



Complementary and integrative health interventions and their association with health-related quality of life in the primary brain tumor population



Dina M. Randazzo^{a,*,1}, Frances McSherry^b, James E. Herndon^c, Mary L. Affronti^{a,d}, Eric S. Lipp^a, Charlene Flahiff^a, Elizabeth Miller^a, Sarah Woodring^a, Susan Boulton^a, Annick Desjardins^a, David M. Ashley^a, Henry S. Friedman^a, Katherine B. Peters^a

^a Department of Neurosurgery, The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, DUMC Box 3624, Durham, NC, 27710, USA

^b Duke Cancer Institute Biostatistics, Duke University Medical Center, Durham, NC 27710, USA

^c Department of Biostatistics and Bioinformatics, Duke University Medical Center, DUMC Box 2717, Durham, NC, 27710, USA

^d Duke University School of Nursing, DUMC 3624, Durham, NC, 27710, USA

ARTICLE INFO

Keywords:

Complementary
Glioma
Health
Integrative
Life
Quality

ABSTRACT

Background and purpose: Little is known about complementary and integrative health intervention usage in the primary brain tumor population. We aimed to identify the percentage of patients using these practices and explore the impact on quality of life.

Materials and methods: Clinical records from patients seen in clinic between December 16, 2013 and February 28, 2014 were reviewed retrospectively. The questionnaires used were a modified version of the International Complementary and Alternative Medicine Questionnaire, the Functional Assessment of Cancer Therapy- Brain Cancer and the Functional Assessment of Chronic Illness Therapy- Fatigue.

Results: 76% of patients utilized a complementary and integrative health modality. The most frequently reported modalities used were vitamins, massage, and spiritual healing, prayer, diet and meditation.

Conclusion: These results confirm the usage of complementary and integrative health practices within the primary brain tumor population; however, there was no evidence of association between use and quality of life.

1. Introduction

According to the Central Brain Tumor Registry of the United States (CBTRUS), the number of new cases of primary brain and other CNS tumors diagnosed in 2018 is estimated to be 85,440 [1,2]. The most aggressive form of brain tumor is the glioblastoma (GBM), which accounts for the majority of all gliomas (55.0%) [1]. After standard treatment with chemoradiation and adjuvant temozolomide, the median overall survival in GBM ranges from 14.6 months to 20.9 months [3,4]. Therapy frequently has long-term side effects including memory loss and fatigue, as well as other potential problems such as hemiparesis or aphasia, depending upon the location of the tumor [5–8]. Given these poor survival outcomes and possible life-changing side effects of therapy, some brain tumor patients go above and beyond standard treatment and seek out alternative therapies in an attempt to

possibly cure their cancer and/or improve their quality of life [9].

Complementary and integrative health (CIH) is the term used for a non-traditional approach to medicine using diverse practices and products that are not part of the standard of care. The CIH practice encompasses many modalities including: alternative medical systems, biologically-based therapies, manipulative and body-based therapies, mind-body therapies and energy-healing therapies [10]. The combination of these alternative practices with mainstream medical care is classified as integrative medicine [11]. According to data from the National Health Interview Survey (NHIS) that was collected in 2002, 2007, and most recently in 2012, the adult use of CIH modalities has remained above 30.0% [12]. Based on the 2012 survey results, the most common CIH therapy among adults was non-vitamin and non-mineral natural products (17.7%). Deep breathing (10.9%), meditation (8.0), chiropractic/osteopathic manipulation (8.4%) and massage (6.9%)

* Corresponding author.

E-mail addresses: dina.randazzo@duke.edu (D.M. Randazzo), frances.mcsherry@duke.edu (F. McSherry), james.herndon@duke.edu (J.E. Herndon), mary.affronti@duke.edu (M.L. Affronti), eric.lipp@duke.edu (E.S. Lipp), cflahiff@duke.edu (C. Flahiff), elizabeth.s.miller@duke.edu (E. Miller), sarah.woodring@duke.edu (S. Woodring), susan.boulton@duke.edu (S. Boulton), annick.desjardins@duke.edu (A. Desjardins), david.ashley@duke.edu (D.M. Ashley), henry.friedman@duke.edu (H.S. Friedman), katherine.peters@duke.edu (K.B. Peters).

¹ Present address: Dina M. Randazzo, DO, MS, The Preston Robert Tisch Brain Tumor Center, University Medical Center, DUMC Box 3624, Durham, NC 27710.

<https://doi.org/10.1016/j.ctcp.2019.05.002>

Received 18 December 2018; Received in revised form 17 May 2019; Accepted 17 May 2019

1744-3881/ © 2019 Published by Elsevier Ltd.

were also reported [12]. Since approximately one-third of the adults in the United States report use of a CIH modality [13], it stands to reason that cancer patients are also amenable to these therapies for potentially alleviating or lessening the effects of treatment, maintaining a healthier lifestyle, having a positive outlook, and improving quality of life [14]. Based on several surveys, between 25.0% and 84.0% of US cancer patients have used some form of CIH with the percentage depending upon the type of cancer and location [9]. We conducted a cross-sectional analysis to document CIH usage among primary brain tumor patients followed at a neuro-oncology outpatient clinic and to assess if these practices had any association with the patient's health-related quality of life (HRQoL).

