment to individual cell growth, this disordered microenvironment increases the dielectric constant of the extracellular electrolytes in the tumor microenvironment [79]. This high dielectric constant around malignant cells better channels the RF current [80]. Furthermore, frequency dispersion (β/δ dispersion [81]) and the Schwan effect [82] help to target the transmembrane proteins and select water-bound states [83] at the membrane. This focusing of the energy from the excitation of signal pathways [84] in the membrane rafts, is expressed in high concentration on the membrane of malignant cells [85]. Energy is absorbed on the membranes of the cancer cells heating them up; mEHT thus applies heterogenic heating of the malignant cells instead of isothermal homogeneity. mEHT uses local heat on tumor cells ranging from 40-43°C [86], while the homogenic average of temperature over a tumor remains under 40°C to avoid blocking the immune cells being active in the heated area.

The real differences between mEHT and conventional HT are seen in both in vitro and in vivo experiments [87], [88]. The clinical studies of mEHT seem to be consistent with the preclinical data. Increased blood-flow is observed [89], increasing both chemo- and radio-sensitivity. A pharmacokinetic trial [90] showed increased permeability of blood vessels.

mEHT shows promising results in various cancer types. Even a delicate organ like the brain can be treated safely [91]. Clinical results for advanced stages of gliomas [92] [93] [94] [95], uterine cervix carcinomas [96], malignant ascites [97], lung cancers [98] [99], pancreas carcinomas [100] [101], prostate cancer [102] [103], colorectal cancers [104] [105], and sarcomas [106] [107] show the potential of mEHT.

Even though mEHT is a local treatment, it can also act systemically via the abscopal effect [108], [109], [110]. This vaccination-like mechanism has been observed in human case reports [111], [112], [113], [114].

Supportive therapies can complement mEHT treatment by aiding in improving quality of life concerns. mEHT has been studied together with Traditional Chinese Medicine (TCM) [115], [116], [117], [118], [119], high-dose vitamin-C [120], and other proven supportive therapies like immune-supporters, painkillers, electrolyte regulators, and many other agents.

This article highlights the potential benefit of a naturopathic integrative approach using mEHT, including an evaluation of the treatment's safety. This research is based on an integrated approach to cancer treatment, with the only constant being that all patients included in the cohort included mEHT as a primary therapy. The article has three main objectives:

1. To assess 5-year survival patterns for the most commonly treated advanced distant metastatic cancer types.
2. Analyze baseline patient characteristics of those using mEHT
3. To evaluate the safety profile of mEHT.

Our objectives are presented with the findings of these treatments over the past 8 years in an integrative naturopathic oncology setting. The retrospective datasets when compared to the historical control of the large NCI database (SEER), show 5-year survival benefit using mEHT within an integrative naturopathic approach.

Methods

Since 2010, the Integrated Health Clinic (IHC) in British Columbia, Canada, has adopted and studied the use of mEHT within their already well-established integrative naturopathic medical. Using mEHT as the central component of therapy, data has been retrospectively collected with the aim of evaluating the potential benefits of an integrated approach to cancer treatment including mEHT. A retrospective data-collection was chosen over a prospective study because of the highly personalized nature of naturopathic oncology treatments, a real-world data approach. Prospective collection of a unified cohort proved to be very challenging. The goal of documentation was to assess the trends in overall survival of patients. As the nature of integrative treatment does not lend itself to single intervention research models, this paper is examining a 'whole systems' approach to treatment, a broader, more integrative framework that considers a range of variables and their interactions [121], [122] and thus offers unique insights given the integrated and interactive nature of variables within this retrospective cohort study.

The Research and Ethics Board (REB) of the Canadian College of Naturopathic Medicine (CCNM) qualified the study

and has provided review and oversight for this research project in order to assure that it meets all scientific and ethical principles, and that it complies with all applicable regulations and standards pertaining to human participant protection. The study was officially cleared by the REB. Following standard ethical procedures, patient charts that were used for this review and any subsequent analysis were kept anonymous, and the identity of the persons was handled with strict confidentiality.

Study design

This is a retrospective cohort study looking at historical data for a group of cancer patients receiving an integrative treatment protocol which includes mEHT. The basic pillars of the protocol include:

1. Primary cancer care
2. Immune system support
3. Best supportive care through treatment
4. Post-treatment (survivorship) care

An integrative protocol does not concentrate on the tumor alone, but rather focusses on the patient as a whole.

Primary cancer care

Cytotoxic treatments are provided along with standard of care treatments to improve efficacy & reduce side effects:

- Using mEHT with EMF to kill cancer cells & enhance conventional CT/RT.
- Intravenous infusion of high dose vitamins & other medicines.
- Direct introduction (injection) of focused cancer fighting agents.
- Targeted supplementation, addressing known molecular targets of each patient's cancer.
- Prescriptive medications, including repurposed drugs used to manage known targets of cancers.
- Sensitization of conventional therapies, maximizing conventional treatment efficacy.

