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ORIGINAL ARTICLE

Sensory changes and lipoprotein ratios in patients with brain cancers during cancer-related therapy: A prospective cross-sectional study

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Abstract

Aim: To identify the sensory changes and lipoprotein ratios and their relationship in brain cancer patients during cancer-related therapy (CRT).

Methods: This was a prospective cross-sectional study with three observation times: before CRT, at 2–3 weeks, and 4–6 weeks after beginning CRT. The changes in patients' symptoms were evaluated using the Memorial Symptom Assessment Scale, and lipoprotein ratios were measured using total cholesterol/ high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol/HDL-c, and triglyceride/HDL-c at the three time points.

Results: Sensory changes such as itching, swelling of the arms and legs, numbness in the hands or feet, tingling in the hands or feet, and changes in the way food tastes and lipoprotein ratios were altered in patients with brain cancer during CRT. The lipoprotein ratios showed a significant positive correlation with sensory changes at each observation time ($p < .05$).

Conclusion: Sensory changes and lipoprotein ratios varied, and their significant relationship was identified during CRT. Lipoprotein ratios should be considered as an indicator for symptom management in patients with malignant brain cancer during CRT.

KEYWORDS

brain cancers, cancer-related therapy (CRT), lipoprotein ratios, sensory changes

1 | INTRODUCTION

Globally, nearly 23,880 new cases of primary malignant brain cancer or cancer in the nervous system have been reported in the United States in 2018. In South Korea, about 2,500–4,500 patients are diagnosed with primary brain cancer every year, and more than 50% of these patients have malignant brain cancer (Jung et al., 2017). Primary malignant brain cancer is highly severe as it negatively affects multiple functions of the human body including physical, psychological, and cognitive function (Boele et al., 2015; Kamran et al., 2016, Kim, 2018; Kim & Byun, 2018).

Among the advanced treatment guidelines for patients with primary brain cancer is concurrent chemoradiotherapy with temozolomide (TMZ). The treatment involves a surgical resection to the extent feasible, followed by cancer-related therapy (CRT) within 6 weeks after surgery. During CRT, the patients receive irradiation therapy with a total dose of 60 Gy, with daily fractions of 2 Gy given 5 days per week for 6 weeks, while 75 mg/m^2 of TMZ is administered every day for 6 weeks during the RT period (Alphandéry, 2018; Witthayanuwat et al., 2018). During CRT, intensive concurrent therapy such as radiotherapy and chemotherapy is administered in patients with primary brain cancer within

a short period of time. However, little is known about the symptoms of patients who undergo CRT. Patients with other types of cancer, such as breast, lung, colon, or gastric cancer, experience various unpleasant symptoms during CRT (Argyriou et al., 2014; Kwekkeboom, 2017; Thomas et al., 2014).

The sensory changes that cancer patients frequently experience are among the symptoms of neurotoxicity, which result from either direct or indirect damage to the neurons, glia, or vascular tissues following CRT (Stone and DeAngelis, 2016). CRT not only acts on dividing cells by interfering with DNA repair and microtubule function, it also affects normal cells. The nervous system contains stem cells that replenish some neuron populations, thus making the system vulnerable to drugs that affect dividing cells (Addington and Freimer, 2016). Neurotoxicity occurred several weeks after initiating CRT; in particular, previous study reported that sensory changes occurred within 2 weeks after initiating CRT (Argyriou et al., 2014; Stone and DeAngelis, 2016). Thus, determining the biological indicators of neurotoxicity is important for symptom management during periods of CRT.

The generation and removal of reactive oxygen species (ROS) is essential for the vital cellular processes in the human body. However, excessive increase or insufficient removal of ROS could be induced by such anticancer agents or radiotherapy during CRT as this therapy can change the normal antioxidant mechanism in the human body (Conklin, 2004; Gupta et al., 2014). The cellular macromolecules including DNA, protein, and lipids easily interact with ROS; the end products of lipid peroxidation can be used to detect excessive amounts of ROS in the human body (Barrera, 2012). Therefore, lipoprotein levels have been used as indicators of ROS production in the human body, and its ratio is more useful in predicting the ROS status compared with other individual indicators (Maia et al., 2014). Changes in sensory perception and lipoprotein levels can be inferred from the same mechanism during periods of CRT based on previous studies.

