Use of Complementary Therapy in Lung Cancer Patients Treated with Chemotherapy and its Effect on Survival: A Cross-sectional Study

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──────── **Abstract** ────────

Aim: Complementary therapies are being increasingly preferred in patients receiving anticancer therapy to strengthen the effect of chemotherapy and control cancer-related symptoms. In this study, we investigated the prevalence of complementary therapy (CT), the factors associated with its use, physician-patient information sharing about CT use, and the effect of CT on the survival and treatment process in lung cancer patients receiving chemotherapy.

Methods: This study was designed as a cross-sectional study including patients who underwent chemotherapy for lung cancer between November 2020 and March 2022 in the department of medical oncology at Tekirdag Namik Kemal University. A structured questionnaire with twenty questions was used. Fluor-18-fluorodeoxyglucose positron emission tomography/CT, and brain magnetic resonance imaging were used to stage the patients. The stages were grouped as early (stages 1B-3A) and advanced (stages 3B-4A).

Results: A total of 242 patients included in the study. One hundred and forty-seven (60.7%) patients reported using at least one type of CT since the first diagnosis. "Families/relatives" (n=128; 63.7%) and "other patients" (n=67; 33.3%) were the primary sources from which patients obtained CT information. The most widely used CT methods were recorded as phytotherapy (79.6%) and apitherapy (59.2%). 125 (85%) of the patients said that they used CT to support their existing anticancer treatments. Of the patients using CT, 94 (63.9%) stated that they did not disclose their use of CT to their physicians. The majority of patients stated that their physicians did not inquire about using CT. In the cox regression analysis performed to determine survival benefit, no survival benefit from the use of CT was determined (hazard ratio=0.86, p=0.495). In the subgroup analysis, the use of CT was associated with survival in early-stage patients, but no survival relationship was found in advanced-stage patients (log-rank p=0.027 and p=0.842, respectively).

Conclusion: The use of CT in conjunction with medical treatment is common among patients with lung cancer. The influence of the oncologist in guiding the use of CT in cancer patients is weak. Additionally, the use of CT does not provide benefits in terms of survival.

Keywords: Lung neoplasms, complementary therapies, phytotherapy, surveys and questionnaires

Introduction

According to the 2021 data, except for skin cancers, lung cancer is one of the most common cancers in the world, and it is the most common type of cancer that causes death in both men and women (1). Surgery, chemotherapy, and radiotherapy are included in the definitive treatment options in non-metastatic stages, while chemotherapy, immunotherapy, and other palliative treatments are among the main treatments in metastatic stages (2). Because the majority of patients are diagnosed in advanced stages, the high mortality rate of lung cancer

persists despite constantly improving medical science and technological opportunities (1,3).

Due to both the disease and difficulties in the treatment process, cancer patients must experience many psychological and physical side effects during the chemotherapy period. This situation both negatively affects patients' compliance with treatment and reduces their quality of life (4). The difficulties experienced by the patients have raised interest in different treatment options, including supportive and complementary therapy (CT), over the years (4-6). As a matter of fact, it has been

reported in previous studies that patients using CT during the treatment process benefited positively (7). However, there is a risk of drug interaction between anticancer and complementary therapies (8). Additionally, its benefit or harm to survival is not yet known (9).

In this study, we investigated the prevalence of CT, the factors associated with the use of CT, and the effect of CT on the survival and treatment processes in lung cancer patients receiving chemotherapy. Additionally, the effect of supplemental therapy on the treatment process and the situation of physician-patient information exchange were examined from the patient's perspective.

Materials and Methods

Compliance with Ethical Standards

This study was performed in line with the principles of the Declaration of Helsinki. The Tekirdag Namik Kemal University Ethics Committee granted formal approval for this study (date: 29.09.2020; approval number: 2020.224.09.11). All participants received information about the purpose of the study and were assured of anonymity and confidentiality before signing a consent form. Informed consent was obtained from all participants in the study.