Immune stimulating therapies

Therapies that improve immune management of cancer, supporting the body's natural defenses:

- Infusions of immunologic medicines such as vitamin C.
- Focused immune support (by injection) such as mistletoe therapy.
- Targeted oral supplementation to support components of the immune system.
- Biological therapy, agents to stimulate immune activity.
- Immunotherapy sensitization by supporting PD-1/PDL-1 and CTLA 4 drugs.

Supportive protocols

Managing the unique issues faced by each patient to maximize quality of life throughout their care:

- Detoxification / Chelation to promote the removal of toxins, heavy metals, and other waste materials.
- Targeted vital organ support for the liver, kidneys, skin, and bowels/biome to normalize function.
- Routine laboratory testing to adhere to best practices and monitor therapies.
- Dietary counselling to optimize treatment outcomes and support metabolic processes.
- Lifestyle counselling to harness the benefits of exercise, stress management, mindfulness, and psycho-social support.
- Acupuncture & TCM, combining classical acupuncture & herbs to support the normal healthy functions of the body.

Post-treatment (survivorship) care

Rehabilitation to continue to live cancer-free and reduce the risk of recurrence using personalized cutting edge survivorship, surveillance, and prevention strategies:

- Intravenous and injections therapies to optimize nutrition and tissue health, electrolyte balance, and normal transport processes in the body.
- Targeted supplementation to address each patient's specific needs.
- Dietary counselling and implementation of dietary strategies with potential anti-cancer benefits.
- Lifestyle counselling to harnessing the benefits of exercise, stress management, mindfulness, and other cancer prevention strategies.
- Detoxification / Chelation to removal of toxins, heavy metals, and other waste materials known to interfere with

proper body function.

Inclusion and exclusion criteria

Eligibility for the study included:

- a biopsy-proven cancer diagnosis;
- distant metastatic disease at the time of diagnosis;
- an assessment of a disease state that could be treated with mEHT;
- ability to travel to IHC for treatment;
- completion of a minimum of 6 mEHT treatments

Exclusion criteria:

- Patients with local disease were excluded from the study in all the investigated cancer types, including locally advanced at the time of inclusion.
- Those who received less than 6 mEHT treatments.
- Patients in which mEHT was contraindicated:
  - those with organ-transplants,
  - those not able to clearly communicate, (like babies, toddlers, elderly under legal representative care, unconscious patients, patients in a coma, etc.),
  - those with blood-born cancers, (only solid tumors were investigated),
  - those that were pregnant,
  - those insensible to heat,
  - those not able to keep the treatment position during the 60-minute mEHT treatment process

Measures

Baseline measures:

- date of diagnosis,
- stage at diagnosis,
- stage at new patient visit,
- complementary treatments,
- previously received therapies including CT/RT

Evaluation measures:

- overall survival was assessed over 5 years using Kaplan-Meier non-parametric estimate,
- quality of life,
- adverse / side effects directly attributable to mEHT

Hyperthermia technique

Local hyperthermia

mEHT was administered with the EHY2000+ system. Treatment areas of 20 cm or 30 cm diameter were used depending on the size and location of the tumor.

mEHT applies radio-frequency (RF) carrier-wave with amplitude modulation with high efficacy [123] and creates a strictly impedance-matched resonant circuit, where the patient is a part (an "electric component") of the RF current loop. The capacitive part of the patient's impedance is compensated for as much as possible. The frequency could be anywhere in the range of beta-delta dispersion (around 10MHz) and for practical purposes 13.56 MHz is used, which is the allowed medical standard. The heterogenic complex impedance of the target guides the RF current for selective heating, with high preciosity [124]. Energy absorption is concentrated on the tumor-cells and their microenvironment [125], with selective targeting of the membrane rafts of malignant cells [126].

The EHY-2000+ is produced in the European Union, approved according to the European Medical Device Directive (CE-MDD), and produced in Good Manufacturing Process under ISO13485 standard, certified by TUV Product Service, Munich, Germany. The EHY-2000+ carries a Health Canada Class III Medical Device License.

Treatment protocol

Integrative therapies including mEHT were administered either concurrently with chemotherapy and/or radiation, or alone as palliative therapy for metastatic solid tumor entities. When indicated, mEHT was performed in accordance with the patient's standard of care protocol to maximize synergistic benefits [127], [128].

Each treatment is 1 hour in duration and is administered under the supervision of the prescribing physician. The mEHT protocol was timed with chemotherapy infusion cycles when it was administered as an adjunctive chemo-sensitizing treatment, (Table 1).

Chemotherapy Schedule	mEHT Schedule
Weekly, Day 1 of 7-Day Cycle	Weekly the day or day after chemo infused
Day 1 of 14-Day Cycle	Day 1 and 3 of 14-Day Cycle
Day 1 and 8 of 21-Day Cycle	Day 1, 3, 8, 10 of 21-Day Cycle
Day 1-3 or 21-Day Cycle	Day 1, 3, 5of 21-Day Cycle

Table 1. Treatment schedule using chemotherapy

With concurrent radiation, mEHT was applied two to three times per week during the course of radiotherapy, attempting to apply mEHT within the shortest time frame before or after the radiation.