2. Materials and Methods

2.1. Ethical considerations

This study was performed in accordance with the ethical standard of the institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards under Duke University IRB approved protocol Pro00053653. All primary brain tumor patients evaluated at The Preston Robert Tisch Brain Tumor Center (PRTBTC) between December 16, 2013 and February 28, 2014 were enrolled in the study after providing written informed consent.

2.2. Study questionnaires

Study participants were asked to complete a packet of questionnaires at their first clinic visit in the aforementioned window by their attending physician. Questionnaires used included: a modified version of the International Complementary and Alternative Medicine Questionnaire (I-CAM-Q), the Functional Assessment of Cancer Therapy-Brain Cancer (FACT-Br) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). The modified I-CAM-Q assessed two broad categories of CIH: “complementary treatments” and “self-help practices”. The “complementary treatments” section included: osteopathic or chiropractic manipulation, homeopathy, acupuncture, herbs, spiritual healing, vitamins/minerals/supplements, Chinese/Ayurvedic medicine, and Energy/Reiki. The “self-help practices” section included: meditation, yoga, Qigong, Tai Chi, relaxation techniques, visualization, attending a traditional healing ceremony, praying for their own health, hypnosis, and eating a special diet. Patients were also allowed to specify an “other” modality if they were participating in a complementary treatment or self-help practice that was not specifically defined in the questionnaire. The questionnaire also included a section on “use of herbs, herbal medicine, vitamins, minerals, other supplements, or homeopathic remedies” for patients to record any of these products used in the last 12 months. For each complementary treatment, self-help practice, and any herbal or dietary supplement products, the following was assessed: any patient use in the last 12 months, the purpose of use, the timing of use relative to the patients' cancer diagnosis (treatment or recurrence), and the patients' rating of the helpfulness of the modality or product. Helpfulness of each modality was rated according to the following categories: “Very,” “Somewhat,” “Not at all,” or “Don't know” [15].

Both the Functional Assessment of Cancer Therapy-Brain Cancer (FACT-Br) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) were used to assess health-reported quality of life in which higher scores are associated with a better quality of life. The FACT-Br and the FACIT-F are validated tools used in combination with the Functional Assessment of Cancer Therapy-General which is a 27-item questionnaire that patients rate their physical, social/family, emotional, and functional well-being on a scale ranging from 0 “not at all” to 4 “very much” [16,17]. The FACT-Br is a 23 item tool that is specific to the brain tumor population assessing items such as

headaches, confusion, seizures, and weakness while the FACIT-F is an additional 13 items assessing the patient's self-report fatigue and the impact it has on their daily functioning [17,18]. These paper copied questionnaires were completed by either the patient or the caregiver at every return appointment.

2.3. Demographic and clinical information

In addition to the questionnaires, a retrospective medical record review was performed by the attending physician. No Health Insurance Portability and Accountability (HIPAA)-defined protected health information (PHI) was collected. Demographic information collected included age, sex, tumor type, World Health Organization (WHO) tumor grade, Karnofsky Performance Status (KPS), marital status, highest level of education, initial date of diagnosis, and tumor status (progressive or stable) at the time of questionnaire completion.

2.4. Statistical analyses

Descriptive statistics were reported for clinical parameters and study outcomes. Frequency distributions were used to summarize categorical variables and means, while standard deviations and quantiles were used for interval variables. Answers left blank on the I-CAM-Q were classified as “Unknown.” Kruskal-Wallis tests were used to assess the relationship between the use of a complementary treatment or self-help practice and the HRQoL measures, and to assess any association between the helpfulness of an individual complementary treatment or self-help practice and HRQoL among the patients who used each modality.

3. Results

This retrospective study included the 845 primary brain tumor patients receiving questionnaires during the time period noted. Of these, 54.4% (460/845) were male and 45.6% (385/845) were female with a median age of 50 years (range: 18–87 years) at the time of assessment. The majority of the patients were married ($N = 469/845$, 55.5%), received a college education or higher ($N = 442/845$, 52.3%), and had a $KPS \geq 80$ ($N = 638/845$, 75.5%) (Table 1). The majority of patients ($N = 588/845$, 69.6%) had high grade tumors (WHO grade III/IV), with GBM being the most common histological diagnosis ($N = 365/845$, 43.2%). Disease status at the time of questionnaire completion was evenly split between patients with recurrent disease ($N = 448/845$, 53.0%) and patients with no disease recurrence ($N = 397/845$, 47.0%).

Out of the 845, 534 individuals (63.2%) reported use of a complementary treatment in the past year (Table 2). The most common complementary treatments were: vitamins/minerals/supplements ($N = 492/845$, 58.2%), massage/bodywork ($N = 85/845$, 10.1%), herbs ($N = 62/845$, 7.3%), spiritual healing ($N = 62/845$, 7.3%), and osteopathic/chiropractic manipulation ($N = 60/845$, 7.1%). The most common vitamins/minerals/supplements reported were: multivitamins ($N = 280/845$, 33.1%), vitamin D ($N = 196/845$, 23.2%), calcium ($N = 115/845$, 13.6%), fish oil/shark/omega 3 ($N = 88/845$, 10.4%) and vitamin C ($N = 54/845$, 6.4%) (Table 3).

