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Review

Non-pharmacological Interventions on Pain and Quality of Life in Chemotherapy Induced Polyneuropathy: Systematic Review and Meta-Analysis

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Abstract. *Background/Aim: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment, resulting in pain, numbness, instability, and thus affecting quality of life (QoL), occasionally leading to discontinuation of chemotherapy. Pharmacological treatments are not sufficient. Non-pharmacological interventions (NPIs) have also been tried. This study aimed to systematically review the efficacy of NPIs on pain and QoL in patients suffering from CIPN. Materials and Methods: The databases searched were Pubmed, Cohrane, and Scopus for randomized controlled trials (RCTs) published in the last 5 years (2017- 2022). Studies were considered eligible, if they assessed adult patients suffering from CIPN because of any chemotherapeutic drug for any type and any stage of cancer and if study protocols included non-pharmacological intervention with a structured protocol. Results: A total of 1,496 records were identified. Finally, 10 RCTs including 495 patients (253 in the intervention group and 242 in the control group) were included for meta-analysis. Intervention protocols included acupuncture (n=6), exercise (n=3), and yoga (n=1). NPIs significantly reduced neuropathic pain. However, the effect on QoL was not significant. Conclusion: NPIs are beneficial in the treatment of pain in patients with CIPN but their impact on QoL is not statistically supported. Larger sample sizes, more homogenous in outcome measures and interventions are needed to further explore NPIs' efficacy on CIPN symptoms.*

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of several common anti-cancer drugs. CIPN is predominantly a sensory neuropathy, pain being the main and most disabling symptom. The increased incidence of cancer worldwide and the extended survival has led to an increase in CIPN occurrence (1). CIPN is of unclear pathophysiology and effective pharmacological treatment options are limited (2).

Various chemotherapeutic agents, such as taxanes, platinum compounds, vinca alkaloids, bortezomib, and thalidomide may cause CIPN (3). Each drug induces CIPN through different mechanisms, such as alterations in ion channels, leading to hyperpolarization and increased neuronal firing in sensory neurons, inhibition of endocannabiboid metabolism or mitochondrial dysfunction.

