Effect of complementary Integrative Oncology on anxiety, depression and quality of life in thoracic cancer patients: A pilot study

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ARTICLE INFO	ABSTRACT
	Purpose: Thoracic-cancer (TC) patients have an extensive toll taken in terms of health-related quality of life (HRQL). Integrative Oncology (IO) is recognized as a valid complement to any Standard-Therapy treatment to improve outcomes in TC patients. The objective of this pilot-study was to evaluate the effect of adding IO (acupuncture, Cognitive-Behavior Therapy and mindfulness) in terms of depression, anxiety and HRQL. *Methods:* TC patients who attended the Thoracic Oncology-Unit from July to September 2018 were invited to participate. A total of 16 patients were included in the study, 8 patients were required to attend 5 weekly sessions of IO and 8 patients were invited as controls. Anxiety, depression and HRQL were measured at baseline and after completing 5 sessions of IO or 5 weeks, using the HADS scale and the QLQ-C30 scale. *Results:* A total of 8 patients in the IO group attended the 5 sessions and 8 patients were followed as controls. Compliance with the therapies was high, none of the patients dropped out from the study. A tendency for improvement in anxiety, fatigue, pain and dyspnea was observed in patients attending IO, though not statistically significant likely due to sample size. *Conclusions:* IO therapies are well accepted among TC patients. Larger studies are necessary with robust sample sizes to improve conclusions regarding outcome improvements.

1. Introduction

Lung cancer (LC) continues to present the highest mortality rate among all cancer types including both sexes according to the latest edition of GLOBOCAN, 2018 [1]. The high mortality burden stems from many factors, including a lack of widely available screening tools, which entails that > 75% of LC cases are diagnosed within the advanced-stage (III and IV), for which therapeutic strategies are limited in terms of long-term efficacy. LC treatment has been mostly based on the use, alone or in combination of radiation, chemotherapy, immunotherapy, targeted therapy and hormonal therapies [2]. In XXXX, the situation is alarming, with over 98% of the patients diagnosed with late-stage disease, and with very limited public resources allocated to this disease [3]. The search for relevant strategies in order to improve health-related quality of life (HRQL) [4], avoid symptoms, decrease adverse effects and increase survival in these patients are even more relevant [5]. Among the detrimental effects of LC, it is well recognized that the diagnosis in itself can be motive for emotional symptoms, including anxiety, stress, depression and fear in both patients and their relatives [6]. Anxiety and depression have been reported in on third of the patients with recently diagnosed of Non-Small Cell Lung Cancer (NSCLC) patients [7], while distress has been registered in 43–58%, compared with other types of cancer [8]. In addition to the burden caused by emotional symptoms, physical symptoms are frequently

Table 1
Baseline characteristics in control and intervention groups.

		Control n = 8 n(%) Mean ± SD	Intervention n = 8 n (%) Mean ± SD	P
Sex	Male	3 (37.5)	1 (12.5)	0.569
	Female	5 (62.5)	7 (87.5)	
Thoracic cancer	Adenocarcinoma	6 (75)	6 (75)	0.543
	Neuroendocrine	1 (12.5)	1 (12.5)	
	Mesothelioma	0 (0)	1 (12.5)	
	Thymic	1 (12.5)	0 (0)	
Stage	III	1 (12.5)	0 (0)	0.302
	IV	7 (87.5)	8 (100)	
Chemotherapy line	1	3	4	0.614
	2	5	4	
Comorbidities	Denied	3	4	0.283
	HTN	2	4	
	HTN + DM	2	0	
	Hypothyroidism	1	0	
ECOG	1	7 (87.5)	8 (100)	0.302
	2	1 (12.5)	0 (0)	
SGA	A	4	6	0.302
	B o C	4	2	
Time from thoracic dx		11.6 ± 13.5	10 ± 18	0.846
Age	years	62.7 ± 11.8	68.6 ± 6.4	0.238
Weight	kg	63.1 ± 11.6	60.2 ± 13.9	0.650
BMI	kg/m^2	25 ± 3.9	35.3 ± 7.5	0.137
Weight loss past6-months	%	7.7 ± 7.6	3.5 ± 3	0.237
AC/S (FAACT)		27.6 ± 11.6	35.3 ± 7.5	0.137
HRQL global status		69.7 ± 17.7	75 ± 14.7	0.534
HRQL pain		31.2 ± 28.7	25 ± 33.3	0.694
HRQL fatigue		36.1 ± 17.5	31.9 ± 9.2	0.562
Albumin	mg/dl	3.5 ± 0.6	3.8 ± 0.3	0.364
Hemoglobin	g/dl	12.7 ± 1.5	12.5 ± 1.5	0.789
Platelets	x10^3/µL	418.1 ± 260	226.2 ± 122.2	0.327
Leucocytes	x10^3/µL	6.7 ± 3.8	5.7 ± 1.4	0.515
Lymphocytes	x10^3/µL	1.07 ± 0.4	1.5 ± 0.4	**0.048**
Neutrophils	x10^3/µL	4.8 ± 3.1	3.5 ± 1.2	0.290