Study Design and Participants

This study was designed as a cross-sectional study including patients who underwent chemotherapy for lung cancer between November 2020 and March 2022 in the department of medical oncology at Tekirdag Namik Kemal University. Archive files were scanned before distributing the questionnaire to the patients who accepted to participate in the study. According to the information scanned from the hospital archives, patients who were 18 years of age or older at the time of their cancer diagnosis, had an adenocarcinoma or squamous cell lung cancer subtype, received chemotherapy for at least 2 months, and used CT for at least 3 months were included in the study. At the time of diagnosis, patients with a life expectancy of <3 months, an Eastern Cooperative Oncology Group (ECOG) performance score of 4, and those diagnosed with different types of cancer together or sequentially were excluded from the study (Figure 1). Computed tomography, fluor-18-fluorodeoxyglucose positron emission tomography/computed tomography, and brain magnetic resonance imaging were used to stage the patients. The stages were grouped as early (stages 1B-3A) and advanced (stages 3B-4A).

Participants were assured that their answers would be kept confidential. Written and verbal consent was received from the patients who accepted to answer the questionnaire. The questionnaire, consisting of 20 questions, was completed by the oncologist through face-to-face interviews.
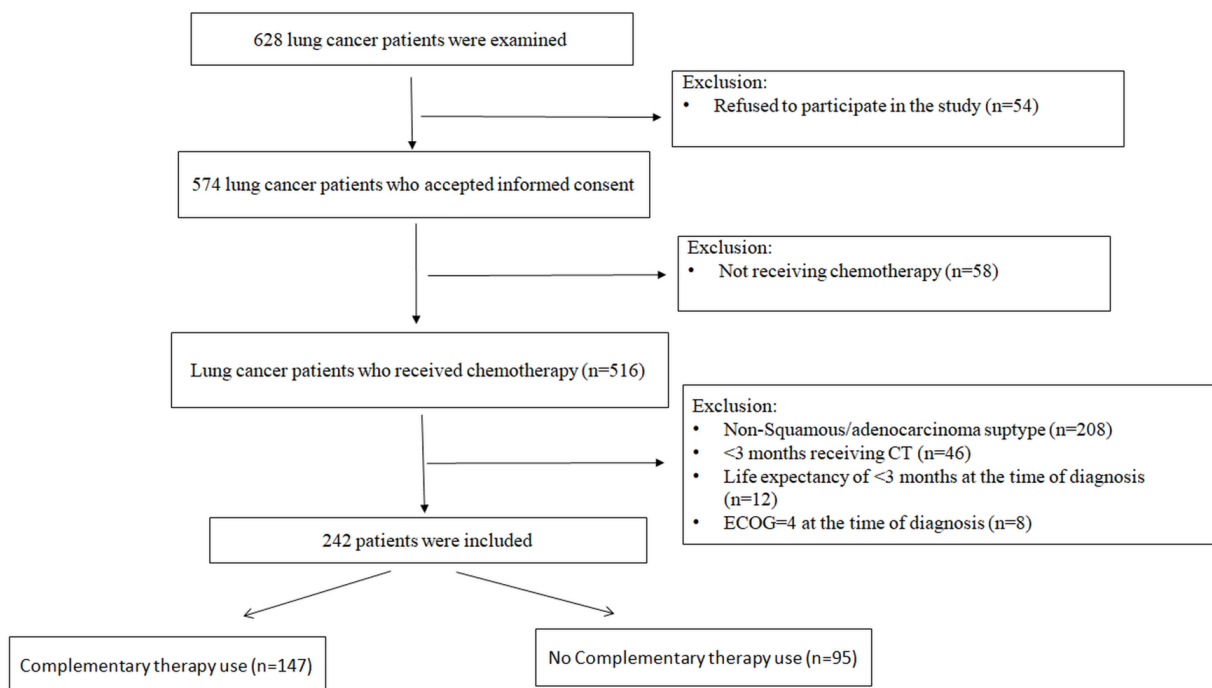

Figure 1. Algorithm for patients' inclusion and exclusion
ECOG: Eastern Cooperative Oncology Group