In a palliative setting, the treatment was typically administered 2-3-times per week for a total of 12-18 treatments. When mEHT was administered as a stand-alone therapy, the most common protocol was three times per week for four weeks.

Variable treatments integrated to the complex therapy protocol

The primary exploratory focus of the study was the use of mEHT as part of an integrative oncology treatment protocol. The one variable that is consistent in this cohort, is the inclusion of a minimum of 6 mEHT treatments as part of their treatment. As previously mentioned, depending on the individualized needs of the patient, additional therapies may also have been included: fWBHT, intravenous supportive therapies, dietary changes, lifestyle changes, nutritional supplementation, and repurposed pharmacological agents.

The majority of patients were recommended to use complementary supportive therapies during the application of mEHT. Dietary and lifestyle recommendations were a part of their comprehensive integrative treatment plan, as were botanicals and specific indicated nutritional supplements. At the end of a course of treatment, patients were advised to wait for three to four weeks to allow for the clearance of cellular and inflammatory debris, before obtaining follow-up imaging or blood work where appropriate.

Statistical methods

The patient's socio-demographic and clinical characteristics were summarized using ANOVA evaluation, including frequencies for categorical variables and mean, median, standard deviation and inter-quartile range for continuous variables. Cross-tabulation has been generated to examine the distribution of patients with different cancer types using mEHT. The

stage of cancer at the time of original diagnosis and the stage when the patients came to the clinic, were tabulated by cancer type.

The main analysis was to determine overall survival rates and stratified by cancer type, and then only those patients with distant disease at the time of diagnosis. In the case of primary brain cancer, we report only the outcomes of patients with glioblastoma multiforme. Patients were followed until death, censoring, or the end of study. Kaplan-Meier non-parametric survival estimate were calculated and plotted for all patients in the qualified cohort and for each type of cancer sub-group. These graphs were composed of the survival rates from patients of IHC, compared to the corresponding SEER database [129] population-based survival rates for the same type and stage of cancer. The analysis was conducted using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

Baseline patient characteristics

A retrospective study was conducted for patients who received mEHT from June 2010 to July 2018. In this period the Integrated Health Clinic treated 1289 patients using mEHT. All together 16,752 mEHT were administered during the study period.

784 (61%) of the total number of patients treated with mEHT met the criteria to be included in the present study, receiving mEHT either as an adjunctive or as a palliative treatment. The patient's characteristics are summarized in Table 2.

Patient's Characteristics	n	%
Number of Patients	785	
Mean Age (y)	57.9	
Gender (male/female)	356 / 428	45.4 / 54.6
Prior Chemotherapy	324	41.3
Prior Radiotherapy	174	22.2
Prior Surgery	338	43.1
Complementary Chemotherapy	335	42.7
Complementary Radiotherapy	49	6.3

Table 2. Characteristic data of patients involved in the study. The age of patients ranged from 7.2 to 98.7 years.

The staging of the malignancy varied from localized to distant metastases, table 3.

Localization of Malignancy	Stage at Diagnosis		Stage at Enrollment	
	n	%	n	%
Localized	183	23.3	106	13.5
Regional	202	25.8	149	19
Distant Metastasis	344	43.9	474	60.5
Brain	54	6.9	54	6.9
Unknown	1	0.1	1	0.1

Table 3. Patients with distant metastases at enrollment. Primary brain cancers are listed separately.

The cancer grouping by location and tissue of origin is shown in Table 4.

Cancer-Group	Frequency	%
Oral Cavity & Pharynx	28	3.6
Digestive System	228	29.1
Respiratory System	80	10.2
Bones & Joints	7	0.9
Soft Tissue (including heart)	18	2.3
Skin	19	2.4
Breast	136	17.3

Female Genital System	74	9.4
Male Genital System	64	8.2
Urinary System	36	4.6
Eye & Orbit	2	0.3
Brain & Nervous System	54	6.9
Endocrine System	11	1.4
Lymphoma	17	2.2
Myeloma	3	0.4
Mesothelioma	3	0.4
Unspecified	4	0.5

Table 4. distribution of cancer-groups in the enrolled patients.

Most of the patients had supportive care of various kind, shown in the Table 5.

Supportive Treatments	Stage at Diagnosis	
	n	%
IV High-dose Vitamin C (25g-100g)	538	68.6
IV Alpha Lipoic Acid (ALA)	48	6.1
IV Dichoroacetate Sodium (DCA)	119	15.2
Other IV	20	2.6
Mistletoe	258	32.9
Other Targeted Supplements	673	85.8

Table 5. Supportive therapies

A total of 528 patients had distant metastases, evaluated as Stage IV in their cancer categories, or with a primary brain tumor, at the time of the enrollment to the study. From these, 399 patients were included in categories with sufficient numbers for evaluation of the cancer type group, table 6.