SGA = Subjective Global Assessment, BMI: Body Mass Index, AC/S = Anorexia Cachexia scale from the Functional Assessment of Anorexia Cachexia Therapy (FAACT) tool. SGA: (B or C) nutritional risk or (A) considered without nutritional risk.
Intervention group: integrative Oncology. Student T test and X^2.

present in LC patients, including pain, nausea, poor well-being, dyspnea, fatigue and cough [8]. These side effects can have an impact in HRQL and be reflected in the physical condition of the patients, as well as their tolerance to oncologic treatment [2,9]. Moreover depression independently in NSCLC has been related with the treatment adherence and poor prognosis [7].

The complementary use of Integrative Oncology (IO) to standard oncologic treatment (i.e. chemotherapy) has gained attention in the last years; this approach focuses in providing the best HRQL possible to cancer patients and previous studies have suggested it has important benefits specifically in LC patients. IO entails six main areas including nutrition, nutritional supplements, physical activity, mind-body therapies, enhancing immunotherapy and complementary therapies [6]. Particularly one of the mind-body therapies, known as Mindfulness-Based Stress Reduction (MBSR), has been associated with reduction of anxiety and depressive symptoms in cancer patients [8]. Mindfulness therapy is described as a mental state that is achieved by intentionally and repeatedly taking consciousness back to this specific moment and the current experience in a calm, non-judgmental way. It praises acceptance of one's feelings, sensations and thoughts, and has been used successfully as a therapeutic strategy [8]. The positive evidence of mindfulness therapy has been described in previous studies in terms of reduction of psychological distress [8] and is considered safe and helpful in LC patients [10].

Acupuncture is a technique derived from Traditional Chinese Medicine, in where specific points on the body are stimulated by inserting needles into the skin [6]. Strong evidence supports its use to control pain and nausea & vomiting induced by chemotherapy [11].

Adverse events are rare, however careful monitoring of blood status parameters should be considered in order to avoid infections in patients with low platelets or white blood cells [11]. Moreover, acupuncture also has been associated with improvements in fatigue in LC patients, in schemes of 2 sessions per week during 2 weeks, thus considering this therapeutic option safe and feasible to complement the oncologic standard treatment [12].

Within the scope of IO, Cognitive Behavior Therapy (CBT) should always be included as a complementary strategy to contribute to the coping process of the disease. The patients understanding of their disease is pivotal to take informed decisions and avoid anguish, which is associated with worse quality of life [13]. The use of positive reframing and active coping has been associated with better quality of life in terminally ill cancer patients [13].

The objective of this study was to evaluate the effect of complementary IO in patients with thoracic tumors. IO included 3 therapies: acupuncture, mindfulness and CBT. Primary endpoint was overall change in anxiety and depression; secondary endpoint included HRQL.

2. Materials and methods

From July to September 2018, a pilot study was undertaken in order to assess the feasibility of providing patients with IO interventions, in terms of compliance, and its effect on clinical outcomes including depression, anxiety and HRQL. Patients who attended the Thoracic Oncology Unit at the XXXXXX in XXXX were invited to receive IO at the XXXX-XXXX, free of any charge. The patient eligibility criteria included histologically confirmed TC, a good performance status (Eastern

Table 2
Changes baseline-5weeks in clinical variables in control and intervention group.