Four hundred thirty-three patients ($N = 433/845$, 51.2%) reported using at least one self-help practice in the past year with the most common being praying for their own health ($N = 379/845$, 44.9%), distantly followed by use of a special diet ($N = 83/845$, 9.8%) and meditation ($N = 79/845$, 9.3%) (Table 2). For all 845 patients, the median of the total number of all complementary treatments or self-help practices used was 1 (range: 0–15). Overall, 76.4% ($N = 646/845$) of patients reported using some form of CIH (a CIH treatment or a self-help practice) with the vast majority of those patients ($N = 618/646$; 95.7%) indicating they used prayer and/or vitamins, minerals, or supplements.

The following complementary treatments were considered “Very” or

Table 1
Demographic characteristics of patients.

	N	%
GENDER		
Male	460	54.4
Female	385	45.6
AGE (years), median (range)	50 (18–87)	
MARITAL STATUS		
Single	76	9.0
Married	469	55.5
Partnership/living with significant other	30	3.6
Divorced	44	5.2
Widowed	9	1.1
Unknown	217	25.7
EDUCATION		
Elementary	6	0.7
High school	133	15.7
Vocational	41	4.9
College	283	33.5
Graduate school/professional degree	159	18.8
Unknown	223	26.4
WHO GRADE		
I-II	223	26.4
III	223	26.4
IV	365	43.2
Unknown	34	4.0
KPS		
100	29	3.4
90	287	34.0
80	322	38.1
70	99	11.7
60 or below	54	6.4
Unknown	54	6.4
RECURRENCE STATUS		
Not recurrent	397	47.0
Recurrent	448	53.0

Abbreviations: KPS, Karnofsky Performance Status.

Table 2
Complementary treatments and self-help practices used by patients.

	N	%
COMPLEMENTARY TREATMENTS		
Use of any CIH treatment	534	63.2
Vitamins/minerals/supplements	492	58.2
Massage/bodywork	85	10.1
Herbs	62	7.3
Spiritual healing	62	7.3
Osteopathic/chiropractic manipulation	60	7.1
Acupuncture	33	3.9
Reiki/energy work	26	3.1
Other self-reported CIH treatment	11	1.3
Chinese/ayurvedic	10	1.2
Homeopathy	10	1.2
SELF-HELP PRACTICES		
Use of any self-help practice	433	51.2
Praying for own health	379	44.9
Special diet	83	9.8
Meditation	79	9.3
Relaxation techniques	71	8.4
Yoga	58	6.9
Visualization	45	5.3
Other self-reported self-help practice	18	2.1
Attended traditional healing ceremony	15	1.8
Qigong	7	0.8
Hypnosis	5	0.6
Tai Chi	4	0.5

Abbreviations: CIH, Complementary and Integrative Health.

“Somewhat” helpful by more than half of patients using the modality: massage/bodywork (N = 67/85; 78.8%), osteopathic/chiropractic manipulation (N = 47/60; 78.3%), spiritual healing (N = 43/62; 69.4%), acupuncture (N = 20/33; 60.6%), homeopathy (N = 6/10; 60.0%), and

Table 3
Herbal medicine and dietary supplements used in the last 12 months by 5 or more patients.^a

	N	%
Multivitamin	280	33.1
Vitamin D	196	23.2
Calcium	115	13.6
Fish oil/shark oil/omega 3	88	10.4
Vitamin C	54	6.4
Vitamin B12	52	6.1
Melatonin	48	5.7
Vitamin B complex	38	4.5
Potassium	36	4.3
Magnesium	30	3.6
Probiotics	30	3.6
Curcumin (Turmeric)	23	2.7
Co Q10	20	2.4
Vitamin E	20	2.4
Biotin	15	1.8
Flaxseed oil	15	1.8
Folic acid	14	1.7
Iron	13	1.5
Glucosamine chondroitin	12	1.4
Zinc	11	1.3
Green/hibiscus tea/extract	8	0.9
Boswellia	7	0.8
Garlic	6	0.7
Cinnamon bark and/or chromium Picolinate	5	0.6
Resveratrol	5	0.6

^a Patients can be included in multiple categories.

Reiki/Energy work (N = 14/26; 53.8%) (Table 4). The self-help practices reported as “Very” or “Somewhat” helpful by more than half of the patients using them were: hypnosis (N = 4/5; 80.0%), relaxation techniques (N = 56/71; 78.9%), meditation (N = 56/79; 70.9%), yoga (N = 39/58; 67.2%), a special diet (N = 53/83; 63.9%), visualization (N = 27/45; 60.0%), and praying for one's own health (N = 196/379; 51.7%).

There were no significant associations between HRQoL (assessed by the FACT-Br total and the FACIT-F) and the use of complementary treatments or self-help practices (Table 5). There were 708 patients with data available for the FACT-Br total scale. FACT-Br total scores for the patients who reported use of any complementary treatment did not differ significantly from the scores for patients who reported no use or patients who did not respond (p-value = 0.16). Similarly, FACT-Br total scores for patients who used any self-help practice did not differ significantly from the scores for patients reporting no use or patients who did not respond (p-value = 0.09). For the FACIT-F, 718 patients had HRQoL data. FACIT-F scores for the patients who indicated use of a complementary treatment did not differ significantly from the scores for patients who reported no use or patients who did not respond (p-value = 0.31). FACIT-F scores for the patients who reported use of any self-help practice did not differ significantly from the scores for patients who indicated no use or patients who did not respond (p-value = 0.17).