Cancer with Distant Metastases at Enrollment	Frequency	%
Distant having n>8	28	3.6
Colon	228	29.1
Breast	80	10.2
Non-Small-Cell Lung Cancer	7	0.9
Pancreas	18	2.3
Soft-tissue	19	2.4
Melanoma	136	17.3
Ovary	74	9.4
Kidney	64	8.2
Prostate	36	4.6
Rectum	2	0.3
Uterus	54	6.9
Head & Neck	11	1.4
Lymphoma	17	2.2
Cholangio	3	0.4
Glioblastoma Multiform	3	0.4

Table 6. Patient with distant metastases at the enrollment

Five-year survival trends

The 5-year survival data for patients with the most commonly treated cancer types and stages was evaluated by Kaplan-Meier (KM) non-parametric estimates. This data was then compared to survival data from the Surveillance, Epidemiology and End Results (SEER) database as a control for evaluation of an integrative approach, in which mEHT was the primary variable being explored. In order to accurately compare with SEER data, only patients with stage IV cancers at the time of diagnosis were included in the KM analysis. SEER KM plots are reflective of stage IV patients at diagnosis and do not include any other stages.

An examination of the data collected from IHC for the past 8 years will be provided. mEHT has been administered to hundreds of patients with over 35 cancer types. Data elements include patient statistics, cancer group & type, treatment(s) used, adverse events, overall survival (OS), diagnostic imaging & blood test results. Overall survival is measured from the time of first diagnosis until the event, censoring, last update, or end of study.

Data and KM curves for the following distant metastatic diseases, and in the case of brain cancer, glioblastoma multiforme, follow: glioblastoma multiforme (n=36 patients, median survival 2.2y mean 2.7y. Fig. 1.), breast cancer (n=72 patients, median survival 5.0y mean 8.2y. Fig. 2.); colon cancer (n=79 patients, median survival 4.0y mean 4.5y. Fig. 3.); non-small-cell lung cancer (n=54 patients, median survival 1.5y mean 1.9y. Fig. 4.); pancreas cancer (n=27 patients, median survival 1.1y mean 1.7y. Fig. 5.); soft-tissue sarcoma (n=16 patients, median survival 3.1y mean 2.7y. Fig. 6.); melanoma (n=12 patients, median survival 2.6y mean 2.7y. Fig. 7.); ovarian cancer (n=33 patients, median survival 3.5y mean 4.2y. Fig. 8.); kidney cancer (n=13 patients, median survival 4.1y mean 4.1y. Fig. 9.); prostate cancer (n=25 patients, median survival 8.3y mean 9.1y. Fig. 10.); rectal cancer (n=13 patients, median survival 4.0y mean 4.1y. Fig. 11.); uterine cancer (n=13 patients, median survival 4.0y mean 4.1y. Fig. 12.); head & neck cancer (n=13 patients, median survival 4.0y mean 4.1y. Fig. 13.); lymphoma (Hodgkin & non-Hodgkin) (n=13 patients, median survival 4.0y mean 4.1y. Fig. 14.), and cholangiocarcinoma (n=13 patients, median survival 4.0y mean 4.1y. Fig. 15.) follow.

Advanced Glioblastoma (GBM)

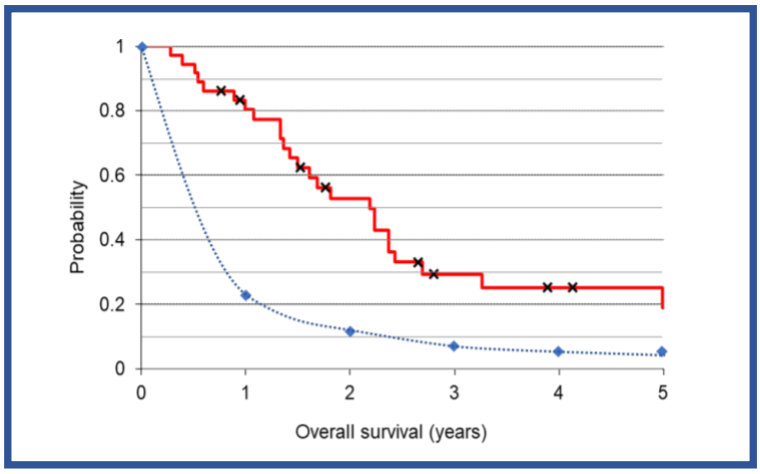

Figure 1 Kaplan-Meier non-parametric estimate of survival of **advanced glioblastoma** multiforme, stage WHO IV. (n=36 patients, median survival 2.2y mean 2.7y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The blue dotted line is to guide the eye.