		Control n = 19	Intervention n = 14	p*
Weight (kg)	Baseline	63.1 ± 11.2	60.2 ± 13.9	0.233
	5-weeks	62.2 ± 10.6	63.8 ± 14.07	
	Δ	−0.9 ± 3.2	3.5 ± 9.4	
	p	0.447	0.320	
BMI (Body Mass Index)	Baseline	25 ± 3.9	25.4 ± 6.1	0.247
	4-weeks	24.6 ± 3.6	26.8 ± 6.5	
	Δ	−0.3 ± 1.28	1.4 ± 4.07	
	p	0.437	0.348	
Hemoglobin (mg/dl)	Baseline	12.7 ± 1.5	12.5 ± 1.5	0.147
	5-weeks	11.7 ± 2.03	12.3 ± 1.4	
	Δ	−0.9 ± 1.3	−0.16 ± 0.4	
	p	0.091	0.379	
Platelets (x10³/μL)	Baseline	387.6 ± 154.7	316.5 ± 123.4	0.135
	5-weeks	282.25 ± 85.5	305.2 ± 55.4	
	Δ	−105.3 ± 146.2	−11.2 ± 82.6	
	p	**0.081**	0.712	
Leucocytes (x10³/μL)	Baseline	6.7 ± 3.8	5.7 ± 1.4	0.114
	5-weeks	5.08 ± 2.6	6.9 ± 3.9	
	Δ	−1.6 ± 1.7	1.1 ± 4.3	
	p	**0.036**	0.466	
Lymphocytes (x10³/μL)	Baseline	1.07 ± 0.4	1.5 ± 0.4	0.757
	5-weeks	1.13 ± 0.4	1.5 ± 0.5	
	Δ	0.06 ± 0.2	0.01 ± 0.3	
	p	0.472	0.929	
Neutrophils (x10³/μL)	Baseline	4.8 ± 3.1	3.5 ± 1.2	0.083
	5-weeks	3.2 ± 2.04	4.4 ± 3.2	
	Δ	−1.6 ± 1.6	0.9 ± 3.4	
	p	**0.028**	0.474	
Albumin (mg/dl)	Baseline	3.5 ± 0.6	3.8 ± 0.3	0.130
	5-weeks	3.7 ± 0.3	3.6 ± 0.6	
	Δ	0.18 ± 0.3	−0.2 ± 0.5	
	p	0.209	0.342	
NLR (Neutrophils/lymphocytes Ratio)	Baseline	4.6 ± 2.1	2.5 ± 1.2	0.041
	5-weeks	3.06 ± 1.3	2.9 ± 1.5	
	Δ	−1.5 ± 2.1	0.4 ± 1.4	
	p	0.069	0.426	
PLR (Platelets/Lymphocytes Ratio)	Baseline	418.1 ± 260.8	226.2 ± 122.2	0.117
	5-weeks	287.1 ± 126.2	221 ± 59.4	
	Δ	−130.9 ± 186.9	−5.2 ± 101.8	
	p	0.088	0.889	

*p = difference between groups.
Paired T test inside each group and Student T test between groups.

Cooperative Oncology Group 0–2), under oncologic standard therapy (systemic chemotherapy and tyrosine kinase inhibitors – TKIs) and a life expectancy of > 3 months. Exclusion criteria included previous or current treatment using acupuncture, psychological attention or mindfulness therapy from another source. All patients who met the inclusion criteria and agreed to participate in the study were included in the intervention arm. Patients who met the inclusion criteria but who could not attend the weekly meetings due to schedule impairment were asked to participate as control subjects, and those who agreed were included in the control arm of the study. Patients in the intervention or control arm of the study were eliminated from the study if they received IO interventions additional to the ones offered in this trial.

2.1. Intervention and procedure

The study included two patient groups; those who were able and agreed to the intervention and a control group comprised of patients who agreed to participate in the study but were unable (all of these patients who lived in another city) to attend the weekly IO sessions. All patients signed a written consent form registered by the Institutional Review Board and the Ethics Committee (XXXXXX)(XXXXXX). The intervention group additionally signed an informed consent preview the beginning of the study to receive acupuncture approved by Institutional Bioethics Committee and comprised attendance to weekly meetings in which patients met in a group setting in order to receive the complementary techniques previously mentioned. The meetings were planned in a group in order for patients to acquire a sense of peer support from other patients undergoing a similar health situation. IO sessions were implemented every Tuesday for 12 weeks from July 3 through September 18 in the "XXXXXX" of the XXXXX, which is an Integrative Oncology Center, focused on bringing IO therapies to patients and primary caregivers.

2.2. Intervention

IO sessions consisted half an hour of acupuncture, 1 h of CBT, 1 h of mindfulness therapy and coffee break between sessions. CBT and mindfulness sessions were given as a group therapy, while acupuncture was given in an individual setting.

Relatives of patients were also invited to participate in the study, changing acupuncture for painting class. CBT was offered in two groups, one that included patients only and one that included caregivers only. Meanwhile, mindfulness therapy was given in a joint group which included patients and primary caregivers.

Three physician acupuncturists implemented acupuncture in half an hour. Interventions were administered weekly. It was developed following a manual protocol based on the Traditional Chinese Medicine intervention. The acupuncturist chose at least ten points, among to regulate Yin-Yang, tonifications of Qi, Xue and Zangfu and remove heat to address constitutional symptoms such as depression/anxiety, hot flashes, cough and fatigue that commonly present in conjunction with pain. The needles (30 mm or 40 mm and 0.30 mm gauge, Wabbo Silverstar San Jacinto CA) were inserted until "De Qi" sensation of soreness, tingling, etc. reported by patients. The needles were left in place for 20 min with brief manipulation at the beginning and the end of therapy. It has been also applied heat in R11 during session. After the 30 min it has been tonificated V13, V15, V17, V18, V20, V23 and one more minute of cupping therapy [14].