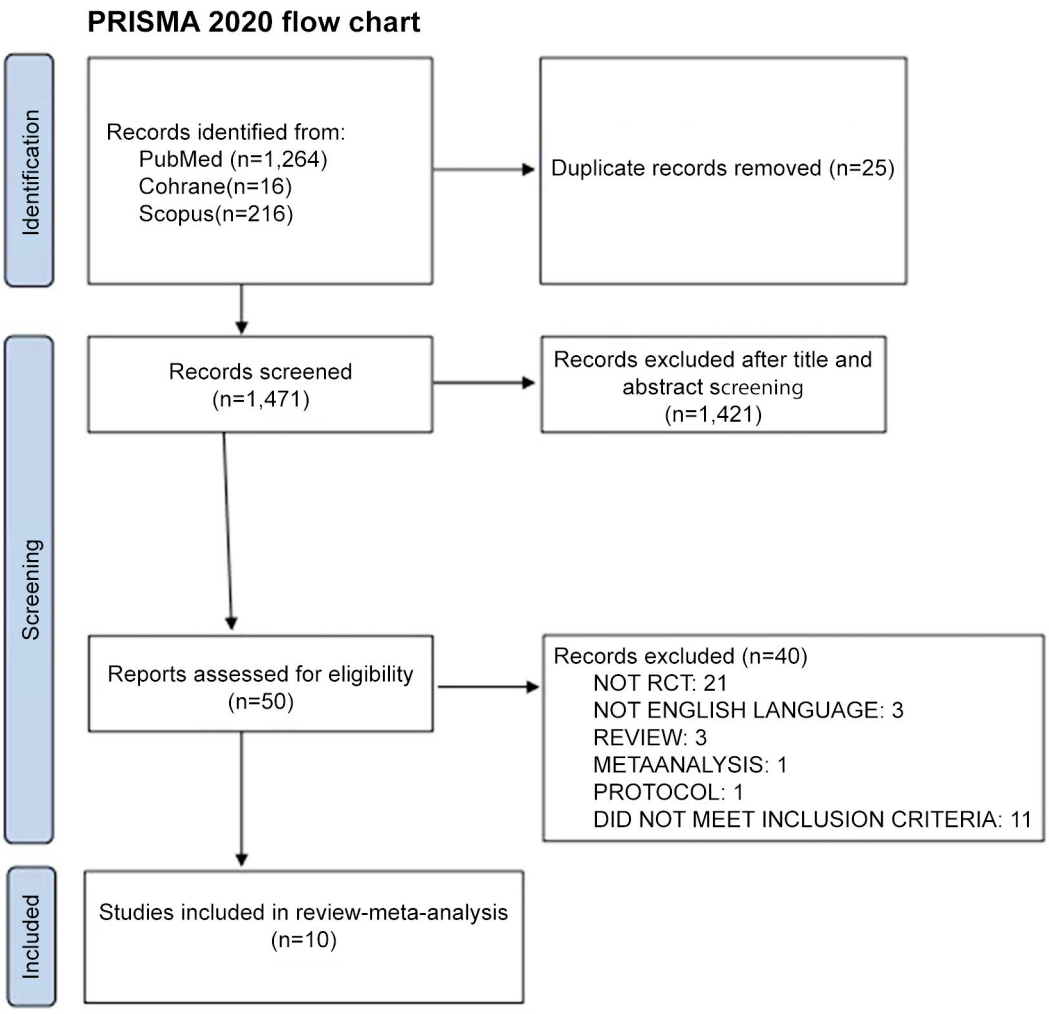

Figure 1. *PRISMA flow chart for the study selection process.*

Moreover, inflammatory processes may also contribute to CIPN development (2). Further risk factors for developing CIPN include the cumulative dose and therapy duration, co-administration of other neurotoxic medications, and comorbidities with diseases that might cause neuropathy, such as diabetes mellitus (4).

CIPN can occur acutely, within the first hours of receiving chemotherapy or months after the infusion. The prevalence is estimated to be 68% in the first month, dropping to 60% at 3 months, and to 30% after 6 months (2), but certain drugs, like taxanes and platinum derivatives might induce polyneuropathy in up to 80% of patients and up to 2 years after infusion (5).

Neurotoxicity may affect dorsal root ganglia and thus, sensory fibers are exclusively affected (6). CIPN may also manifest as a length-dependent neuropathy, due to axonal degeneration, predominantly sensory. Motor and autonomic fibers are less commonly involved. The predominance of sensory involvement results in pain, numbness, paresthesia, loss of sensation, instability, and gait disturbance due to loss of deep sensation (proprioception) (7). Motor symptoms, such as weakness, or autonomic dysregulation, like arrhythmias or postural hypertension, are seldom encountered. The constellation of these symptoms interferes with the daily activities and impairs quality of life (QoL) (8). Most of the symptoms persist, are non-responsive to medication and in many cases are irreversible (4).

Persistence of CIPN symptoms may limit the effectiveness of chemotherapy, as the dose may be reduced or even further, treatment may be temporarily discontinued (2).

Since the exact pathophysiological mechanism by which anticancer drugs damage peripheral nerves remains unknown, neither prevention nor treatment guidelines exist. To date, only duloxetine is moderately recommended for CIPN (5), whereas for other drugs commonly used for neuropathic pain in other conditions, like tricyclic antidepressants and antiepileptic drugs, results are inconclusive (9, 10).

On that grounds, non-pharmacological interventions (NPIs) have been widely tried, ranging from herbals and dietary supplements to specific physiotherapeutic interventions. The body of literature is growing, but still, the sample is small, and conclusions are inconsistent. The main advantage of NPIs is that generally are very well tolerated and safe, and furthermore, do not interact with chemotherapeutic agents. Thus, NPIs offer an alternative to the management of CIPN symptoms, where pharmacological treatments have failed to succeed (11).

CIPN presents with a variety of symptoms, pain being the most common. Randomized controlled trials (RCTs) that have studied the effectiveness of physiotherapy interventions, yoga, acupuncture and other NPIs have focused on various symptoms, most commonly pain. Systematic reviews (SRs) and meta-analyses (MAs) have already been conducted in order to explore the effectiveness of various interventions on different patient populations. Many SRs and MAs focus on acupuncture whereas others on physical exercise. The present SR and MA was designed to include all non-pharmacological modalities studied by RCTs the last 5 years, and to investigate their effectiveness on pain and QoL.

Materials and Methods

This SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure complete reporting.

Protocol and registration. The protocol of this overview can be found on OSF.IO (12).

Literature search. A comprehensive literature search of RCTs was performed in September 2022 and included papers published over the last 5 years in the Pubmed, Cohrane, and Scopus.

The literature search was composed of the Medical Subject Headings (MeSH) and free-text words for ((((neuropathy) OR (CIPN)) AND ((chemotherapy) OR (cancer)) AND ((physical therapy) OR (electrotherapy) OR (Shock wave ultrasound) OR (laser) OR (electrophysical agent) OR (tens) OR (neuromuscular electric stimulation) OR (thermotherapy) OR (acupuncture) OR (yoga)))) and were implemented for different databases.

Only full text original articles, written in English language and published in indexed peer-review journals were eligible for inclusion. Cross-sectional studies, case reports, published abstracts, dissertation materials, and conference presentations were not included.

The reference lists of all the appraised articles were screened for relevant citations that might have been missed from the electronic searches. Once all articles were found, duplicate articles were removed. Two reviewers (MP and MS) independently screened the titles and abstracts for eligibility and examined the full text of the articles for final decision (Figure 1).