Study Questionnaire

To compare with the surveys in the literature, some of the survey questions were selected to be similar to the CT survey studies in the literature (6,10,11). The questionnaire was divided sequentially into four sections according to the areas of interest of the questions. In the first part (5 questions), the demographic attributes of patients and clinical characteristics were included. The histories of CT use before the disease, the level of knowledge of the patients about CT, and the sources from which they obtained CT information were questioned in the second section (6 questions). The questions in the third part (4 questions) were for determining the CT methods they used. CT methods (Phytotherapy, Apitherapy, Vitamin Supplements, Acupuncture, Homeopathy, Mushroom Supplements, and Cupping Therapy) were questioned in a manner similar to previous studies' questionnaires. In the fourth part (5 questions), the reasons given by the patients for applying for CT, their status in sharing it with their physicians, and the benefits and harms of CT for them were questioned. The questionnaire was designed in Turkish, and simple, clear expressions were used for the questions. In questions with multiple answers, the participants were instructed to select any or all appropriate responses. A pre-test including 10 people was conducted to see if the questions were clear, and some questions were changed at the end of these pre-tests. The survey study was started in its final form.

Statistical Analysis

Categorical measurements were summarized in numbers and percentage values, and continuous measurements were summarized as mean and standard deviation. The chi-square test or Fisher's exact test were used to assess the relationship between variables. Using retrospective data from the electronic record system, overall survival time (OS) was calculated as the time from the diagnosis time to the date of death or the patient's last follow-up. Survival analyses were performed using the Kaplan-Meier method, and the Log-Rank test was used for group comparison. A univariate analysis of factors affecting survival was performed with the Cox proportional-hazards model. All statistical analyses were performed using SPSS version 26.0 (IBM Corb, Armonk, NY). Statistical significance is defined as a p-value less than 0.05.

Results

Relationship between the characteristics of the patients and complementary therapy

The study was completed with 242 patients who agreed to complete the questionnaire. The median age was 64 years (range: 32-84 years). Ninety-two (38.2%) patients died during the follow-up period because of cancer-related reasons. Of the included patients, 147 (60.7%) reported that they used at least one type of CT. General characteristics of patients according to the status of CT use are demonstrated in Table 1.

Two hundred one (83.1%) patients had knowledge about CT. "Families/relatives (n=128; 63.7%)" and "other patients (n=67; 33.3%)" were the primary sources from which patients with CT knowledge obtained information (Table 2).

The number of patients who had knowledge about CT before the diagnosis of the disease was 99 (40.9%), and 42 (17.4%) patients stated that they used CT for different reasons before they were diagnosed with cancer. Additionally, the patients who had used CT for another reason before the diagnosis received CT more during the chemotherapy than the patients who had not used it before the diagnosis (p<0.001) (Table 1).

Reasons for and disclosures about using CT with a physician

Sixty-nine (28.5%) patients reported that they found the current treatments "insufficient" in providing recovery. 75.4% (n=52) of these patients said they used CT during the chemotherapy process. In the analysis, it was determined that the patients who reported the conventional treatment as "inadequate" used CT statistically significantly more than those who reported it as "adequate" (p=0.003).

Fifty-three (36.1%) patients told their doctors about their CT use. Age, gender, educational status, performance status, and disease stage were not determined to be associated with disclosing CT usage with physicians (p=0.282, p=0.607, p=0.284, p=0.632, p=0.092, respectively). The reasons for using CT, the answers of their physicians when they shared their CT usage with their physicians, and the reasons why patients avoided informing their doctor about CT are shown in Table 3.

Thirty-two (21.8%) patients using CT said that they greatly benefited from it, and 54 (36.7%) of them said that they partially benefited. Two (1.4%) patients said that they suffered from CT damage. Fifty-nine (40.1%) patients answered "neutral" about the CT they received. It was found that patients who reported a positive response to CT (beneficial or partially beneficial) strongly advised other patients to use CT more frequently (p<0.001).

Complementary therapy methods

While 44.9% (66) of the users stated that they used only one type of CT, the remaining reported that they used more than one type of CT. The most common CT methods used by the patients using CT were recorded as phytotherapy (79.6%) and apitherapy (59.2%). Detailed results are shown in Table 4.