The CBT consisted in attempting a positive change of emotions through changing thoughts and behavior in 60 min sessions every Tuesday. This therapy aims to change the perceptions of thoughts with the premise that how a person thinks has an effect on their emotions and behavior [2].

2.3. Outcomes measures

All patients were evaluated in terms of anxiety, depression and HRQL using the validated questionnaires. Evaluation was performed at baseline and following the completion of 5 weekly sessions, which was considered the meeting compliance cut-off point in order for patients to be included in the final analysis. Additional variables collected included sex, TC subtype, stage, chemotherapy line, comorbidities, ECOG performance status, Subjective Global Assessment (SGA), age, weight, body mass index (BMI), weight loss in the previous 6 months, anorexia-cachexia scale, and biochemical parameters extracted from routine laboratory assessments.

2.4. Anxiety and depression evaluation

The Hospital Anxiety and Depression Scale (HADS) was recently validated in XXXXX oncologic population with the following diagnostic score; Anxiety or Depression: normal 0–5, light 6–8, moderate 9–11 and severe > 12 [15].

2.5. Quality of life evaluation

HRQL was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire [16,17]. Sores regarding the functional, symptoms and single item scales can be interpreted after a linear transformation of raw scores in a range of 0–100, as described by the European Organisation for Research

Anxiety	Control group Mean ± DE	Δ	Intervention group Mean ± DE	Δ	p
T0	5.5 ± 4.5	0 ± 2.2	5.25 ± 3.4	-1.5 ± 1.9	0.169
T1	5.5 ± 4.5		3.7 ± 2.8		
p	1		0.064		

Figure 1. Paired T test inside each group and Student T test between groups.

A) Anxiety changes after 5 weeks in control group

B) Anxiety changes after 5 weeks with Integrative Oncology

CONTROL GROUP

INTERVENTION GROUP
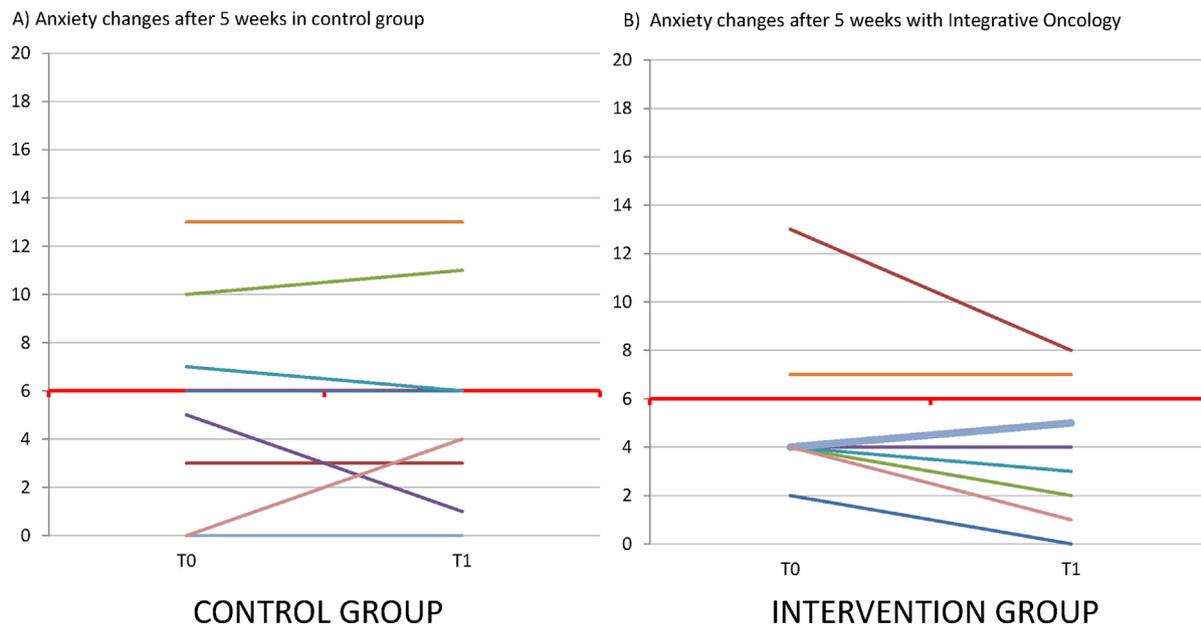
Fig. 1. Anxiety changes baseline-5weeks assessment in thoracic patients with and without integrative therapies.

Depression	Control group Mean ± DE	Δ	Intervention group Mean ± DE	Δ	p
T0	6.6 ± 5.3	-1 ± 4.24	3.8 ± 3.9	-0.8 ± 2.8	0.946
T1	5.6 ± 4.9		3 ± 1.6		
p	0.526		0.414		

Paired T test inside each group and Student T test between groups.