4. Discussion

In our study population, we have shown that the use of CIH is prevalent in patients with primary brain tumors. In the 2007 National Health Statistics [13], only 38.0% of all adults living in the United States reported using some form of CIH; however, CIH usage in adults diagnosed with cancer was 83.0% in one study by a comprehensive cancer center [14]. In our study, 76.4% of primary brain tumor patients reported using a complementary treatment or a self-help practice with the use of prayer and/or vitamins, minerals, or supplements being the two primary modalities used.

Looking at the entire cancer population and not exclusively brain cancer, the 2007 National Health Interview Survey for cancer symptom

Table 4
Helpfulness of modalities used.^a

	HELPFULNESS - N (%)					TOTAL
	Very	Somewhat	Not at all	Don't Know	Unknown	
COMPLEMENTARY TREATMENTS						
Vitamins/minerals/supplements	57 (12%)	49 (10%)	3 (1%)	80 (16%)	303 (62%)	492
Massage/bodywork	46 (54%)	21 (25%)	0 (0%)	1 (1%)	17 (20%)	85
Herbs	16 (26%)	13 (21%)	1 (2%)	5 (8%)	27 (44%)	62
Spiritual healing	36 (58%)	7 (11%)	1 (2%)	3 (5%)	15 (24%)	62
Osteopathic/chiropractic manipulation	29 (48%)	18 (30%)	4 (7%)	3 (5%)	6 (10%)	60
Acupuncture	12 (36%)	8 (24%)	4 (12%)	2 (6%)	7 (21%)	33
Reiki/energy work	10 (39%)	4 (15%)	1 (4%)	4 (15%)	7 (27%)	26
Chinese/ayurvedic	1 (10%)	3 (30%)	1 (10%)	3 (30%)	2 (20%)	10
Homeopathy	4 (40%)	2 (20%)	0 (0%)	2 (20%)	2 (20%)	10
SELF-HELP PRACTICES						
Praying for own health	170 (45%)	26 (7%)	2 (1%)	30 (8%)	151 (40%)	379
Special diet	36 (43%)	17 (21%)	0 (0%)	7 (8%)	23 (28%)	83
Meditation	35 (44%)	21 (27%)	1 (1%)	3 (4%)	19 (24%)	79
Relaxation techniques	32 (45%)	24 (34%)	0 (0%)	1 (1%)	14 (20%)	71
Yoga	26 (45%)	13 (22%)	1 (2%)	2 (3%)	16 (28%)	58
Visualization	18 (40%)	9 (20%)	1 (2%)	4 (9%)	13 (29%)	45
Traditional healing ceremony	7 (47%)	0 (0%)	0 (0%)	3 (20%)	5 (33%)	15
Qigong	3 (43%)	0 (0%)	0 (0%)	1 (14%)	3 (43%)	7
Hypnosis	4 (80%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	5
Tai Chi	0 (0%)	1 (25%)	0 (0%)	2 (50%)	1 (25%)	4

^a Total only includes patients who reported using each modality. Patients can be included in multiple modalities.

management reported that vitamin and mineral supplements were used by 76.6% of cancer patients with multivitamins, fish oil and calcium reported most frequently [14,19]. Among the PRTBTC brain tumor patient population included in this analysis, 58.2% of patients stated using a vitamin, mineral or supplement with multivitamins (33.1%), vitamin D (23.2%), calcium (13.6%) and fish oil/omega 3 (10.4%) being the most frequently used supplements (Tables 2 and 3). Dosages of vitamins/minerals/supplements were not collected in this study. Due to the frequent need for steroid treatment which can lead to osteoporosis in this patient population, we assumed the calcium and/or vitamin D supplementation was used as osteoporosis prophylaxis. We could speculate on the rationale for each supplement used in the cancer patient population, but there is limited data to determine any benefit (for symptom management or survival) or risk especially if these supplements could potentially counteract the activity of conventional treatments [20–31]. The significant use of vitamin/mineral supplementation in cancer patients, and the minimal information available on the interactions between these supplements and conventional treatments, indicates that more clinical studies are required to study the

combination effects.

The use of vitamin supplementation, praying for one's own health, massage, a specialized diet, and meditation were the most frequently reported treatments or practices. While a number of patients reported helpfulness of used modalities, many other patients did not answer the helpfulness question. For example, among the 492 patients that reported using vitamins, minerals and/or supplements, 303 (61.6%) did not answer the question of helpfulness. Because of the large percentage of “unknown” (i.e. missing) answers, associations between patient-reported helpfulness of the CIH treatments and self-help practices with HRQoL would not be meaningful. Given this, we looked at associations between HRQoL and the more global questions regarding use of any complementary treatment or any self-help practice. No association between the use of any complementary treatment or any self-help practice and HRQoL was evident in this study. As noted above, these results are likely impacted by the amount of missing responses. Alternatively, the rationale for the lack of correlation was the fact that other factors were more important in the determination of a patient's HRQoL. For instance, if a patient's tumor was progressive and there was more of a functional

Table 5
Association of complementary treatments and self-help practices with HRQoL.