Some studies examined the specific sensory changes in cancer patients during CRT (Cardoso et al., 2018; Stone and DeAngelis, 2016); however, these studies could not fully describe the underlying mechanisms that caused these changes. Furthermore, previous studies were mostly focused on the proportion of cancer patients receiving CRT more than twice. Because of this, evidence regarding the specific symptoms of brain cancer patients is limited, especially during periods of CRT. Therefore, this study aimed to determine the relationship between sensory changes and lipoprotein ratios in patients with primary malignant brain cancer who received an initial CRT.

2 | METHODS

2.1 | Study design and sampling

This prospective study was conducted from January 2015 to December 2017 in a hospital with more than 1,500 beds; data collection was performed prior to the initiation of CRT, 2–3 weeks after the initiation of CRT, and 4–6 weeks after the initiation of CRT. In our study, CRT was performed three times in accordance with the previous study (Davis, 2016; Minniti et al., 2017), which described the most frequently observed symptoms in patients with CRT. Convenience sampling was conducted in a hospital or outpatient clinic. This study was approved by the institutional review board of a single university hospital in South Korea with more than 1,300 beds (IRB no. B-1513/398–313).

2.2 | Participants

The participants of this study were patients with newly diagnosed primary brain cancer who underwent initial CRT in the hospital. The participants received concurrent chemoradiotherapy (CRT) with TMZ after tumor resection and adjuvant TMZ. The participants received CRT for 6 weeks and were irradiated with a total dose of 60 Gy with daily fractions of 2 Gy given 5 days per week for 6 weeks. TMZ was administered at 75 mg/m^2 per day for 6 weeks during the RT period. A diagram of the process of participant selection is presented in Figure 1.

2.3 | Inclusion and exclusion criteria

Participants (≥19 years old) who were newly diagnosed with primary malignant brain cancer classified as anaplastic astrocytoma or glioblastoma multiforme on tumor histological analysis by a pathologist, and who received CRT in an inpatient or outpatient clinic setting after a tumor

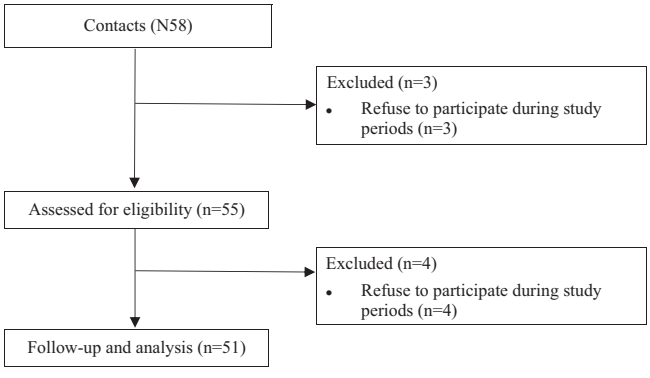

FIGURE 1 Diagram of the process of patient selection

resection, who either experienced or did not experience sensory changes, and who had a Karnofsky Performance Score of ≥70 during periods of CRT, were included. In contrast, participants who received medications for lipid control, who developed endocrine disorders, and who had psychological or cognitive problems that could cause communication problems were excluded.

2.4 | Sample size

The appropriate sample size was calculated using the following formula (Hulley et al., 2013):

$$N = [(Z\alpha + Z\beta)/C]^2 + 3.$$

where α is 0.05, β is 0.8, and r is 0.2. The calculated sample size for this study was 33, and the total participants was 51. The formula is appropriate for calculating minimum number of samples reflecting incidence rate of malignant brain tumors (Hulley et al., 2013).

2.5 | Measures

2.5.1 | Sensory changes with Memorial Symptom Assessment Scale

Sensory changes were assessed using Memorial Symptom Assessment Scale (MSAS). This scale was designed to assess the common physical symptoms experienced by a person with cancer (Portenoy et al., 1994). The MSAS is a 32-item inventory rated on a four-point Likert-type scale; its purpose is to measure the three dimensions: frequency, severity, and distress. The validity and reliability were well evaluated in a previous study and were easy to use for symptom detection (Chang et al., 2004). In this study, we selected five symptoms that were highly associated with neurotoxicity in cancer patients as reported in a previous study. The severity dimension in the MSAS was used to determine the symptoms experienced by the participants and was described on a four-point categorical scale, with one point as slightly severe and four points as very severe. The participants' symptom severity score was >2 (moderate); the participants were allowed to provide the same score on more than two symptom changes at each time.