A) Depression changes after 5 in control group

B) Depression changes after 5 weeks with Integrative Oncology
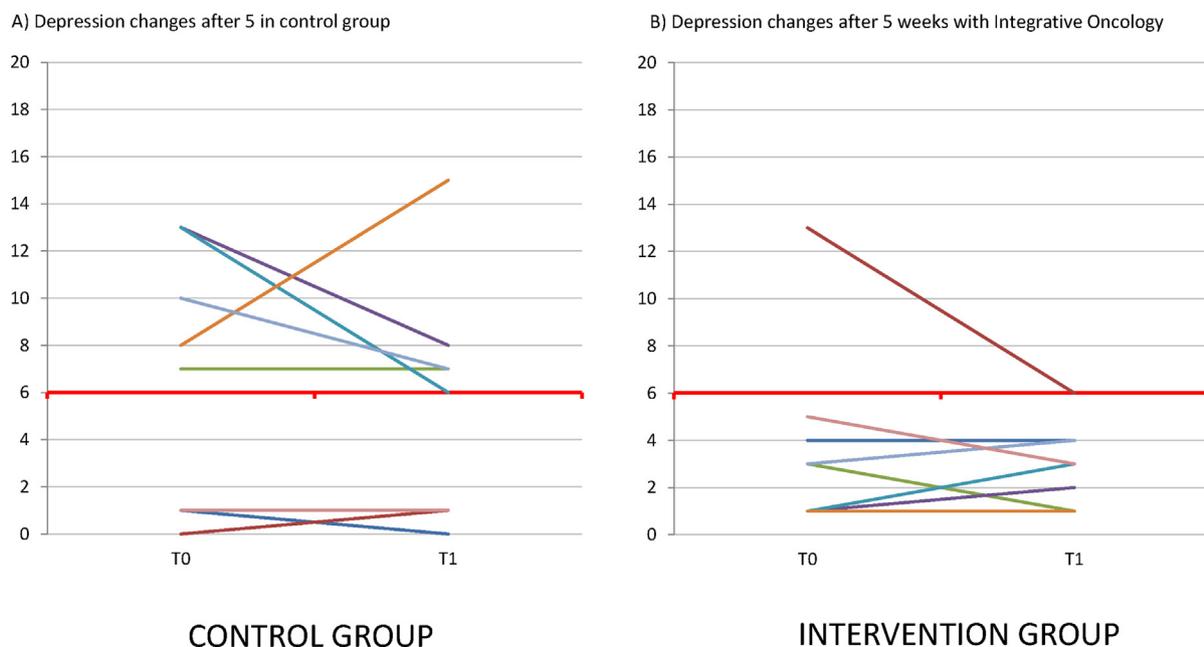
CONTROL GROUP

INTERVENTION GROUP

Fig. 2. Depression change baseline-5weeks assessment in thoracic patients with and without integrative therapies.

Table 3
HRQL changes baseline-5 weeks in control and intervention group.

		Control n = 8	Intervention n = 8
Global health status/ QoL	Baseline	75 (50–83.33)	75 (66.67–89.58)
	5-weeks	66.67 (41.66–81.24)	66.67 (52.08–81.24)
	p	1	0.257
Physical Functioning	Baseline	70 (48.33–85)	80 (73.33–86.67)
	5-weeks	76.66 (46.66–89.99)	80 (73.33–93.33)
	p	0.798	0.729
Role Functioning	Baseline	75 (25–95.83)	83.33 (54.16–95.83)
	5-weeks	100 (70.83–100)	91.66 (66.67–100)
	p	0.246	0.168
Emotional Functioning	Baseline	83.33 (66.67–89.58)	87.5 (75–100)
	5-weeks	83.33 (60.41–100)	91.67 (68.75–97.91)
	p	0.865	0.833
Cognitive Functioning	Baseline	83.33 (50–95.83)	83.33 (70.83–95.83)
	5-weeks	83.33 (66.67–100)	83.33 (70.83–100)
	p	0.144	0.705
Social Functioning	Baseline	66.67 (50–83.33)	83.33 (66.67–95.83)
	5-weeks	75 (66.67–100)	83.33 (54.1–95.83)
	p	0.078	0.891
Fatigue	Baseline	38.88 (22.22–44.44)	33.33 (22.22–41.66)
	5-weeks	27.77 (5.55–50)	22.22 (13.88–33.33)
	p	0.799	0.084*
Nausea and vomiting	Baseline	41.66 (8.33–66.67)	8.33 (0–33.33)
	5-weeks	25 (4.16–45.8)	0 (0–29.16)
	p	0.068	0.414
Pain	Baseline	16.67 (16.67–58.33)	8.33 (0–58.33)
	5-weeks	16.67 (0–50)	0 (0–0)
	p	0.751	0.197
Appetite Loss	Baseline	50 (0–91.66)	0 (0–33.33)
	5-weeks	16.66 (0–91.66)	0 (0–0)
	p	0.414	0.102
Insomnia	Baseline	33.33 (8.33–58.33)	16.66 (0–33.33)
	5-weeks	33.33 (33.33–66.67)	16.65 (0–33.33)
	p	0.480	0.414
Dyspnea	Baseline	22.22 (11.11–44.44)	16.66 (0–33.33)
	5-weeks	22.22 (2.77–41.66)	11.11 (0–11.11)
	p	0.593	0.102