Scale ^a	Any CIH treatment used?	N	Minimum	Median	Maximum	Kruskal-Wallis test P-value
FACT-Br total (N = 708)	Yes	464	41	136	184	0.16
	No	180	72	137	184	
	Unknown	64	75	128	179	
FACIT-Fatigue (N = 718)	Yes	474	3	38	52	0.31
	No	185	3	38	52	
	Unknown	59	8	34	52	
Scale ^a	Any Self-help practices used?	N	Minimum	Median	Maximum	Kruskal-Wallis test P-value
FACT-Br total (N = 708)	Yes	409	41	139	184	0.09
	No	159	71	134	184	
	Unknown	140	46	131	181	
FACIT-Fatigue (N = 718)	Yes	423	3	39	52	0.17
	No	164	5	38	52	
	Unknown	131	5	37	52	

Abbreviations CIH, Complementary and Integrative Health; HRQoL, health-related quality of life; FACT-Br, functional assessment of cancer therapy-brain; FACIT, functional assessment of chronic illness therapy; N, number of patients.

^a Higher scores = Better QoL. FACT-Br total range of possible scores = 0–184. FACIT-F range of possible scores = 0–52. Includes only patients with QoL data.

decline where they could not read, write or were hemiplegic, more than likely their HRQoL would be affected negatively.

Nonetheless, previous studies have also reported no increase in HRQoL, but did show a high rate of patient satisfaction with CIH usage. In the 2006 article by Armstrong [32], 88.0% of primary brain tumor patients who used CIH reported satisfaction even though overall self-reported HRQoL was not significantly different from non-CIH users. In addition, Verhoef [33] reported that two-thirds of brain tumor patients that used CIH found it useful, while total scores on the FACT-Br were not different from non-users. In fact, the subscale scores for physical and functional well-being and the brain subscale depicted a lower HRQoL in those who used CIH; yet, a majority of brain tumor patients reported it was helpful [33]. Whether it was the patients' need to be proactive in their treatment, a placebo effect, or there is an unmeasured benefit from the CIH used that was undetectable in the HRQoL surveys, such as an alleviation of symptoms or a provision of peace or hope, patients perceived their CIH usage to be helpful. To understand better the effects of CIH use on a patient's disease trajectory and HRQoL, a longitudinal prospective analysis would be required to provide a timeline as to the reasons why a person started a specific modality and whether or not their HRQoL improved over time.

To date, this is the largest study of CIH use in primary brain tumor patients at a single institution. Although a large percentage of individuals responded about their use or non-use of specific complementary treatments and self-help practices, 14.8% of patients did not respond regarding their use of complementary treatments and 28.8% did not respond about use of self-help practices. Among those who did indicate use of a modality, some patients did not provide the additional information regarding the reason for use, the helpfulness of that modality, or the timing of use relative to their cancer treatment or recurrence. Due to the large amount of missing data, it was impossible to draw any definite conclusions regarding CIH usage and HRQoL. As such, a larger study with a complete data set may be able to show that some of these modalities may affect HRQoL measures.

Since two of the most commonly encountered symptoms in the primary brain tumor population are difficulty with neurocognitive functioning and fatigue [34], another study limitation was the length and complexity of the I-CAM-Q questionnaire. The complexity and length (3 pages) of the modified I-CAM-Q may have caused fatigue and/or confusion resulting in partial completion of the questionnaire by the patient. In future studies, we will use a shorter, more focused and simplified questionnaire in hopes of avoiding patient fatigue and enabling increased questionnaire completion. Other CIH studies have used more interactive and personalized approaches to encourage survey completion including using a nurse or aide to ask the questions. Although this may be a beneficial approach that gleans more information or guarantees a more complete questionnaire, given the large number of patients seen at our clinic, this approach may not be feasible.

The majority of CIH studies report that most patients do not inform their oncologists of their CIH usage, which may indicate that the patients are not comfortable discussing their complementary treatment methods in a face-to-face discussion [35–37]. Knowing that a majority of brain tumor patients use some form of CIH intervention indicates the importance of physicians discussing these complementary treatments with the patients as there may be unknown implications to their health and their treatment outcome. Discussing CIH use in clinic visits may help in future CIH-related clinical studies by providing CIH information in the clinical record, which could eventually supplement missing data in questionnaires. The discussion of CIH usage at the clinic visit will assist both the practitioner and patient in developing informed treatment plans and minimizing possible drug interactions. Patients that utilize the self-help techniques should also inform their oncologists because if it has improved their HRQoL, it may do so for others. It will also give the practitioner a means to provide a holistic approach to patient care if prayer, spirituality, diet, exercise and other modalities are explored in the clinic visit. Through open communication and

documentation, the safety and efficacy of CIH modalities may be determined.