2.5.2 | Lipoprotein ratios

Total cholesterol (TC) /high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) /HDL-c, and triglyceride (TG)/HDL-c were used as indicators of lipoprotein ratios in this study. The lipoprotein ratios showed physiological significance and clinical usefulness in cancer patients (Lozano et al., 2008; Ray and Husain, 2001; Kim 2018). The cut-off value of lipoprotein ratios is presented in Table 1, and the selection of cut-off values was based on a previous study (Lozano et al., 2008; Millán et al., 2009). To determine the lipoprotein ratios, blood samples were collected from the brachial vein of the participants after fasting for ≥6 hr prior to CRT. The samples were analyzed with an enzymatic method using the Toshiba 200FR (Toshiba Co., Tokyo, Japan).

2.6 | Statistical analysis

Data were analyzed using SPSS statistical software (version 25.0; IBM, Armonk, NY, USA). The general and disease-related characteristics of the participants were analyzed using descriptive statistics. The frequency of symptoms related to sensory changes and lipoprotein ratios according to periods of CRT were analyzed using Fisher's exact test or Chi-square statistic with post-hoc Wilcoxon signed rank test. Correlation analysis was performed to analyze the relationship between lipoprotein ratios and sensory changes according to the periods of CRT; *p* values less than .05 were considered significant.

3 | RESULT

3.1 | General and disease-related characteristics

A total of 51 participants who met the study criteria were included. The general and disease-related characteristics of the participants are presented in Table 2. The mean age of the participants was 55.76 years (standard

TABLE 1 Cut-off values of the lipoprotein ratios

Characteristics	Normal	Risk for OS[a]
TC/HDL-c	<3.5	≥3.5
LDL-c/HDL-c	<2.5	≥2.5
TG/HDL-c	<3.0	≥3.0

Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; OS, overall survival.

[a]The cut-off value of lipoprotein ratios is presented in Table 1, and the selection of cut-off values was based on a previous study (Lozano et al., 2008; Millán et al., 2009).

TABLE 2 General and disease-related characteristics of participants

Characteristics	Categories	n (%)	Mean±SD
Age (years)	19–39	7 (13.73%)	55.76 ±5.71
	40–64	31 (60.78%)	
	Above 65	13 (25.49%)	
Gender	Male	30 (58.82%)	
	Female	21 (41.18%)	
Education level	High school or less	12 (23.53%)	
	At least some college	39 (76.47%)	
Employment	Employed	32 (62.75%)	
	Not employed	19 (37.25%)	
Marital status	Unmarried	14 (27.45%)	
	Married	34 (66.67%)	
	Widowed/ divorced	3 (5.88%)	
Smoking	Yes	17 (33.33%)	
	No	34 (66.67%)	
Hypertension	Yes	19 (37.25%)	
	No	32(62.75%)	
Diabetes	Yes	17 (33.33%)	
	No	34 (66.67%)	
Tumor location	Frontal lobe	16 (31.37%)	
	Temporal lobe	13 (25.49%)	
	Occipital lobe	12 (23.53%)	
	Parietal lobe	6 (11.77%)	
	Other	4 (7.84%)	
Tumor size	<3 cm	31 (60.78%)	
	≥3 cm	20 (39.22%)	
Tumor histology and grade	Anaplastic astrocytoma	19 (37.25%)	
	Glioblastoma multiforme	32 (62.75%)	
Extent of the resection	Gross total resection	29 (56.87%)	
	Subtotal resection	17 (33.33%)	
	Partial resection	5 (9.80%)	

Abbreviation: SD, standard deviation ($N = 51$).

deviation = 5.71 years), with middle-aged adults (40–-64 years) forming the largest group (60.78% of the participants). Most of the participants were men, were married, were employed, and completed a Bachelor's degree (58.82%, 66.67%, 62.75%, and 76.47%, respectively). The proportion of nonsmokers was higher than that of smokers (66.67% vs. 33.33%). The number of participants with chronic disease such as hypertension and diabetes were fewer than those without chronic disease. The most common tumor locations were the frontal lobe (31.37%), temporal lobe (25.49%), occipital lobe (23.53%), and parietal lobe (11.77%). More participants were diagnosed with glioblastoma multiforme (62.75% vs. 37.25%). Most of the participants underwent gross total tumor resection (56.87%).