Wilcoxon test.
Functional scales were graphed in Supplement 1.
Bold words were graphed in Supplements 2.

and Treatment of Cancer (EORTC); the higher the score, the better functional status. In terms of symptomatic scales, lower score represent lower presence of symptoms [18].

2.6. Statistical analysis

For descriptive purposes, continuous data were summarized as arithmetic means and standard deviation (SD), whereas categorical variables were summarized as proportions. Chi squared and student *t*-test were performed to analyze baseline differences between groups. Baseline and post treatment comparisons were assessed as differences over time and were analyzed using a paired *t*-test, Wilcoxon test for Quality of life scales. A *p*-value of ≤0.05 (two-sided) or lower was considered statistically significant. SPSS for MAC version 20 was employed to perform all analyses (IBM, Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

We invited 30 patients from the Thoracic Oncology Unit and their primary caregivers to participate in the study and attend the sessions of

the XXXX imparted through 12 weeks. Eight TC patients completed 8 ± 3 sessions of IO. A control group with 8 patients not participating in any of the sessions was included. Reasons for inability to participate in the IO sessions included living out of town or having an already occupied schedule on the day the sessions took place.

There were no significant differences between the intervention and the control group in most of the variables at the beginning of the study (Table 1). The mean age of the patients was 62.7 ± 11.8 in the control group and 68.6 ± 6.4 in the intervention group (p = 0.238). Most patients were females in the control (n = 5; 62.5%) and the intervention (n = 7; 87.5%) group (p = 0.569). Patients mostly had a good (ECOG = 1) performance status in both the control group (n = 7; 87.5%) and the intervention (n = 8; 100%) group (p = 0.302). Last, as expected most patients had stage IV disease in the control group (n = 7; 87.5%), and the intervention group (n = 8; 100%) (p = 0.302). The only biochemical variable that showed significant differences was Lymphocytes (1.07 ± 0.4 control group and 1.5 ± 0.4 intervention group, p = 0.048), without showing significant changes after 5 weeks (Table 1). Clinical deterioration in terms of the before-mentioned variables was observed only in the control group, and included platelet reduction (p = 0.081), leucocyte reduction (p = 0.036) and neutrophil reduction (p = 0.028), however there were no statistically significant changes between groups. No differences were observed in terms of BMI and weight in either patient group (Table2). Fig. 1 shows the change in terms of anxiety between the control and intervention group (p = 0.169).

3.2. Anxiety and depression

A decrement in anxiety in the intervention group (Δ −1.5 ± 1.9) was observed, compared to the control group, although this observation did not reach statistical significance (p = 0.064). No changes were registered in terms of anxiety in the control group (Δ 0 ± 2.2, p = 1.0). The changes per patient can be observed in Fig. 1 A) for the control group and B) for intervention group.

Fig. 2 shows the changes in depression scores observed in patients at baseline and after 5 weeks of the intervention. Both groups showed a non-significant reduction in the mean score of depression [-1 ± 4.24 control vs. −0.8 ± 2.8 intervention, p = 0.946).

3.3. HRQL

HRQL changes can be observed in Table 3. There were not significant changes in functional scales of quality of life. An improvement in the Role Functioning Scales was observed in both the intervention as well as the control group (Supplement 1). The symptomatic scales for HRQL and their changes are visualized in Fig. 3. We observed an improvement in pain (p = 0.197), fatigue (p = 0.084), and dyspnea (p = 0.102) in the intervention group, though none of these values reached statistical significance (Supplement 2). Notably, no change was observed in the control group in terms of dyspnea and pain (Table 3) (Supplement 2). Last, nausea and vomiting showed improvement in both groups (p = 0.414), though interestingly nausea and vomiting were completely abolished in the intervention group (median score = 0 at the end of 5 sessions).