This cross-sectional study of the use of complementary treatments and self-help practices among primary brain tumor patients has uncovered some interesting use patterns. In order to better assess efficacy, a longitudinal study of integrative medicine could be performed. A review of CIH usage should be obtained with the medication list at every clinic visit which would not only circumvent the possibility of under-reporting, but could also reduce the fatigue of answering the I-CAM-Q. By incorporating CIH use into the clinical record, a longitudinal study could be performed by reviewing patient records instead of requiring the I-CAM-Q. Including CIH modalities into the medication list could also provide more detailed information about use and dose of supplementation, use and frequency of modalities, start and stopping times of the practice, and a more objective assessment of helpfulness and how it all relates to the HRQoL of an individual. Ultimately, a prospective longitudinal analysis can also be used to examine the interaction with concomitant chemoradiation, along with any possible antitumor effects of these individual treatments with chemotherapy. Unfortunately, most of the studies of CIH are poorly powered, not placebo controlled, and not highly regarded in the medical community. Only 13.5% of the subjects in this study reported that any CIH usage was recommended by their physician, probably due to limited and controversial data. In fact, 58.2% of our brain tumor patients used vitamins/minerals/supplements with only 7.8% of patients reporting they were recommended by a physician. This uncertainty in CIH leaves patients grasping for any information that will improve their quality of life or survival, and may make them willing to go to extremes, which may be harmful. For instance, the maximum number of recorded supplements by one individual in this study was 18. The side effects and possible interactions with other medications, as well as the financial burden of taking all these supplements, are just a few of the issues that patients risk. Because of the lack of knowledge regarding many CIH, specifically possible unknown interactions or side effects, most providers tend to discourage their use while a patient is under treatment. For the safety of the patient and to further advance the field of integrative medicine, more research is needed on the safety and efficacy of these supplementary treatments.

5. Conclusion

In this study, 76.4% of our primary brain tumor patients reported using CIH. There was no association between any use of a complementary treatment or self-help practice reported via the I-CAM-Q and HRQoL. Because of the responder burden due to the length of the questionnaires and the possible cognitive impairment in this population, there needs to be a more succinct tool to acquire CIH information from the patient. To lessen the impact of questionnaire burden, taking a holistic approach may be useful. Asking the patient about their complementary treatments and self-help practices will open communication between the provider and patient and hopefully instill a greater degree of trust in this relationship. CIH usage should be reviewed at every clinic as a means to determine and record what they are taking in order to monitor the possible risks and benefits of the modality and its interaction with standard treatment. Given the large proportion of primary brain tumor patients utilizing CIH, more research is needed to discern the efficacy of each modality and its impact on HRQoL.

Author disclosure statement

The Authors declare that they have no conflict of interest.

Funding

This work was supported by Duke University Medical Center, The Preston Robert Tisch Brain Tumor Center eIRB Pro00053653.

Acknowledgements

The authors would like to thank the patients for their participation in this study and the staff at the PRITBTC for their dedication to both the patients and research. Special thanks goes to Jennifer Jackman, Ph.D. and Wendy Gentry for their contributions with editing.