3.2 | Sensory changes in participants during CRT

Sensory changes in participants according to periods of CRT are presented in Figure 2. All participants had no sensory changes prior to the initiation of CRT, and those who met the study criteria did not experience sensory changes. The participants experienced itching (29.41%), swelling of the arms or legs (25.49%), tingling in the hands or feet (17.65%), numbness in the hands or feet (15.69%), and changes in the way food tastes (11.76%) at 2–3 weeks after initiating CRT. At 4–6 weeks after initiating CRT, the participants experienced tingling in the hands or feet (27.17%), changes in the way food tastes (24.69%), numbness in the hands or feet (18.51%), swelling of the arms or legs (16.05%), and itching (13.58%). All symptoms had significant difference among all three time periods ($p < .05$).

3.3 | Lipoprotein ratios during CRT

Lipoprotein ratios according to the periods of CRT are shown in Table 3. All participants did not exhibit abnormal lipoprotein ratios prior to the initiation of CRT; all participants received medications for lipid control. The LDL/HDL-c ratio (39.22%) was abnormally high at 2–3 weeks after initiating CRT. TG/HDL-c (45.10%), LDL-c/HDL-c (43.14%), and TC/HDL-c (41.18%) were abnormally high at 4–6 weeks after initiating CRT. There was a significant difference in lipoprotein ratios between the normal group and risk group according to the periods of CRT ($p < .05$).

3.4 | Relationship between sensory changes and lipoprotein ratios during CRT

Analysis of the relationship between sensory changes and lipoprotein ratios during CRT is presented in Table 4. TG/HDL-c ratio showed a significant positive correlation with sensory changes at 2–3 weeks after CRT. By contrast, TG/HDL-c, TC-HDL-c, and LDL-c/HDL-c showed a

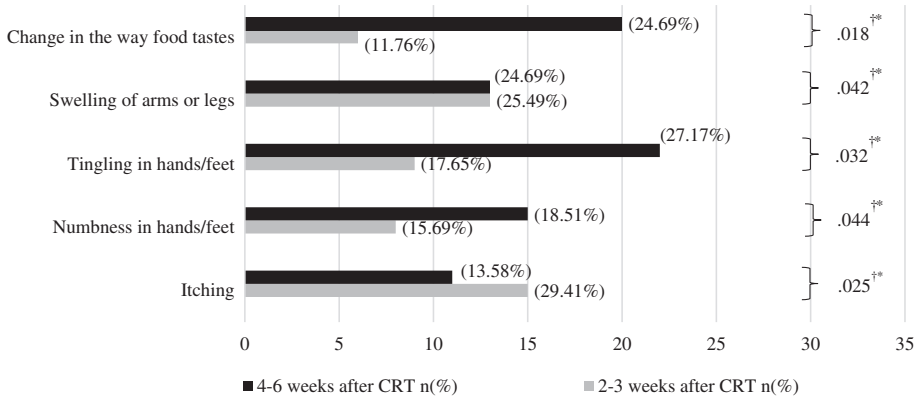

FIGURE 2 Sensory changes in participants during CRT. CRT, cancer-related therapy. †Participants were allowed to provide the same answer more than twice regarding the symptoms they experienced. †Based on Fisher's exact test or Chi-square statistic with Wilcoxon singed rank test. *$p < .05$. All participants had no sensory changes above five symptoms at baseline at before CRT ($n = 51$)

TABLE 3 Lipoprotein ratios in participants during CRT

		Before CRT n (%)	2–3 weeks after CRT n (%)	4–6 weeks after CRT n (%)
TC/HDL-c[a]*	Normal	51 (100.0%)	35 (68.63%)	30 (58.82%)
	Risk level	0 (0.0%)	16 (31.37%)	21 (41.18%)
LDL-c/HDL-c[a]*	Normal	51 (100.0%)	31 (60.78%)	29 (56.86%)
	Risk level	0 (0.0%)	21 (39.22%)	22 (43.14%)
TG/HDL-c[a]*	Normal	51 (100.0%)	32 (62.75%)	28 (54.90%)
	Risk level	0 (0.0%)	19 (37.25%)	23 (45.10%)

Abbreviation: CRT, cancer-related therapy ($N = 51$). HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
[a]Based on Fisher's exact test or Chi-square statistics.
*$p < .05$.