Advanced Metastatic Breast Cancer

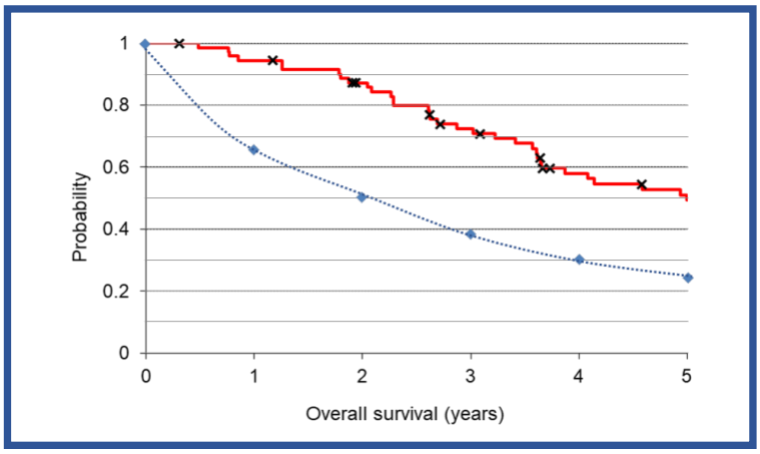

Figure 2. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized breast tumor**, stage WHO IV. (n=72 patients, median survival 5.0y mean 8.2y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

Advanced Metastatic Colon Cancer

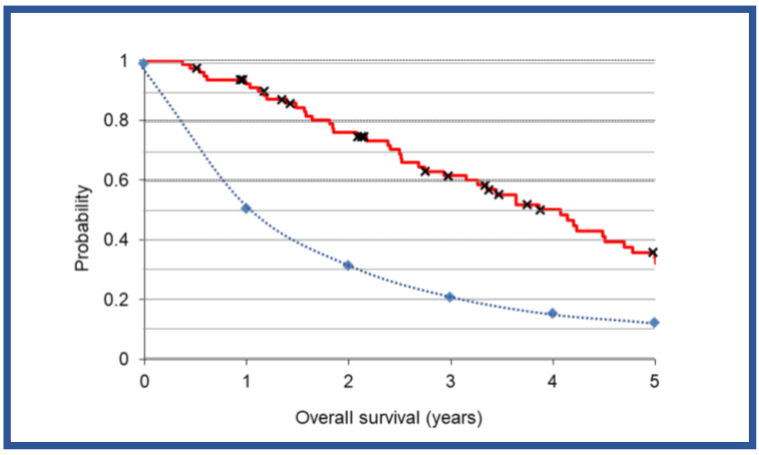

Figure 3. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized colon cancer**, stage WHO IV. (n=79 patients, median survival 4.0y mean 4.5y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

Advanced Metastatic Non-Small Cell Lung Cancer

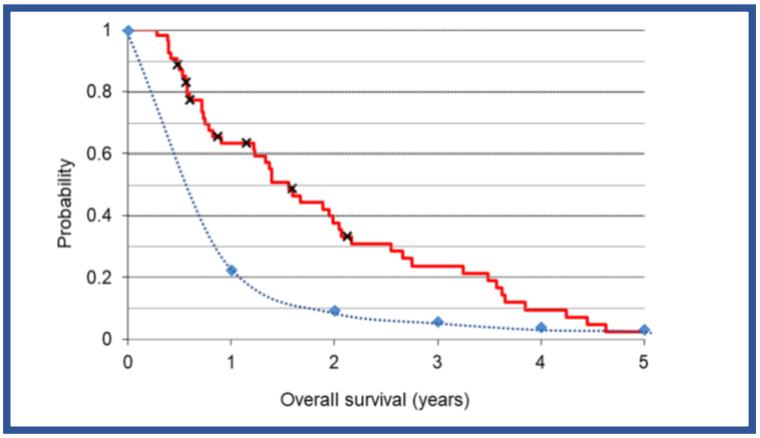

Figure 4. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized non-small-cell-lung cancer** (NSCLC), stage WHO IV. (n=54 patients, median survival 1.5y mean 1.9y.) The solid red line is the 5y survival of patients treated by integrative approach

with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

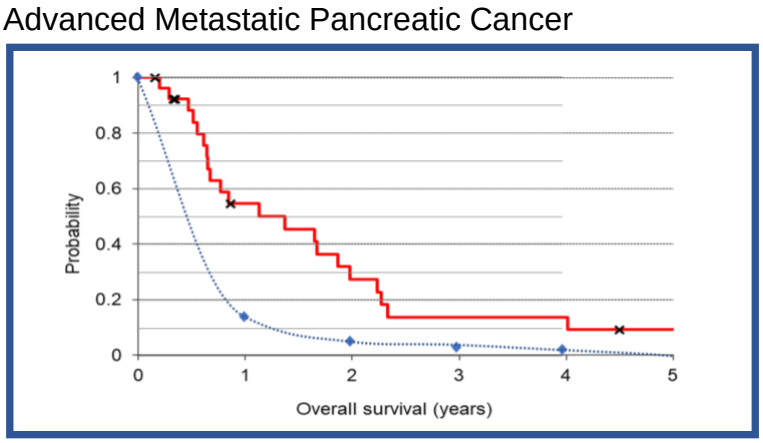

Figure 5. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized pancreas cancer**, stage WHO IV. (n=27 patients, median survival 1.1y mean 1.7y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