References

- Q.T. Ostrom, H. Gittleman, G. Truitt, A. Boscia, C. Kruchko, J.S. Barnholtz-Sloan, CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015, *Neuro-Oncol.* 20 (suppl_4) (2018) iv1–iv86 <https://doi.org/10.1093/neuonc/ny131>.
- Q.T. Ostrom, H. Gittleman, P. Liao, T. Vecchione-Koval, Y. Wolinsky, C. Kruchko, J.S. Barnholtz-Sloan, CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014, *Neuro-Oncol.* 19 (suppl_5) (2017) v1–v88 <https://doi.org/10.1093/neuonc/nox158>.
- R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R.O. Mirmanoff, R. European Organisation for, T. Treatment of Cancer Brain, G. Radiotherapy, G. National Cancer Institute of Canada Clinical Trials, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *N. Engl. J. Med.* 352 (10) (2005) 987–996 <https://doi.org/10.1056/NEJMoa043330>.
- R. Stupp, S. Taillibert, A. Kanner, W. Read, D.M. Steinberg, B. Lhermitte, S. Toms, A. Idbaih, M.S. Ahluwalia, K. Fink, F. Di Meo, F. Lieberman, J.J. Zhu, G. Stragliotto, D.D. Tran, S. Brem, A.F. Hottinger, E.D. Kirson, G. Lavy-Shahaf, U. Weinberg, C.Y. Kim, S.H. Paek, G. Nicholas, J. Burna, H. Hirte, M. Weller, Y. Palti, M.E. Hegi, Z. Ram, Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial, *JAMA* 318 (23) (2017) 2306–2316 <https://doi.org/10.1001/jama.2017.18718>.
- B.V. Taylor, J.C. Buckner, T.L. Cascino, J.R. O'Fallon, P.L. Schaefer, R.P. Dinapoli, P. Schomberg, Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma, *J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol.* 16 (6) (1998) 2195–2201 <http://www.ncbi.nlm.nih.gov/pubmed/9626221>.
- K.B. Peters, M.J. West, W.E. Hornsby, E. Waner, A.D. Coan, F. McSherry, J.E. Herndon 2nd, H.S. Friedman, A. Desjardins, L.W. Jones, Impact of health-related quality of life and fatigue on survival of recurrent high-grade glioma patients, *J. Neuro-Oncol.* 120 (3) (2014) 499–506 <https://doi.org/10.1007/s11060-014-1574-3>.
- G. Pelletier, M.J. Verhoef, N. Khatri, N. Hagen, Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues, *J. Neuro-Oncol.* 57 (1) (2002) 41–49 <http://www.ncbi.nlm.nih.gov/pubmed/12125966>.
- K.D. Hodgson, A.D. Hutchinson, C.J. Wilson, T. Nettelbeck, A meta-analysis of the effects of chemotherapy on cognition in patients with cancer, *Cancer Treat Rev.* 39 (3) (2013) 297–304 <https://doi.org/10.1016/j.ctrv.2012.11.001>.
- M. Tascilar, F.A. de Jong, J. Verweij, R.H. Mathijssen, Complementary and alternative medicine during cancer treatment: beyond innocence, *Oncol.* 11 (7) (2006) 732–741 <https://doi.org/10.1634/theoncologist.11-7-732>.
- NCCIH, Complementary, Alternative, or Integrative Health: What's in a Name? (2018) <https://nccih.nih.gov/health/integrative-health>.
- U.S. Department of Veterans Affairs, VA Research on Complementary and Integrative Health, CIH, 2018, <https://www.research.va.gov/topics/cih.cfm>.
- T.C. Clarke, L.I. Black, B.J. Stussman, P.M. Barnes, R.L. Nahin, Trends in the Use of Complementary Health Approaches Among Adults: United States, 2002–2012, *National Health Statistics Reports* (79), (2015), pp. 1–16 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4573565/>.
- P.M. Barnes, B. Bloom, R.L. Nahin, Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007, *National Health Statistics Reports* (12), (2008), pp. 1–23 <http://www.ncbi.nlm.nih.gov/pubmed/19361005>.
- M.A. Richardson, T. Sanders, J.L. Palmer, A. Greisinger, S.E. Singletary, Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology, *J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol.* 18 (13) (2000) 2505–2514 <https://doi.org/10.1200/JCO.2000.18.13.2505>.
- S.A. Quandt, M.J. Verhoef, T.A. Arcury, G.T. Lewith, A. Steinsbekk, A.E. Kristoffersen, D.L. Wahner-Roedler, V. Fonnebo, Development of an international questionnaire to measure use of complementary and alternative medicine (I-CAM-Q), *J. Altern. Complement. Med.* 15 (4) (2009) 331–339 <https://doi.org/10.1089/acm.2008.0521>.
- D.F. Cella, D.S. Tulsky, G. Gray, B. Sarafian, E. Linn, A. Bonomi, M. Silberman, S.B. Yellen, P. Winicour, J. Brannon, K. Eckberg, S. Lloyd, S. Purl, C. Blendowski, M. Goodman, M. Barnicle, I. Stewart, M. McHale, P. Bonomi, E. Kaplan, S. Taylor IV, C.R. Thomas Jr., J. Harris, The Functional Assessment of Cancer Therapy scale: development and validation of the general measure, *J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol.* 11 (3) (1993) 570–579 <https://ascopubs.org/doi/pdf/10.1200/JCO.1993.11.3.570>.
- M.A. Weitzner, C.A. Meyers, C.K. Gelke, K.S. Byrne, D.F. Cella, V.A. Levin, The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors, *Cancer* 75 (5) (1995) 1151–1161 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7850714.
- I. Montan, B. Lowe, D. Cella, A. Mehnert, A. Hinz, General population norms for the functional assessment of chronic illness therapy (FACT)-Fatigue scale, *Value Health* 21 (11) (2018) 1313–1321 <https://doi.org/10.1016/j.jval.2018.03.013>.
- J.G. Anderson, A.G. Taylor, Use of complementary therapies for cancer symptom management: results of the 2007 national health interview survey, *J. Altern. Complement. Med.* 18 (3) (2012) 235–241 <https://doi.org/10.1089/acm.2011.0022>.