TABLE 4 Relationship of sensory changes and lipid peroxidation in participants during CRT

Characteristics	Categories	Itching	Numbness in the hands or feet	Tingling in the hands or feet	Swelling of the arms or legs	Change in the way food tastes
Before CRT	TC/HDL-c	—	—	—	—	—
	LDL-c/HDL-c	—	—	—	—	—
	TG/HDL-c	—	—	—	—	—
2–3 weeks after CRT	TC/HDL-c	.18	.22	.30*	.06	.09
	LDL-c/HDL-c	.10	.16	.39*	.12	.18
	TG/HDL-c	.18	.34*	45*	.20	.35*
4–6 weeks after CRT	TC/HDL-c	.21	.47*	.38*	.15	.11
	LDL-c/HDL-c	.16	.19	.42*	.18	.41*
	TG/HDL-c	.34	.51*	.44*	.47*	.56*

Abbreviations: CRT, cancer-related therapy; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride ($N = 51$).

significant positive correlation with sensory changes at 4–6 weeks after CRT.

4 | DISCUSSION

Several studies on cancer patients have been performed to determine the specific tumor markers, suitable treatment, and medication guidelines (Alphandéry, 2018; Davis, 2016). These efforts have been made to develop advanced treatments that can effectively treat cancer. However, studies on symptom management in cancer patients have not made sufficient progress, as the majority of previous studies were performed at a single time point and focused only on the identification of symptoms of cancer patients. Thus, further studies on symptom

management in cancer patients are warranted to determine why the symptoms occur, and an additional observation should be performed during CRT.

During CRT, various chemical reactions destroy tumor cells or inhibit cell growth in the human body. The principle of radiotherapy is to ionize molecular structures of tumor cells; when the cells are ionized, ROS are produced (Stone and DeAngelis, 2016; Kim and Byun, 2018). Furthermore, antineoplastic agents used for chemotherapy affect the antioxidant concentration in the human body (Conklin, 2004; Gupta et al., 2014). During CRT, oxidative stress (the imbalance between the level of ROS generation and removal) occurs, which means that the rate of ROS production is higher than its removal (Argyriou et al., 2014; Barrera, 2012). Concurrent chemoradiotherapy (CRT) could improve the median survival and is an effective treatment for primary brain cancer (Davis, 2016; Kamran et al., 2016). However, CRT includes a combination of radiotherapy and chemotherapy, which could possibly increase ROS levels, and is administered within a short period of time. Thus, unintended side effects can occur during periods of CRT but they have not been sufficiently reported.

One of the most frequent symptoms experienced by cancer patients during CRT is sensory changes. Sensory changes in cancer patients undergoing such treatment have been frequently reported in some research. The reasons for the occurrence of sensory changes in cancer patients during periods of CRT (Kwekkeboom, 2017; Minniti et al., 2017; Stone and DeAngelis, 2016) were as follows: sensory changes are primarily caused by neurotoxicity; various processes can also occur as a result of neurotoxicity, which can affect sensory perception. During cancer treatment, tumor cells are destroyed or their growth is suppressed, but normal cells can be affected unintentionally (Maia et al., 2014). Many studies reported that the ROS levels in patients who received CRT is increased, and imbalance in ROS levels during CRT are known to cause neurotoxicity (Gupta et al., 2014). Radiotherapy involves the use of ionizing radiation and can shrink or eliminate tumors by increasing ROS production inside cancer cells (Minniti et al., 2017). However, some cancer cells become resistant to radiotherapy because the cells develop a tolerance to the molecules. Furthermore, chemotherapy agents may reduce the antioxidants and tissue glutathione levels. The indicators of ROS levels were evaluated in previous cancer studies, and lipid peroxidation was used to determine ROS levels, especially individuals at risk of oxidative stress. The lipid bilayer forms the basis of a cell membrane, and ROS can easily interact with cell membrane, DNA, and lipids. Therefore, lipid peroxidation is used as an indicator of ROS increase in cells, and lipid ratios represent the individual lipid levels (Barrera, 2012; Lozano et al., 2008).