Inclusion criteria included: 1. Only RCTs were included; 2. Studies that involved adults only; 3. Studies including cancer patients with a diagnosis of CIPN; 4. Any cancer diagnosis and any stage of disease; 5. Any chemotherapeutic agent; 6. Any non-pharmacological intervention with a structured protocol; 7. Evaluation of neuropathic pain and quality of life (QoL) as outcome.

Exclusion criteria included: 1. Chemotherapy induced polyneuropathy (CIPN) was not the main disease; 2. Pharmacological intervention was the only intervention without information on NPIs; 3. Concurrent diseases that may lead to neuropathy: diabetes mellitus, rheumatologic disease, vitamin deficiency, metabolic diseases, endocrinopathies; 4. NPIs beginning concomitantly to chemotherapy treatment, before any manifestation of polyneuropathy, for prevention.

Individual searches were compared and in case of disagreement, a consensus was reached regarding the inclusion of each study. If needed, a third reviewer was consulted (IM).

Data extraction. Both reviewers extracted data from 10 eligible studies which included: authors, date of publication, type of research design, number of subjects, epidemiologic data (age, sex), type of malignancy and stage of the disease, chemotherapeutic agent, NPIs (type and protocol design), outcome measures (pain, QoL). The characteristics and results of the included RCTs are presented in Table I.

Risk of bias. Two authors (MP, MS) independently examined the quality of enrolled studies using the PEDro scale (13). The PEDro scale consists of 11 items encompassing external validity (item 1), internal validity (items 2 to 9), and statistical reporting (items 10 to 11).

Each study included in the review was scored based on the following 11 criteria:

1. Eligibility criteria and source; 2. Random allocation; 3. Concealed allocation 4. Baseline comparability; 5. Blinding of participants; 6. Blinding of therapists; 7. Blinding of assessors; 8. Adequate follow-up (>85%); 9. Intention-to-treat analysis; 10. Between-group statistical comparisons; 11. Reporting of point measures and measures of variability.

Items are rated yes or no (1 or 0) according to whether the criterion is clearly satisfied in the study. A total PEDro score is achieved by adding the ratings of items 2 to 11 for a combined total score between 0 to 10. A total PEDro score of 8-10 was considered excellent, 6-8 good, 4-5 fair, and 0-3 poor. The PEDro scale is freely available online (14). PEDro scores are detailed in Table II.

Data synthesis and statistical meta-analysis. To analyze the effect of NPIs on neuropathic pain and QoL in CIPN patients, we estimated the weighed mean differences and 95% confidence intervals (CIs) from each study using MetaView Review Manager Version 5.4 (15). For weighted mean differences, a point estimate of zero reflected "no effect," and less than zero favored the NPI intervention. Statistical heterogeneity was assessed by using the χ^2 test ($p<0.1$). The I^2 statistic was also calculated, and we considered I^2 >50% to indicate significant heterogeneity across studies (16).

Table I. *Characteristics of the included studies.*

Author(s) year	Sample size IG/CG	Age	Sex (F%)	Intervention	Control	Cancer type Stage	Chemo therapy	Outcome measure_1 pain	Outcome measure_2 QoL	Result
Bao 2021 (18)	27/24	59.7	80	AC 10 treatments /8 weeks	UC	Breast, colon, other	Taxanes, Platinum	---	FACT/GOG-Ntx	Improve QoL in 8 weeks
D Alessandro 2019 (19)	15/14	57.68	58.62	AC 10 (30 min) for 5 weeks	UC	Breast gastrointestinal genitourinary hematologic Any stage		VAS	EORTC QLQ-C30	No significant changes in total score of EORTC and pain by VAS at 5w
Han 2016 (25)	52/52	62.46	43	AC 3 cycles	UC	Multiple Myeloma Any type, any stage		VAS	FACT/GOG-Ntx	Significantly superior to pain/QoL at 12w
Lu 2020 (21)	20/18	54	100	AC 8 weeks	UC	Breast I-III	Taxanes	BPI SF	FACT-NTX 11 ITEM	Reduction in pain, improvement in QoL at 8w
Iravani 2020 (20)	20/20	57.95	63.2	AC 3/w, 4 weeks	UC	Breast Colorectal Lung Ovarian Prostate	Taxane Platinum Doxorubicin	NRS	---	Improvement in pain at 8w
Molassiotis 2019 (22)	44/43	57.1	72.4	AC 2/w 8 weeks	UC	Breast, Colorectal I-IV	Oxaliplatin Carboplatin Cisplatin Paclitaxel Docetaxel Capecitabine Bortezomib	BPI SF	FACT/GOG-Ntx	Improvement in QoL/pain at 8w
Bao 2020 (17)	21/20	61.7	100	Yoga 8 weeks (5 times per week)	UC	Breast, Gynecologic I-III	Carboplatin Docetaxel Paclitaxel	NRS	FACT/GOG-Ntx	Improvement in pain and functional outcome at 8w
Dhawan 2020 (24)	22/23	50.5	81.9	Strengthening and balancing exercise for 10 weeks.	UC	Ovary, Lung, Cervix, Other		Leeds	EORTC QLQ-C30	Reduced pain Improved QoL at 10 w
Zimmer 2018 (1)	17/13	68.53	29.4	Exercise endurance, resistance balance training 2/w 4 weeks	UC	Colorectal	Oxaliplatin, Bevacizumab, Regorafenib, Trastuzumab	---	FACT/GOG-NTX	No difference in QoL Only NTX neuropathic symptom subscale differed significantly at 4 w
Saraboon and Siriphorn 2021 (23)	15/15	45.07	100	Intensive balance exercise program on a foam pad 2/w 6 weeks	UC	Ovary, Cervix	Paclitaxel, Carboplatin Cisplatin	---	FACT-Taxane	Not significant effect in QoL