- W.Z. Du, Y. Feng, X.F. Wang, X.Y. Piao, Y.Q. Cui, L.C. Chen, X.H. Lei, X. Sun, X. Liu, H.B. Wang, X.F. Li, D.B. Yang, Y. Sun, Z.F. Zhao, T. Jiang, Y.L. Li, C.L. Jiang, Curcumin suppresses malignant glioma cells growth and induces apoptosis by inhibition of SHH/GLI1 signaling pathway in vitro and vivo, *CNS Neurosci. Ther.* 19 (12) (2013) 926–936 <https://doi.org/10.1111/cns.12163>.
- F. Thayyullathil, A. Rahman, S. Pallichankandy, M. Patel, S. Galadari, ROS-dependent prostate apoptosis response-4 (Par-4) up-regulation and ceramide generation are the prime signaling events associated with curcumin-induced autophagic cell death in human malignant glioma, *FEBS open bio* 4 (2014) 763–776 <https://doi.org/10.1016/j.fob.2014.08.005>.
- M.A. Romero-Hernandez, P. Eguia-Aguilar, M. Perezpena-DiazConti, A. Rodriguez-Leviz, S. Sadowinski-Pine, L.A. Velasco-Rodriguez, J.R. Caceres-Cortes, F. Arenas-Huetero, Toxic effects induced by curcumin in human astrocytoma cell lines, *Toxicol. Mech. Methods* 23 (9) (2013) 650–659 <https://doi.org/10.3109/15376516.2013.826768>.
- W. Zhuang, L. Long, B. Zheng, W. Ji, N. Yang, Q. Zhang, Z. Liang, Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy, *Cancer Sci.* 103 (4) (2012) 684–690 <https://doi.org/10.1111/j.1349-7006.2011.02198.x>.
- K.M. Wesa, S. Cunningham-Rundles, V.M. Klimek, E. Vertosick, M.I. Coletton, K.S. Yeung, H. Lin, S. Nimer, B.R. Cassileth, Maitake mushroom extract in myelodysplastic syndromes (MDS): a phase II study, *Cancer. Immunol. Immunother. : CII* 64 (2) (2015) 237–247 <https://doi.org/10.1007/s00262-014-1628-6>.
- Y. Masuda, H. Inoue, H. Ohta, A. Miyake, M. Konishi, H. Nanba, Oral administration of soluble beta-glucans extracted from *Grifola frondosa* induces systemic antitumor immune response and decreases immunosuppression in tumor-bearing mice, *International journal of cancer, J. Int. Cancer* 133 (1) (2013) 108–119 <https://doi.org/10.1002/ijc.27999>.
- Y.M. Wang, B.Z. Jin, F. Ai, C.H. Duan, Y.Z. Lu, T.F. Dong, Q.L. Fu, The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials, *Cancer Chemother. Pharmacol.* 69 (5) (2012) 1213–1220 <https://doi.org/10.1007/s00280-012-1828-8>.
- R.F. Chun, B.E. Peercy, E.S. Orwoll, C.M. Nielson, J.S. Adams, M. Hewison, Vitamin D and DBP: the free hormone hypothesis revisited, *J. Steroid Biochem. Mol. Biol.* 144 (Pt A) (2014) 132–137 <https://doi.org/10.1016/j.jsbmb.2013.09.012>.
- X.H. Shu, L.L. Wang, H. Li, X. Song, S. Shi, J.Y. Gu, M.L. Wu, X.Y. Chen, Q.Y. Kong, J. Liu, Diffusion efficiency and bioavailability of resveratrol administered to rat brain by different routes: therapeutic implications, *Neurotherapeut. : J. Am. Soc. Exp. Neurotherapeut.* 12 (2) (2015) 491–501 <https://doi.org/10.1007/s13311-014-0334-6>.
- Q.H. Yang, J.N. Xu, R.K. Xu, S.F. Pang, Antiproliferative effects of melatonin on the growth of rat pituitary prolactin-secreting tumor cells in vitro, *J. Pineal Res.* 42 (2) (2007) 172–179 <https://doi.org/10.1111/j.1600-079X.2006.00403.x>.
- J. Reichrath, S. Reichrath, K. Heyne, T. Vogt, K. Roemer, Tumor suppression in skin and other tissues via cross-talk between vitamin D- and p53-signaling, *Front. Physiol.* 5 (2014) 166 <https://doi.org/10.3389/fphys.2014.00166>.
- I. Bairati, F. Meyer, E. Jobin, M. Gelinas, A. Fortin, A. Nabid, F. Brochet, B. Tetu, Antioxidant vitamins supplementation and mortality: a randomized trial in head and neck cancer patients, *International journal of cancer, J. Int. Cancer* 119 (9) (2006) 2221–2224 <https://doi.org/10.1002/ijc.22042>.
- T. Armstrong, M.Z. Cohen, K.R. Hess, R. Manning, E.L. Lee, G. Tamayo, K. Baumgartner, S.J. Min, A. Yung, M. Gilbert, Complementary and alternative medicine use and quality of life in patients with primary brain tumors, *J. Pain Symptom Manag.* 32 (2) (2006) 148–154 <https://doi.org/10.1016/j.jpainsymman.2006.02.015>.
- M.J. Verhoef, N. Hagen, G. Pelletier, P. Forsyth, Alternative therapy use in neurologic diseases: use in brain tumor patients, *Neurology* 52 (3) (1999) 617–622 <http://www.ncbi.nlm.nih.gov/pubmed/10025798>.
- B. Flechl, M. Ackerl, C. Sax, K. Dieckmann, R. Crevenna, A. Gaiger, G. Widhalm, M. Preusser, C. Marosi, Neurocognitive and sociodemographic functioning of glioblastoma long-term survivors, *J. Neuro-Oncol.* 109 (2) (2012) 331–339 <https://doi.org/10.1007/s11060-012-0897-1>.
- K. Takagi, G. Maskarinec, D.M. Shumay, Y. Tatumura, H. Kakai, Communication between physicians and cancer patients about complementary and alternative medicine: exploring patients' perspectives, *Psycho Oncol.* 11 (3) (2002) 212–220 <https://doi.org/10.1002/pon.552>.
- C. Arslan, M. Guler, Alternative medicine usage among solid tumour patients receiving chemotherapy, *Eur. J. Cancer Care* 26 (5) (2017), <https://doi.org/10.1111/ecc.12530>.
- J.K. Wortmann, A. Bremer, H.T. Eich, H.P. Wortmann, A. Schuster, J. Fuhner, J. Buntzel, R. Muecke, F.J. Protz, J. Huebner, Use of complementary and alternative medicine by patients with cancer: a cross-sectional study at different points of cancer care, *Med. Oncol. (Northwood, London, England)* 33 (7) (2016) 78 <https://doi.org/10.1007/s12032-016-0790-4>.