In this study, there were changes in the frequency of sensory symptoms in brain cancer patients during periods of CRT. Some symptoms such as itching and swelling of arms and legs were less frequent but other symptoms such as numbness in the hands or feet, tingling in the hands or feet, and changes in the way food tastes were frequently observed during periods of CRT. In the early stage of CRT or in patients who received initial cancer therapy, acute itching and swelling were reported as allergic reactions to the treatments (Addington and Freimer, 2016; Cardoso et al., 2018). Hence, the results of this study supported those of previous studies, and these symptoms will be monitored using immunologic indicators. Furthermore, sensory symptoms due to an allergic response need to be closely monitored at the early stage of CRT. Changes in skin sensation in cancer patients who received CRT were reported at different periods after initiation of CRT and were described as burning or aching. Numbness or tingling sensation was a result of the damage to the peripheral nervous system, which is one of the symptoms of neurotoxicity, during CRT (Cardoso et al., 2018; Zanville et al., 2016). TMZ has been used in the treatment of malignant brain cancer, especially grade 3 or 4 brain cancer, and was reported to improve the outcomes. It is an oral alkylating agent that controls DNA methylation, thus preventing tumor cell proliferation (Alphandéry, 2018). However, alkylating agents can induce neurotoxicity in cancer patients, and symptoms of neurotoxicity like pain often occur at the early stage of cancer therapy (Argyriou et al., 2014). Thus, pain assessments are needed during this period to evaluate the level of pain. Taste alterations and smell changes in cancer patients receiving chemotherapy were frequently observed in previous studies and are attributed to damage to taste cell receptors and nerves involved in taste perception and reduction in the amount of saliva produced due to neurotoxicity (Cardoso et al., 2018; Murtaza et al., 2017). Taste receptor cells or nerves are easily destroyed and rapidly replaced in the early weeks of CRT, and damage to these cells or nerves may cause various problems such as medication administration, weight loss, depression, and decline in quality of life. In this study, the frequency of symptoms such as changes in the way food tastes was observed in the early periods and worsened during the periods of CRT; thus, medical staff should pay attention to the factors that may aggravate these symptoms and monitor other medical problems described above.

The presence of lipoprotein ratios as indicators of oxidative stress were identified at both 2–3 weeks and 4–6 weeks after CRT. Further, the number of patients who were at risk for oxidative stress was increased based on the periods of CRT. ROS can easily react with

polyunsaturated fatty acids, and some cell membranes such as those of lipid, proteins, and DNA are vulnerable to ROS attack (Addinton and Fremier, 2016; Barrera, 2012; Ray and Huisain, 2001). Based on these results, ROS levels can remain uncontrolled or worsen; hence, some efforts are needed to manage ROS levels during periods of CRT. In particular, sensory changes, which showed a significant correlation with lipoprotein ratios, were commonly observed at 4–6 weeks after initiation of CRT than at 2–3 weeks after initiation of CRT. In previous studies, immunological parameters were only used as indicators for detecting sensory changes in cancer patients. Unfortunately, sensory nerve cells do not replicate; hence, damage to these cells can be irreversible (Stone and DeAngelis, 2016). Therefore, lipoprotein ratios need to be considered as indicators for managing sensory changes in brain cancer patients who received CRT.

The unpleasant sensory changes have potential impact on the quality of life in the long journey for cancer patients; thus, this study was conducted to determine these indicators. However, several previous studies regarding malignant brain cancer were focused only on the survival periods of cancer patients as the severity of their disease increases during CRT. Moreover, these previous studies were only performed at a single time point, same as those of cross-sectional studies. Therefore, additional studies are warranted to determine the extent of symptom management in brain cancer patients during CRT. Although ROS are essential for various vital processes such as signal transduction and the ability of phagocytes to carry out their bactericidal activity, ROS should be monitored to prevent excessive production.

5 | LIMITATIONS

There were several limitations in this study. First, this study used three time points to analyze symptom changes and lipoprotein ratios. However, further study is still warranted to perform further observations at other time points. Second, as there are several types of cancer-related therapies for primary malignant brain cancers, further study is needed to determine other types of CRT and analyze the specific sensory changes and lipoprotein ratios therein.

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CONFLICTS OF INTEREST

The author has no conflicts of interest to disclose.

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