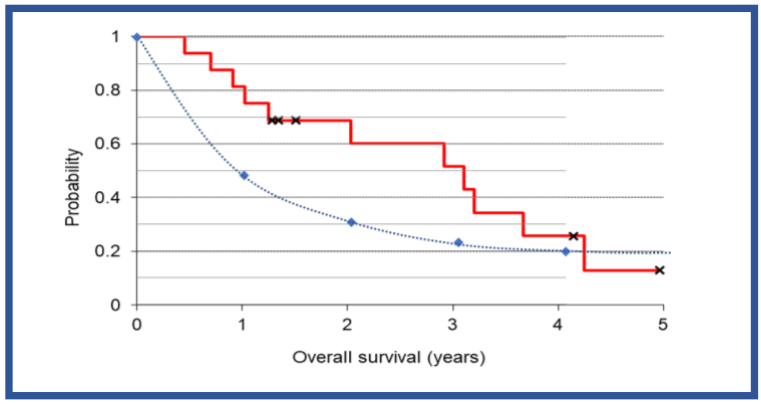

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Figure 6. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized soft-tissue sarcoma**, stage WHO IV. (n=16 patients, median survival 3.1y mean 2.7y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

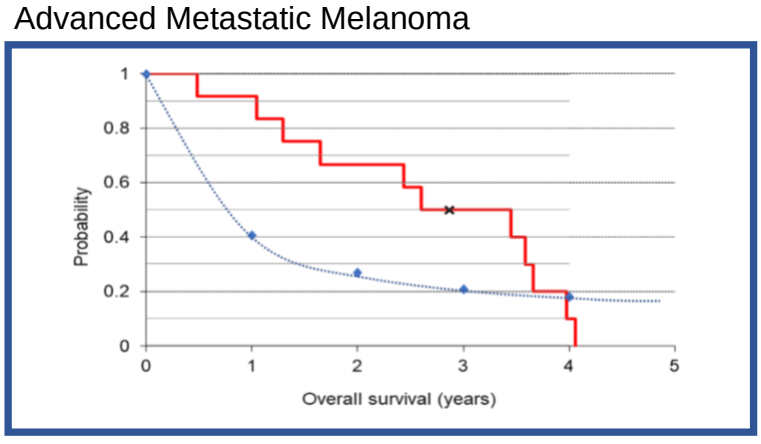

Figure 7. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized melanoma**, stage WHO IV. (n=12 patients, median survival 2.6y mean 2.7y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

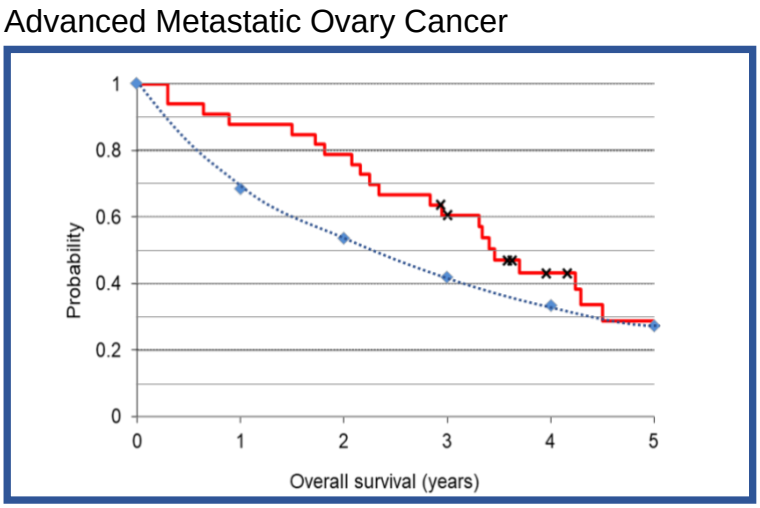

Figure 8. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized ovary cancer**, stage WHO IV. (n=33 patients, median survival 3.5y mean 4.2y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

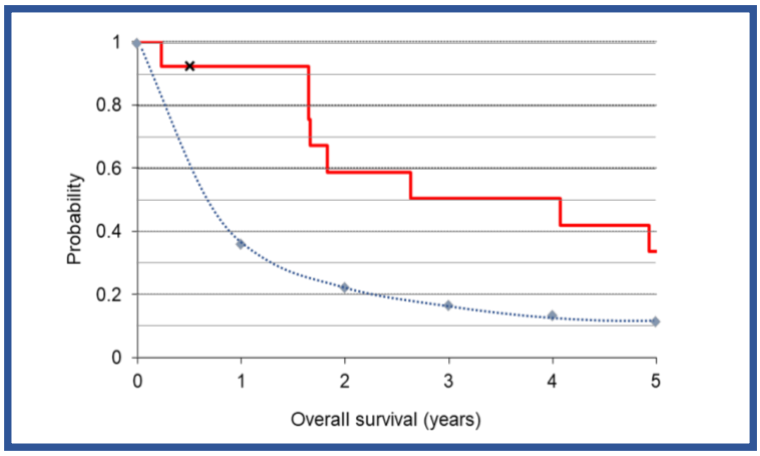

Figure 9. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized kidney cancer**, stage WHO IV. (n=13 patients, median survival 4.1y mean 4.1y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