IG: Intervention group; CG: control group; F: Female; QoL: quality of life; AC: acupuncture; UC: usual care; w: week; VAS: Visual Analogue Scale; BPI SF: Brief Pain Inventory—short form; NRS: Numeric Rating Scale; FACT/GOG-NTX: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity; EORTC QLQ-C30: European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core Scale.

Results

Characteristics of included trials. Ten RCTs were finally included in this systematic review. Detailed characteristics of the included RCTs are presented in Table I. In total, 495 patients were initially included (253 intervention group, 242 controls). The RCTs involved as an intervention acupuncture (n=6), exercise (n=3), or yoga (n=1). From the 10 included RCTs, 7 assessed pain and 9 assessed QoL (6 studies assessed both QoL and pain).

Most studies confirmed CIPN based on reported symptoms, mainly tingling and pain, or any other symptom suggestive of CIPN (1, 17-23). Only two studies used neurophysiological criteria to determine CIPN (24, 25). All studies shared similar excluding criteria, such as metastatic disease (1, 17, 21-24), diabetes mellitus (19, 20, 24), alcoholism (19, 20), and preexisting neuropathy (19-22, 24, 25).

Depending on the intervention, specific exclusion criteria were mentioned. RCTs on acupuncture stated as exclusion criteria needle phobia, bleeding disorders or lymphedematous limbs (22), pacemakers (18), having received acupuncture in the past (18, 19, 21, 22) or suffering from severe heart, liver, kidney disease or seizures (20, 21, 25). RCTs on exercise insisted on excluding patients with severe comorbidities, like coronary heart disease, respiratory insufficiency, severe hypertension, gross obesity, and musculoskeletal problems (1, 24). The RCT on yoga excluded patients if had been practicing yoga before (17).

Characteristics of participants. Average age ranged from 45.1 to 68.5 years. The number of participants varied from 29 to 104 (Table II). Three studies included only females (17, 21, 23). Five studies included more females than males, with a percentage ranging from 58.6% to 81.9% (18-20, 22, 24) and the rest two studies included males proportionally more than females with a range of 29.4% to 43% females (1, 25). In the eight RCTs where women predominated, the main type of cancer was breast cancer and gynecological cancers (ovarian, cervical), whereas in the remaining two studies, the main type of cancer was solely multiple myeloma (25) or colorectal cancer (1). Other types of cancer were also included across studies: genitourinary, hematological, prostate, lung, and lymphoma (19, 20, 24). Many chemotherapeutic agents were reported, most commonly taxanes (17, 18, 20-23), platins (1, 17, 18, 20, 22, 23), doxorubicin (20), bortezomide and capecitabine (22), monoclonal antibodies and regorafenib (1). In three RCTs chemotherapeutic agents were not specified (19, 24, 25).

Cancer and chemotherapeutic treatment history varied between studies. In two studies, chemotherapeutics were given concomitantly to intervention (22, 24), in four studies a 3-month distance from the end of chemotherapy treatment was a prerequisite (17, 18, 20, 25) and in the remaining four studies, history of chemotherapeutics treatment was not specified (1, 19, 21, 23). Quality appraisal classified six studies as high-quality investigations (1, 17, 18, 20-22) and four studies as good (19, 23-25).

The effectiveness of NPIs on pain and QoL was explored across included studies. Because follow up studies varied regarding the follow-up time point, the MA imported scores that were collected on or close to the 8^{th} week after intervention. That was exact for five studies: Bao (2020, 2021), Lu, Iravani, and Molassiotis. For the rest of the studies, it was the 4^{th} week (Zimmer), the 5^{th} week (D'Alessandro), the 6^{th} week (Saraboon & Siriphorn), 10^{th} week (Dhawan), and 12^{th} week (Han).