Survival Analysis

The median OS (mOS) for all patients was 15.7 months (range, 5.1-181). The mOS of the patients using CT was 16.2 months, and the mOS of the patients not using CT was found to be 15.4 months, and there was no statistically significant difference between the two groups (log-rank p=0.494). The relationship between patient characteristics and CT types used and survival was examined using univariate Cox regression analysis. Complementary therapy use did not have any effect on survival [hazard ratio (HR)=0.86, 95% confidence interval (CI): 0.57-1.32, p=0.495]. In the analysis performed, poor ECOG performance status (HR=1.83, 95% CI: 1.05-3.21, p=0.034), the presence of metastases (HR=2.71, 95% CI: 1.73-4.24, p<0.001), advanced disease stage (HR=2.49, 95% CI: 1.28-4.84, p=0.007), and the absence of a surgical history (HR=0.51, 95% CI: 0.29-0.90, p=0.020) were associated with shorter survival time (Table 5).

Patients were divided into two subgroups: "early stage" and "advanced stage". It was found that the use of CT in early-stage patients was associated with survival (mOS=42.37 months, 95% CI: 18.30-66.44, log-rank p=0.027), while the use of CT in advanced-stage patients was not statistically significantly associated with survival (mOS=20.57 months, 95% CI: 16.48-24.66, log-rank p=0.842) (Figure 2).

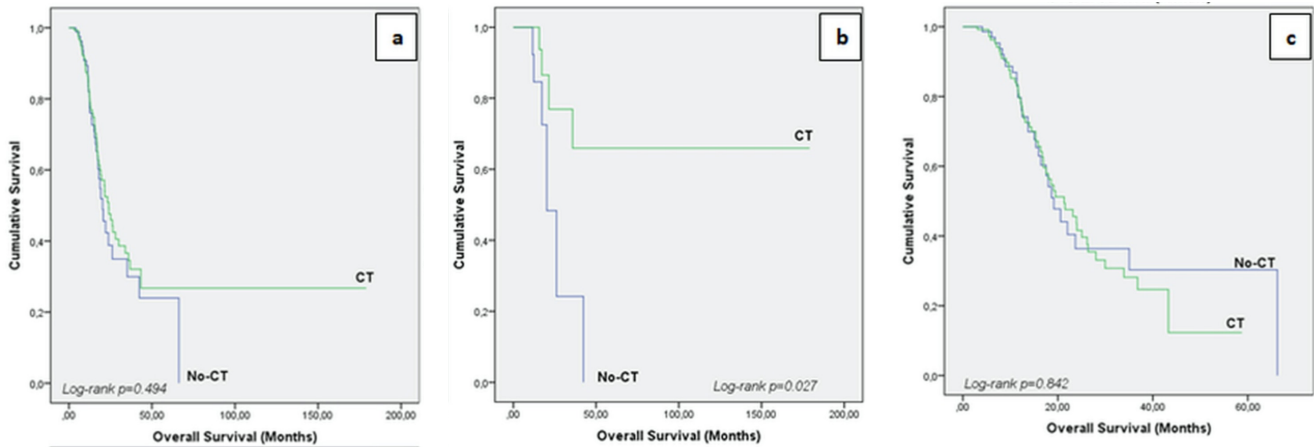| Table 1. Distribution of the characteristics of the patients according to their status of complementary therapy use				
		Complementary Medicine		
Variables	**Total N (%)**	**No N (%)**	**Yes N (%)**	**p-value***
Age				
<65	126 (52.1)	48 (38.1)	78 (61.9)	0.700
≥65	116 (47.9)	47 (40.5)	69 (59.5)	
Sex				
Male	213 (12.0)	88 (41.3)	125 (58.7)	0.076
Female	29 (88.0)	7 (24.1)	22 (75.9)	
Education				
Iliterate	14 (5.8)	5 (35.7)	9 (64.3)	0.540
Primary School	202 (83.5)	79 (39.1)	123 (60.9)	
High School	20 (8.3)	10 (50.0)	10 (50.0)	
University	6 (2.5)	1 (16.7)	5 (83.3)	
ECOG status				
0-1	200 (82.6)	81 (40.5)	119 (59.5)	0.387
≥2	42 (17.4)	14 (33.3)	28 (66.7)	
Histopathology				
Squamous	113 (53.3)	47 (41.6)	66 (58.4)	0.486
Adenocarcinom	129 (46.7)	48 (37.2)	81 (62.8)	
Metastatic status				
Metastatic	127 (52.5)	48 (37.8)	79 (62.2)	
Non-metastatic	115 (47.5)	47 (40.9)	68 (59.1)	0.625
Stage				
Early	37 (15.3)	16 (43.2)	21 (56.8)	
Advanced	205 (84.7)	79 (38.5)	126 (61.5)	0.589
Previous conventional treatments				
Radiotherapy	115 (100.0)	51 (44.3)	64 (55.7)	0.123
Surgery	57 (100.0)	24 (42.1)	33 (57.9)	0.614
Previous complementary therapy				
Yes	42 (17.4)	3 (7.1)	39 (92.9)	
No	200 (82.6)	92 (46.0)	108 (54.0)	**<0.001**
*Chi-square test or Fisher's exact test was performed. Significance level set at <0.05 ECOG: Eastern Cooperative Oncology Group				