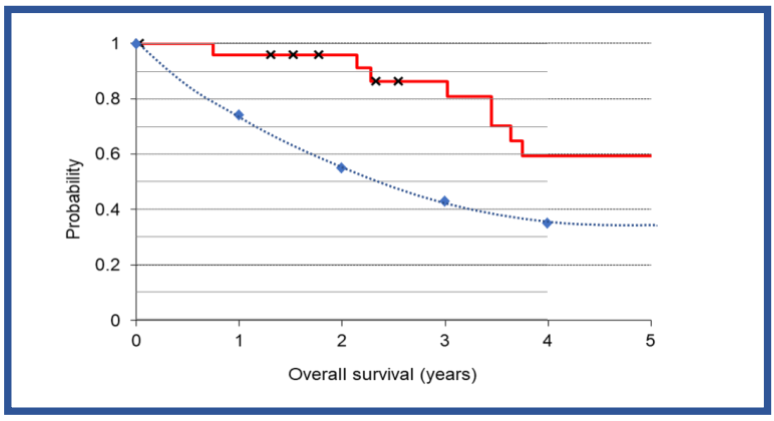

Figure 10. Kaplan-Meier non-parametric estimate of survival of **advanced, metastasized prostate cancer**, stage WHO IV. (n=25 patients, median survival 8.3y mean 9.1y.) The solid red line is the 5y survival of patients treated by integrative approach with mEHT. The crosses (**x**) are the censored patients. The ♦ symbols are from the SEER database by years. The dotted blue line is to guide the eye.

Safety of mEHT

In accordance with the second objective of the study, the safety of HT administration was also monitored. Several studies contend that the low levels of usage and the period of decreasing use of HT in clinical practice is primarily due to the fact that there was not adequate technology to safely heat and monitor temperature in cancerous and non-cancerous tissues [46], or that the technology was used incorrectly, failed to produce desired outcomes, and thus fell short in its acceptance as an effective treatment option [130]. However, recent technological advances in both hardware and monitoring software make the use of mEHT easier to manage, more effective, and safe. The findings from this study echo the claims in the literature regarding HT's safety profile.

The IHC administered 16,752 mEHT treatments between June 2010 and June 2018 and found the incidence of having an adverse event to be <0.1% (n=12). The most common adverse event was first-degree burn (n=7), followed by transient subcutaneous fibrosis (n=5) affecting the fat pad over the pubic bone. However, no participants dropped out of the study due to adverse events or side effects.

Discussion

Key results

The primary objective of this paper was to investigate the role of mEHT in overall five-year survival rates. The majority of patients treated in this study had metastatic disease (66.2% at the time of their enrollment in the study). As such, these patients were receiving palliative treatment and seeking complementary care to improve their overall survival time. The application of treatment was not done to have curative intent and thus the risk of life altering negative interaction was low in all patients.

Moroz et al (2001) identify the lack of randomized control groups and the confounding effect of other treatments, as the two main problems confronting mEHT research [28**].** This study does not avoid either of these limitations. Although the direct correlation of mEHT interventions to specific patient outcomes cannot be measured given the research design employed, the overall trends in improved patient outcomes coupled with the very high safety profile, demonstrate that these integrative mEHT treatments certainly warrants further investigation.

As the KM graphs above show, trends with mEHT as the treatment variable consistently displayed positive outcomes in survival probability and overall five-year survival rates. While the samples for each particular type of cancer are small (r = 12-79) all graphs show increased survival when compared to the SEER control data. A few results deserve particular attention. The mEHT treatment group in distant metastatic breast (graph 1) and distant metastatic colon (graph 2) show increased survival probability and survival time (dropping from 1.0 to 0.5 and 1.0 to 0.4 respectively) compared to the SEER data set (dropping from 1.0 to below 0.3 and from 1.0 to 0.15 respectively). Preliminary results also show promising survival trajectories for glioblastoma multiforme and non-resectable pancreatic adenocarcinoma. The differences between five-year survival endpoints in glioblastoma multiforme show positive trends, with the mEHT group dropping from 1.0 to just over 0.5 at the two-year mark compared to the SEER data set which shows a steep drop from 1.0 to 0.2 at two years. Even greater differences are apparent in non-resectable pancreatic adenocarcinoma, with the mEHT group dropping from 1.0 to 0.3 over a two-year period compared to SEER data showing a drop from 1.0 to 0.2 in the first year alone.