Pain. Seven out of ten RCTs assessed effectiveness on pain. Pain was mainly evaluated using a 11-point numeric rating scale (NRS) ranging from '0' representing "no pain" to '10' representing "pain as bad as you can imagine" or "worst pain imaginable (17, 20) or visual analogue scale (VAS) (19, 25). Two studies (21, 22) used brief pain inventory—short form (BPI-SF), an instrument used to evaluate the severity of pain in cancer patients, including neuropathic pain and interference of pain in the patient's life (26). BPI measures pain on a 11-point scale (from 0-10), where higher scores indicate worse pain and interference. The remaining two studies used different tools to evaluate pain. Dhawan *et al*. (24) utilized Leeds Assessment of Neuropathic Symptoms and Signs, a standardized tool that comprised 7 items and scores can range from 0 to 24. No significant difference in pain was found by D'Alessandro *et al*. (19). Five studies described significant differences in pain perception after intervention (20-22, 24, 25). Bao *et al*. (17) found that pain did not improve significantly after 8 weeks, but only after 12 weeks.

The forest plot describing Data synthesis was generated using MetaView Review Manager Version 5.4 (15). The analysis showed that, overall, the NPIs (yoga, acupuncture, and exercise) significantly improved the pain scores in the experimental group (Standardized mean difference: -0.56; 95% confidence interval=-0.83 to -0.28; Z=4.02; $p<0.0001$) with low heterogeneity $Chi^2=9.78$, $I^2=39\%$ (Figure 2A).

Running a sensitivity analysis, where only five studies that used acupuncture as an intervention were included (19-22, 25), pain was still significantly improved in the experimental group (Standardized mean difference: -0.62; 95% confidence interval=-0.99 to -0.26; Z=3.37; $p<0.0007$) with low heterogeneity $Chi^2=8.58$, $I^2=53\%$ (Figure 2B). The rest two studies were unique, each one using different NPI. Yoga (17) improved pain after 12 weeks, but not in the timeframe of 8 weeks, used to assess all studies. Strengthening and balancing exercise (24) also improved pain.

QoL. Nine out of ten included RCTs assessed the effectiveness of various NPIs on QoL. In order to assess

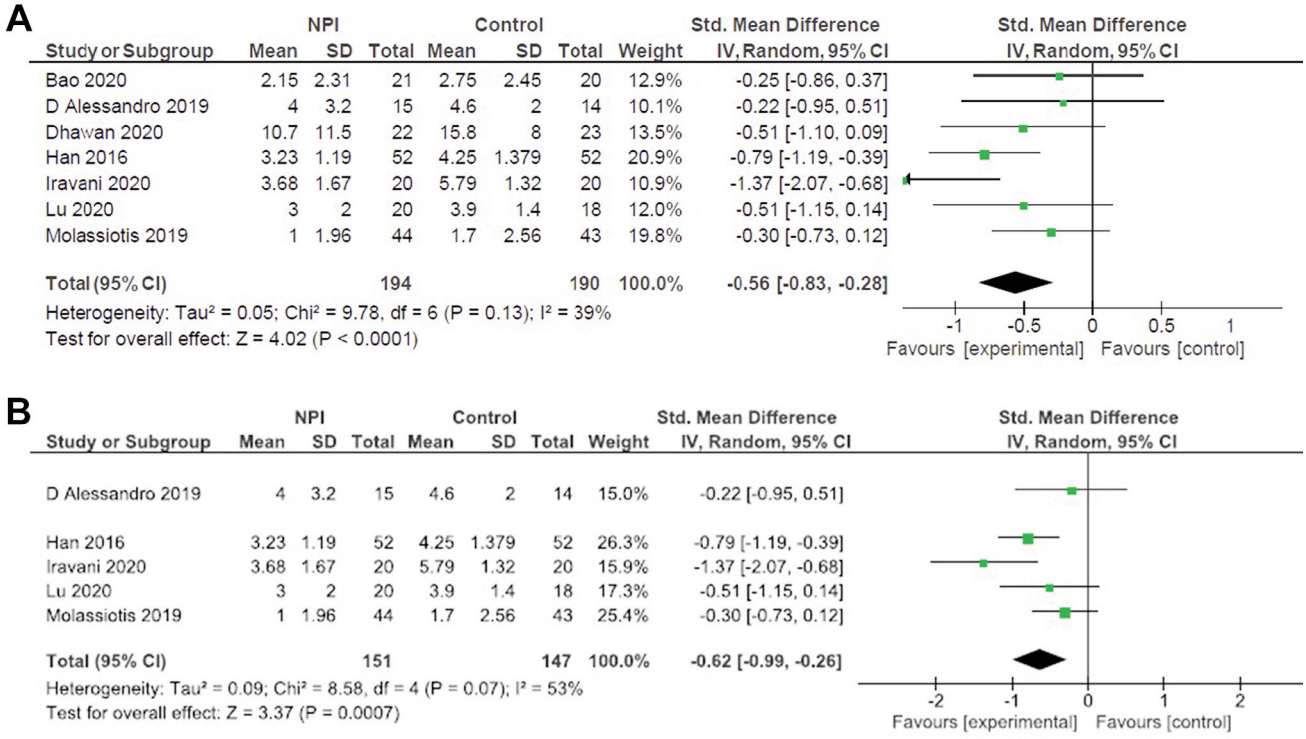

Figure 2. *Effect of non-pharmacological interventions on pain. A) Forest plot of the effect of all non-pharmacological interventions (NPIs) on pain in patients with chemotherapy-induced peripheral neuropathy (CIPN). B) Forest plot of the effect of acupuncture on pain in patients with CIPN.*