4. Discussion

The use of IO in order to compliment standard oncological therapies (chemotherapy, radiotherapy, targeted therapy and immunotherapy) in cancer patients has the potential to improve management of emotional and physical burden for both patients and caregivers. Nonetheless, evidence is only recently emerging in terms of the benefit of this intervention, and therefore the implementation of clinical studies in order to assess the efficacy of this strategy is urgently needed. This study shows the feasibility of adding weekly IO sessions in addition to the
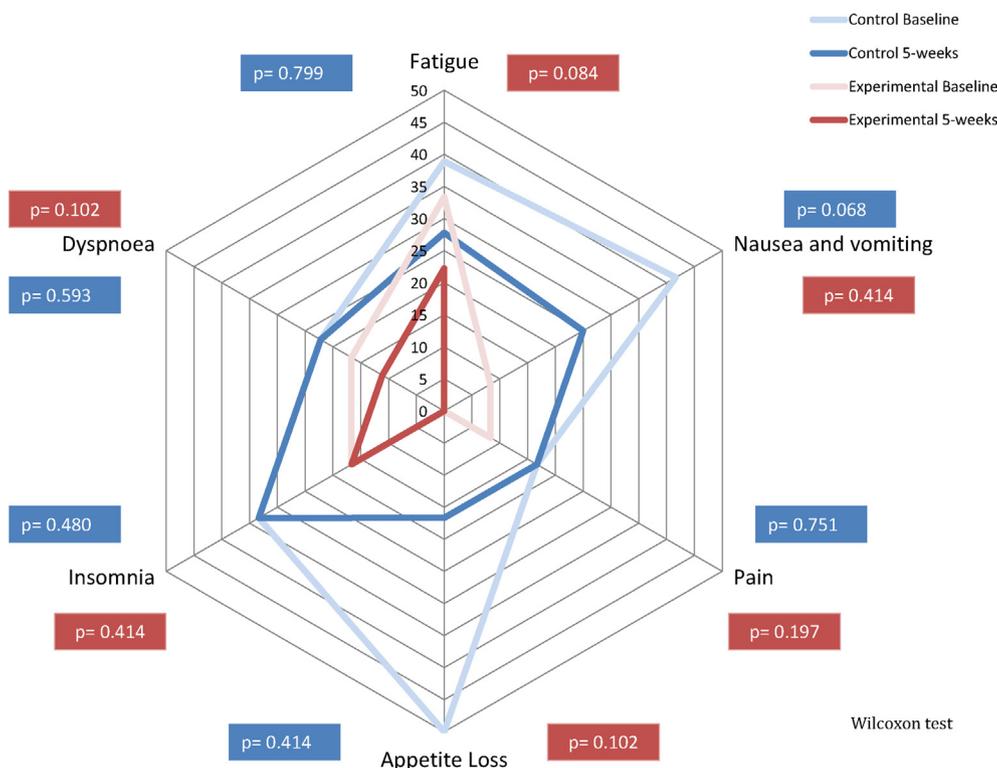
Fig. 3. HRQL–Changes in symptomatic scales in thoracic cancer patients between control and intervention group.

standard oncological therapy for TC patients in an institutional setting, with the close supervision of the attending oncologist and a - + highly specialized team in supportive care.

Among the study findings, we identified that patients respond well to the offer of having complementary therapies designed for coping with their disease. Among the 30 patients invited to participate in the study, all showed interest, however accessibility is also important. The XXXX is a nation-wide reference center, and patients treated at the Thoracic Oncology Unit come from all states in the nation, therefore many are unable to benefit from all the additional therapies offered at centers such as XXXX due to inability to travel so frequently. A total of 8 patients were finally included in the study, and interestingly none of the patients dropped out or stopped attending the meetings, with a median of 8 meetings attended per patient, we identified a high level of compliance. Among the reasons for missing attendance patients mentioned having a medical oncology consult at the same time, chemotherapy administration, scheduled radiology (PET-CT) studies, or health-related impairments. Notably, none of the patients reported losing interest or not finding the intervention beneficial.

This study also shows the possible benefit in terms of symptom improvement that can be reached with the addition of IO in TC patients with advanced disease. IO can include a lot of different-approach therapies as mentioned before, but the strategic combination of them can be chosen according to disease-type and their particularly necessities, and therefore a tailored strategy can be offered for patients with diverse needs. LC is mostly diagnosed within the advanced stage context; therefore oncological treatment is administered aiming for disease control rather than with a curative purpose. Patients with a disease of these characteristics, and who are presented with a poor prognosis must be professionally guided in terms of acquiring the psychological skills that will allow them to better handle their current health situation [2]. Further, there are a myriad of complimentary interventions, such as acupuncture, which have been shown to improve the physical symptoms that negatively impact HRQL in these patients. The results of this pilot study show a tendency, though not reaching statistical significance, to improve anxiety, fatigue, pain and dyspnea. No differences