Figure 2. Kaplan-Meier survival curve by CT status, a) All patients, b) Early stage, c) Advanced stage
CT: Complementary therapy

Table 2. Sources of CT information of the patients		
	n	**%**
Friends/family	128	63.7
Internet/social media	70	34.8
Other patients	67	33.3
TV/radio	29	14.4
Health centers	17	8.5
Book/newspaper/magazine	9	4.5
Education centers	2	1.0
CT: Complementary therapy		

Table 3. The reasons of the patients for using complementary therapy and their status of sharing these with their physicians	
Why did you use CT? (n=147)	
	n (%)
To reduce the side effects of my treatments	51 (34.7)
To improve physical well-being	42 (28.6)
To support my treatments	125 (85.0)
To feel better and step up my hope	56 (38.1)
Desire to do everything possible to fight the disease	39 (26.5)
If you received CT and shared this with your doctor, how did your doctor react? (n=53)	
	n (%)
Suggested me to stop treatment	6 (11.3)
Encouraged me to continue treatment	26 (49.1)
Neither suggested nor recommended	21 (39.6)
If you have not shared this with your doctor despite having CT, what is the reason? (n=94)	
	n (%)
Because my doctor never asked me about this	82 (87.2)
I thought my doctor couldn't understand me	3 (3.2)
I thought my doctor wouldn't approve the use	9 (9.6)
CT: Complementary therapy	

Discussion

In this study, we investigated the prevalence of CT, CT types, the patients' sources of CT information, predictive factors for CT, and the effect of using CT on survival in lung cancer patients receiving chemotherapy. In our study, we found that the prevalence of using CT was 60.7%. In a study that has been conducted in 8 different European countries, including only lung cancer patients, the prevalence of use of CT has been reported to be 23.6% (10). The prevalence has been reported to be 45% in a study conducted in America and 41% in a study conducted in Asia (11,12). Dağtaş Gülgün and Kaya (13), in a previous study conducted in Turkey, reported the use of CT to be 56.5%, similar to the prevalence in our study, and Erbaycu et al. (14) reported the use of CT to be 27.4% in lung cancer patients receiving chemotherapy. These differences in CT usage rates may be related to differences in belief or culture, geographical differences between regions, or differences in confidence in conventional treatments (15,16). In our study, no relationship was found between