QoL two different scales were mainly used, the 11-item neurotoxicity-specific extension of the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity (FACT/GOG-NTX) (1, 17, 18, 21-23, 25) and European Organisation for the Research and Treatment of Cancer QoL Questionnaire Core Scale (EORTC QLQ-C30), a 30-item tool to assess QoL in cancer patients (19, 24). In the MA, symptom subscales, where higher scores represent worse QoL, were included. In all but three studies (1, 19, 23), QoL improved after NPIs.

The forest plot describing Data synthesis was generated using MetaView Review Manager Version 5.4 (15). The analysis showed that, overall, the NPIs (yoga, acupuncture, and exercise) did not significantly improve the QoL scores in the experimental group (Standardized mean difference=0.03; 95% confidence interval=-0.38 to 0.44; Z=0.13; p=0.90) showing high heterogeneity, Chi^2=35.88, I^2=78% (Figure 3A).

Running a sensitivity analysis, when only the five studies that used acupuncture as an intervention were included (18, 19, 21, 22, 25), QoL did not seem to improve (Standardized mean difference=-0.04; 95% confidence interval=-0.63 to 0.55; Z=0.15; p=0.88), Chi^2=24.76, I^2=84% (Figure 3B). Furthermore, when only the three studies that used exercise as an intervention were included (1, 23, 24) QoL did not improve (Standardized mean difference: 0.18; 95% confidence interval=-0.75 to 1.11; Z=0.38; p=0.70), Chi^2=10.90, I^2=82% (Figure 3C). The only study that used yoga showed significant improvement after 12 weeks, but not in the timeframe of 8 weeks, used to assess all studies.

Discussion

This SR examined the effects of different NPIs (acupuncture, yoga, strengthening, and balancing exercise) on patients suffering from CIPN across 10 RCTs. In total, 495 patients were included. The MA showed that overall, NPIs significantly reduced neuropathic pain. On the contrary, the effect on QoL was not supported. The above conclusions apply when all NPIs were lumped together, but also when each NPI was analyzed separately.

These results suggest that almost any type of NPIs reduces pain in patients suffering from any type of cancer and receiving any type of chemotherapeutics. However, QoL is a more complicated outcome to measure and obviously, pain relief alone is not enough to improve QoL. Patients suffering from CIPN do not just have to cope with polyneuropathy symptoms, but they also have to deal with the prospective of a chronic disease with probable more severe adverse effects of drugs than the numbness and neuropathic pain.