The results from this retrospective study show promise for the inclusion of mEHT within an integrated cancer care setting. To our knowledge this is the first study that examines its potential impact on 5-year survival rates, however there are already studies that support the utilization of mEHT in cancer treatment. Van der Zee et al. noted extended duration of local control in locally advanced bladder, cervical, and rectal cancer when HT was combined with radiotherapy (55% complete response rates) versus radiotherapy alone (39% complete response rates). Results were most promising for cervical cancer where combination treatment led to a complete response rate of 83% compared to 57% with radiotherapy alone. Furthermore, this study also noted an improvement in 3-year survival rates from 27% to 51% in the radiotherapy group versus the combination therapy group. In a 2016 meta-analysis, the combination of HT and radiation in locally recurrent breast cancers enhanced the complete response rates by 22% when compared to radiation alone. In these studies, toxicity related effects did not significantly differ between the groups.

Studies examining the effects of combination therapy with chemotherapy and HT have also demonstrated positive results. Patients with esophageal squamous cell carcinoma treated with bleomycin, cisplatin and HT noted a histological benefit of 58.3% in the combination group, compared to 14.3% with chemotherapy alone [131]. Side effect profiles were similar in both arms of the study. Maluta et al. noted an improvement in median overall survival from 11 to 15 months for the treatment of locally advanced pancreatic cancer with chemoradiation and regional HT compared to chemoradiation alone [132]. There was no noted increase in toxicity with the addition of HT. An in vitro study demonstrated the effect of HT combined with gemcitabine on apoptotic cell death in cultured human pancreatic cancer cell lines [133]. The outcome

showed that HT enhanced the cytotoxicity of gemcitabine. This mechanism may be responsible for the positive results reported in Maluta's study on advanced pancreatic cancer [133]. Similarly, when Vujaskovich Z. et al (2010) followed locally advanced breast cancer patients they demonstrated enhanced therapeutic efficacy of liposomal doxorubicin combined with HT [134]. Dewey (1984) looked at the interaction of HT with radiation and chemotherapy and found that the effectiveness of both radiation and chemotherapy may be greatly enhanced by applying HT as a combined therapy [135]. Gillette (1984) concluded the same [136]. These results suggest that selective heating of a tumor relative to the surrounding normal tissue should prove to offer a therapeutic gain when combined with radiation and chemotherapy.

Although the results from this study favor the use of mEHT in cancer treatment, it is important to note that patients were not separated into those that underwent mEHT as an adjunctive treatment, versus those that used it as a stand-alone therapy for palliation. The authors acknowledge that this distinction may have shifted the outcomes. Further, some patients used mEHT throughout their disease course receiving more treatments, while others used it for a specific time during the course of treatment, and not throughout their care. These distinctions may have also had an impact on individual disease progression and thus survival outcomes.

The importance of the findings of this retrospective analysis needs to be placed within the larger context of integrative cancer therapy. There was a very low incidence of treatment related side effects with mEHT administration (see table 6). Furthermore, there is a consistent general trend of increased survivorship when compared with the control SEER data (Graphs 1-7). While the direct causes of the trends cannot be attributed to one intervention alone in this study, results suggest that further study is warranted to adding mEHT as an integrated therapy for metastatic cancer patients undergoing cancer treatment.

Additional study limitations and directions for future research

Due to the nature of this assessment, there are a number of biases that deserve to be mentioned. The patients followed by IHC self-selected to undergo treatment at the facility. The patients also have self-funded their treatment, and therefore it could be assumed that they were generally of higher socioeconomic status. Furthermore, patients were required to travel to the IHC facility for treatment, therefore those individuals not well enough to travel would have been excluded, due to their inability to access treatment.

The many variables applied in treatment and the large variation in the use of integrative treatments between patients makes any direct correlation between outcomes and specific interventions challenging. The small patient numbers per cancer type (r = 12-79) and generally late disease stage (see table #3) also limits the interpretation of this data. Larger numbers of patients followed for a longer period of time would of course strengthen claims regarding the trends noted here. Based on these identified limitations, a prospective study is now underway at the IHC to assess the effectiveness of mEHT on overall survival and progression free survival, combined with ongoing quality of life assessments.

Conclusion

This paper highlights the results of an eight-year, retrospective analysis assessing the role of mEHT on five-year cancer survival rates at the Integrated Health Clinic in British Columbia, Canada. While this study acknowledges a number of significant limitations, general trends outlined in this work do offer promising outcomes in both safety and efficacy of mEHT. Results in survival rates differed significantly, insofar as improvement, when compared to the SEER dataset. Regarding the safety of the device, documented adverse events were low (n=12) in the 784 total participants included in the study sample. These positive findings indicate that more rigorous research with a larger sample size is both timely and relevant to better understanding the role of mEHT within an integrated cancer treatment strategy.

- Preliminary results show **promising survival trajectories** for all ten most commonly treated cancer types we reviewed in this retrospective data analysis.
- mEHT proves to be **a safe adjunctive treatment** in integrative oncology.
- Further research is necessary to assess the effectiveness of mEHT using a larger sample population and over a longer period of time.

mEHT is a safe treatment with very few adverse events or side effects, allowing patients to maintain a higher quality of life. Moreover, our initial data indicates that the addition of this therapy into an integrative oncology setting provides benefits to OS and to quality of life (QoL).

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