Table 4. CT preferences, phytotherapy and apitherapy products of the patients	
	n (%)
Complementary therapy types	
Phytotherapy	117 (79.6)
Apitherapy	87 (59.2)
Vitamin supplements	12 (8.2)
Acupunctur	3 (2.0)
Homeopathy	3 (2.0)
Mushrooms supplements	3 (2.0)
Cupping therapy	2 (1.1)
Herbal supplements for phytotherapy (n=117)	
Green tea	38 (32.5)
Carob	24 (20.5)
Turmeric	24 (20.5)
Ginger	19 (16.2)
Linden tea	19 (16.2)
Black cumin	13 (11.1)
Grape seed/molasses	12 (10.3)
Sugar beet	11 (9.4)
Black mulberry	7 (6.0)
Thyme	6 (5.1)
Stinging nettle	6 (5.1)
Pistachio	4 (3.4)
Camomile tea	4 (3.4)
Pine cone	3 (2.6)
Garlic	3 (2.6)
Hypericumperforatum	3 (2.6)
Purslane	3 (2.6)
Juniper grass	2 (1.7)
Grapefruit	1 (0.9)
Carob molasses	1 (0.9)
Bee products for apitherapy (n=87)	
Honey	76 (87.4)
Propolis	21 (24.1)
Pollen	11 (12.6)
Royal jelly	3 (3.4)
Bee venom	1 (1.1)
CT: Complementary therapy	

the use of CT and age, gender, education level, or disease characteristics. However, it was determined that the patients who found conventional treatments insufficient to provide a cure tended to use CT more.

In our study, the most common causes for the patients' using CT were to increase the effectiveness of anti-cancer treatments (85%), to feel better or raise hope (38.1%), and to reduce the side effects of chemotherapy (34.7%), in accordance with the most common reasons for using CT for cancer patients reported in previous studies (17-19). However, 41.5% of the patients stated that they did not benefit from CT treatment. Results similar to the results of our study have been reported as 46.8% in the study of Ceylan et al. (20) and 48% in the study of Samur et al. (21). Despite the high rate of patients stating that they did not benefit, and although the fact that only 2 (1.4%) of the CT users in our study stated that they were harmed by CT use shows that CT can be reliable, note that they may not be able to distinguish the side effects experienced by the patients receiving concurrent chemotherapy as chemotherapy-related or CT-related.

When the patients' information sources for CT were inquired about, families and close friends (63.7%) and the internet and social media (34.8%) were found to be the main sources. Physicians and health centers accounted for 8.5% of information sources. Similarly, in the study of Naja et al. (11), in which only lung cancer patients were included, friends (48%) and the media (40%) were reported to be the most common sources, while health professionals remained only 2%. The fact that social media and the internet are among the top sources of information is an acceptable result in a digitized world where access to the internet has become easier (22). However, the fact that healthcare professionals are not preferred as a source of information for CT usage may make it difficult for patients to access reliable CT information.

CT users and oncologists do not adequately discuss CT. Previous literature reports the percentage of patients who share their CT use with their physician as 12.5% to 58% (11,23-25). Consistent with the published studies, 37.3% of the patients in our study informed their physicians about CT usage. In our inquiry into the reasons lying

Table 5. Cox regression analyses of factors for overall survival			
Variable	Category	HR (95% CI)	p-value*
Age	<65/≥65	0.93 (0.62-1.41)	0.746
ECOG PS	0-1/≥2	1.83 (1.05-3.21)	**0.034**
Histologic type	SCC/Adeno	1.24 (0.82-1.88)	0.300
Education	A/B**	0.74 (0.37-1.48)	0.399
Sex	Female/Male	0.66 (0.36-1.22)	0.184
Metastasis status	No/Yes	2.71 (1.73-4.24)	**<0.001**
Stage	Early/Advanced	2.49 (1.28-4.84)	**0.007**
History of radiotherapy	No/Yes	0.92 (0.61-1.39)	0.699
Surgical history	No/Yes	0.51 (0.29-0.90)	**0.020**
Complementary therapy	No/Yes	0.86 (0.57-1.32)	0.495
Phytotherapy	No/Yes	0.76 (0.50-1.14)	0.184
Green tea	No/Yes	1.19 (0.71-1.99)	0.520
Carob	No/Yes	0.94 (0.45-1.94)	0.865
Turmeric	No/Yes	0.98 (0.49-1.96)	0.963
Ginger	No/Yes	0.86 (0.39-1.86)	0.692
Linden tea	No/Yes	0.45 (0.14-1.44)	0.178
Black cumin	No/Yes	0.74 (0.23-1.70)	0.482
Grape seed/molasses	No/Yes	0.72 (0.26-1.95)	0.514
Sugar beet	No/Yes	1.38 (0.50-3.75)	0.535
Apitherapy	No/Yes	1.23 (0.81-1.88)	0.331
Honey	No/Yes	1.19 (0.77-1.84)	0.427
Propolis	No/Yes	1.64 (0.82-3.26)	0.161
Pollen	No/Yes	0.77 (0.28-2.09)	0.602
Vitamin supplements	No/Yes	0.75 (0.31-2.32)	0.748
ˢSignificant values are indicated in bold. *The Cox Proportional-hazards model was used. Significance level set at <0.05. **A: Iliterate and primary school, B: High school and university			
ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, CI: Confidence interval			