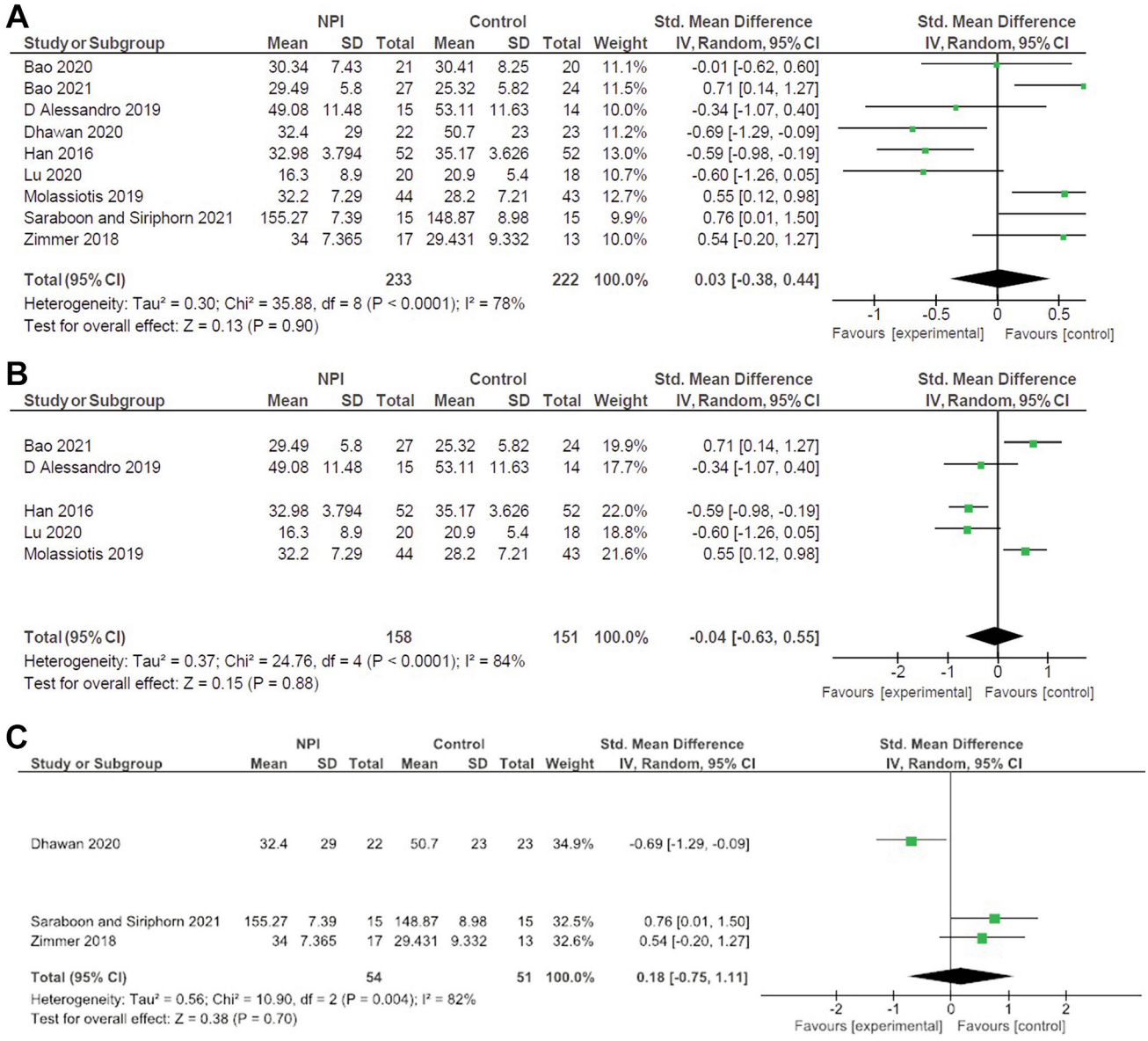

Figure 3. *Effect of non-pharmacological interventions on quality of life. A) Forest plot of the effect of all non-pharmacological interventions (NPIs) on quality of life (QoL) in patients with chemotherapy-induced peripheral neuropathy (CIPN). B) Forest plot of the effect of acupuncture on QoL in patients with CIPN. C) Forest plot of the effect of exercise on QoL in patients with CIPN.*

Acupuncture is widely used for chronic pain conditions, such as back and neck pain, headaches, and other musculoskeletal problems, but its value remains controversary since differences from placebo are modest (27, 28). Nevertheless, it remains a therapeutic option for those conditions where medical treatment has poor results, and this is also the case in CIPN. Physical exercise is also considered effective in reducing pain in chronic syndromes (29, 30) but the choice of specific parameters remains controversial and should be based on the patient's preference and the therapist's skills (31).

Overall, NPIs are considered at least moderately effective in chronic pain syndromes, as in CIPN, even though the mechanisms by which each intervention reduces pain is not clear. Acupuncture might reduce pain by inhibition of cyclooxygenase, release of endogenous opioids, and modulation of nociception (32) and physical exercise might act by increasing the pain threshold (29).

The results of several SRs and MAs on the effectiveness of NPIs on chronic pain, and more specifically on neuropathic pain, justify their use, and this is true for CIPN as well.

Table II. *Risk of bias of the included studies.*

Author (ref)	1. Eligibility criteria	2. Randomized allocation	3. Concealed allocation	4. Comparable at baseline	5. Blinded subjects	6. Blinded therapist	7. Blinded assessors	8. Adequate follow-up	9. Intention-to-treat analysis	10. Group comparisons	11. Point-estimated and variability	Total score
Bao 2020 (17)	+	+	+	+	–	+	–	+	+	+	+	9_11
D'Alessandro 2019 (19)	+	+	+	+	–	–	+	–	+	+	+	8_11
Dhawan 2020 (24)	+	+	+	+	–	–	–	+	+	+	+	8_11
Han 2016 (25)	+	+	+	+	–	–	–	+	+	+	+	8_11
Iravani 2019 (20)	+	+	+	+	–	–	–	+	+	+	+	9_11
Lu 2020 (21)	+	+	+	+	–	–	–	+	+	+	+	8_11
Molassiotis 2019 (22)	+	+	+	+	–	–	+	+	+	+	+	9_11
Bao 2021 (18)	+	+	+	+	+	–	+	+	+	+	+	10_11
Zimmer 2018 (1)	+	+	+	+	–	–	–	+	+	+	+	8_11
Saraboon 2021 (23)	–	+	+	+	–	–	+	+	+	+	+	8_11

PEDro scores of 0-3 are considered 'poor', 4-5 'fair', 6-8 'good, 9-10 'excellent'; a total PEDro score of 8/10 is optimal [Cashin *et al.* (12)].

Regarding effectiveness on QoL, results are more confusing and less straight forward. This is due to a great deal to the heterogeneity of scales used to measure QoL across studies.