were observed in functional scales of quality of life. However, it is important to note that the comparisons were performed at baseline and after only 5 weeks from the start of the intervention, and therefore it is likely that more pronounced differences could have been observed at a later time throughout the treatment. Nonetheless, as this was a pilot study we were unable to foresee if patients would comply with the duration of the intervention (12 weeks), and so an early point for data recollection was considered. A future study will include a larger sample size, and a longer follow-up in order to identify outcomes. It is also important to highlight the additional knowledge generated by the conduction of this study. IO was received in a group context among patients with a similar diagnosis and prognosis. The patients persisted in continuing to receive IO therapies even after the study was finished, which shows that these interventions can be beneficial in helping patients find peer support from individuals undergoing similar situations. Although these were not planned as primary or secondary outcomes for this trial, the observations are important since they represent the helpful strategy which IO offers in order for patients to better handle their emotional and physical symptoms. The primary caregivers were also invited to participate in the IO sessions, with the exception of acupuncture changed by painting, and while some of them participated in a small number of sessions, the lack of continuity impeded performing an accurate evaluation.

The combination of the therapies chosen to bring a complementary support of symptoms of TC patients was well accepted and continued by patient initiative.

As previously mentioned, IO comprises multiple therapies that can be administered using different combinations, therefore it is necessary to study patients with similar diagnoses and include appropriate tools that can positively reflect in terms of the emotional and physical wellbeing of patients and their primary caregivers. In this study, none of the IO interventions were studied independently, and therefore the interpretation of our data might be limited in terms of identifying if an intervention alone is responsible for the improvements seen. However, it is important to mention that the combination of the interventions was designed in order to impact patients' psychological, physical and

emotional well-being, which are closely intertwined, therefore it is possible that the results might be due to the combination rather than to each specific intervention.

The outcomes studied represent important setbacks for patient wellbeing and therefore we aimed to measure the intervention as the combination of three different therapies. Among the individual components of the IO strategy, previous studies have shown them to be effective in different outcomes. For example, a previous study compared treatment with acupuncture or opioids for the treatment of dyspnea, a common and difficult to treat symptom in LC patients. Patients allocated to receive acupuncture showed a higher improvement in dyspnea scales, compared to receiving opioids alone or an opioid/acupuncture combination; the same phenomenon was observed in terms of anxiety [19]. Acupuncture has also demonstrated to statistically reduce cancer related fatigue (CRF) measure using the Brief Fatigue Inventory (BFI) after two weeks of acupuncture stimulation (LI-4, Ren-6, St-36, KI-3, and Sp-6) twice per week [12].

Another individual component of the therapies which were included in the IO intervention was the Cognitive behavior therapy (CBT), which is a psychotherapeutic approach that emphasizes the significance of how our thinking affects the way we feel and a licensed cognitive behavior therapist could aid in developing skills to recognize, counteract and manage problematic thoughts and beliefs [2]. In the case of mindfulness, it has been shown to be efficacious in reducing anxiety and depression severity [20].

Timely and acceptable psychological interventions with demonstrated efficacy are important components which should be included in the integral care of cancer patients, particularly in patients with dim prognosis where oncologic therapy is given without curative intent, as a component of comprehensive cancer care [21].

Several limitations are inherent to the design of this pilot study, particularly the small number of patients included and the short time to data collection, however these will be considered in future, larger size trials, in order to reach more robust conclusions. An interesting proposal from these early results is the stratification of patients in terms of the presence or not of clinically manifested depression and anxiety, as we are to this point unsure whether IO therapy is useful as a treatment strategy in patients who already present this condition, or if it can be used as a preventive strategy in those who are at risk of developing it. Other considerations for the design of a future larger study include a longer follow-up period (8 and 12 weeks), and assessment of caregiver burden for the patients'caregiver. Other important observations include the fact that by the end of the study, patients within the experimental group had reduced the presence of nausea, vomiting, pain and appetite loss to 0 in the HRQL questionnaire, which highlights the potential efficacy of these interventions, however as previously mentioned a larger sample size is required to assess significance.

5. Conclusions

IO offered as a complementary strategy to standard oncologic therapy is well accepted and produces a high level of compliance for the patients who accept to participate. We did not find statistically significant improvements in terms of anxiety, pain, fatigue and dyspnea in this pilot study of TC patients. Future studies are necessary in order to better quantify the effect of IO using a larger patient selection and a longer follow-up to data recollection.

Author's contribution

Raquel Menéndez-Aponte y Guzmán: The conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted. **Jenny Georgina Turcott Chaparro:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted. **Amanda De la Piedra Gómez:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted. **Victoria Margarita Sandoval Eslava:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted. **Gina Carolina Tarditi Ruiz:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted. **Ilse Merari Tapia Garduño:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted. **Irma Gallegos Figueroa:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted. **Oscar Arrieta:** The conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

Disclosure statement

Ethical approval

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent

"Informed consent was obtained from all individual participants included in the study."

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.05.003.

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