behind this situation, 87.2% of the patients using CT attributed the reason for not sharing their CT status to the fact that the physicians did not ask any specific questions about this issue. In the study of Arıkan et al. (26), it has been reported that 92.5% of the patients attributed the reason for not sharing this situation with their physicians to the same cause. The main reason that patients are not sharing their use of CT could be their perception of CT methods as safe and unharmful instrumentation that can be used along with chemotherapy (27). However, hiding CT use from the treating physician raises the risk of life-threatening outcomes due to drug-CT interactions (8,28).

Consistent with the literature, the most common CT method used in our study was found to be herbal medicine/phytotherapy (79.6%) (10,29,30). The frequent use of phytotherapy in cancer patients is caused by the thought that it is natural and therefore not harmful (30). However, anti-cancer treatments have a narrow therapeutic range. The interaction of CT methods, especially herbal products, with antineoplastic drugs may change the serum levels of conventional treatments (28,31,32).

Although the patients have reported a high benefit from CT, there is no consensus among physicians and patients on the effectiveness of CT because of the limited evidence-based results (33). The studies with survival analysis are also limited. In the study of Pathak et al. (34) that included advanced-stage lung cancer patients, no contribution was determined to OS in the patients using vitamin and mineral supplements as CT. Chen et al. (35) reported that CT did not contribute to survival in their study with Chinese advanced-stage cancer patients. McCulloch et al. (36) reported that the use of CT improved OS in patients with localized lung cancer. In both studies conducted by Bae et al. (37) and Liu et al. (38), it was found that the use of CT-prolonged survival in advanced-stage lung cancer. Johnson et al. (39) reported in a study conducted in the USA, in which different cancer types were included, that the use of CT did not contribute to OS in early-stage patients. In our study, the use of CT did not have a statistically significant contribution to OS.

Study Limitations

Our study has several limitations. Firstly, it was a single-center study. Second, despite the researcher's physician informing the patients about confidentiality and safety, patients were able to conceal their true CT prevalence because the questionnaires were administered in a clinical setting. Third, the small number of early-stage patients and the division of the stages into early and advanced limited the generalizability of the findings. Lastly, depending on the chemotherapy chosen, the treatment effect or the adverse events that may result from the treatment may affect the results. The strengths of our study are that all the respondents were patients receiving active chemotherapy, that it was conducted with a comprehensive survey of a single cancer type, and that it included survival analysis.

Conclusion

Although the clinical utility of CT is questioned, its use along with medical treatment in lung cancer patients is common. For this reason, clinicians should question, follow, and guide their patients about complementary therapies that have a risk of interaction with anticancer therapies. Multicenter studies with more patients must generalize the results.

Ethics

Ethics Committee Approval: The Tekirdag Namik Kemal University Ethics Committee granted formal approval for this study (date: 29.09.2020; approval number: 2020.224.09.11).

Informed Consent: Informed consent was obtained from all participants in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.C., K.K., O.A., E.S.S., Design: E.C., K.K., Y.I., O.A., E.S.S., Data Collection or Processing: E.C., Y.I., Analysis or Interpretation: E.C., Y.I., O.A., Literature Search: E.C., Y.I., E.S.S., Writing: E.C., K.K., Y.I.

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