The FACT/GOG-NTX questionnaire (33) consists of four domains about physical, emotional, social, and functional well-being and a domain with nine questions on additional concerns. The first two subscales are designed so that high scores represent high QoL, while the latter are designed oppositely. In the last domain with the additional concerns, some of them are quite specific on CIPN symptoms, such as numbness, tingling and discomfort in hands and feet (referring to superficial sensation problem), trouble feeling the shape of small objects and buttoning buttons, difficulty in walking and others (referring to deep sensation problem), and it is designed so that higher scores reflect worst QoL.

The EORTC QLQ-C30 includes three subscales: a Functional (physical, role, emotional, cognitive, social), a Global Health Status, and a symptom scale. The first two subscales are designed so that high scores represent high QoL whereas the symptom subscale is graded the opposite way (high score represents low QoL) (34). The symptom subscale consists of nine questions, none of them directly connected to CIPN, with the slight exception of pain, because pain may be caused by any factor other than CIPN.

Last, ECOG Performance Status scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability in a general way, and not specifically in relation to CIPN (35). It is clear that only FACT/GOG-NTX questionnaire addresses QoL problems in the prism of CIPN, whereas EORTC QLQ-C30 and ECOG Performance Status scale assess QoL in the prism of a general functional status that might be affected by other factors, rather than CIPN.

WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". The various developed scales try to incorporate various aspects of everyday living. In the case of cancer, QoL is affected by the disease itself, prognosis, and adverse effects of antineoplastic treatment other than CIPN, such as complications of surgery or radiation. Therefore, it is quite impossible to isolate the effect of CIPN on QoL without taking into account all other coexisting confounders.

Strengths and limitations. This SR comes from a highly selected but small source of data. The included RCTs presented a low risk of bias. Only studies that assessed post treatment effect of NPIs were included, whereas those that examined possible preventive effects were not. In assessing QoL, only symptom subscales, wherever existed, were used in MA. Regarding the timing of assessment, follow up at 8 weeks was chosen, because it was the most commonly referred follow-up

date. This study has also some limitations, that are common in the field. The number of studies and sample sizes are small. Lack of blinding of both subjects and investigators is inevitable in many cases. There is also a variety of cancer type, chemotherapeutic agents, timing of intervention across studies or in some cases not clarified. CIPN is diagnosed most often clinically, but on some occasions, diagnosis is based on electrophysiological data. Finally, CIPN has heterogeneity in its symptoms' presence and severity.

Conclusion

This SR and MA provides evidence that NPIs, of any kind, acupuncture, physical exercise, and yoga are significantly beneficial for CIPN, regarding the alleviation of pain compared to control. NPIs might be efficient regarding the improvement of QoL, but this parameter did not reach statistical significance. This is probably due to the heterogeneity of outcome measures and their inability to measure QoL improvements depended on CIPN.

Since NPIs are safe and do not interact with other drugs, their use in CIPN patients is justified, especially for pain relief, improving treatment compliance and overall prognosis. Future studies, with larger samples, more homogenous in terms of interventions and population characteristics, and better selection of scales, are needed to further explore NPIs' efficacy on CIPN symptoms.

Conflicts of Interest

The Authors declared no potential conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: Papadopoulou Marianna; Stamou Magda; Tsivgoulis Georgios. Literature search: Papadopoulou Marianna; Stamou Magda; Bakalidou Daphne. Data analysis: Papadopoulou Marianna; Zis Panagiotis; Michopoulos Ioannis. Writing original draft: Papadopoulou Marianna; Michopoulos Ioannis. Critically revised the work: Moschovos Christos; Zouvelou Vasiliki; Tzartos John; Chroni Elisabeth; Tsivgoulis Georgios.

References

1 Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, Rudolph R, Streckmann F and Baumann FT: Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Support Care Cancer *26(2)*: 615-624, 2018. PMID: 28963591. DOI: 10.1007/s00520-017-3875-5

2 Colvin LA: Chemotherapy-induced peripheral neuropathy: where are we now? Pain *160 Suppl 1(Suppl 1)*: S1-S10, 2019. PMID: 31008843. DOI: 10.1097/j.pain.0000000000001540

3 Brayall P, Donlon E, Doyle L, Leiby R and Violette K: Physical therapy-based interventions improve balance, function, symptoms, and quality of life in patients with chemotherapy-induced peripheral neuropathy: a systematic review. Rehabilitation Oncology *36(3)*: 161-166, 2021. DOI: 10.1097/01.REO.0000000000000111

4 Duregon F, Vendramin B, Bullo V, Gobbo S, Cugusi L, Di Blasio A, Neunhaeuserer D, Zaccaria M, Bergamin M and Ermolao A: Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol *121*: 90-100, 2018. PMID: 29198853. DOI: 10.1016/j.critrevonc.2017.11.002

5 Hou S, Huh B, Kim HK, Kim KH and Abdi S: Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. Pain Physician *21(6)*: 571-592, 2018. PMID: 30508986.

6 Jin Y, Wang Y, Zhang J, Xiao X and Zhang Q: Efficacy and safety of acupuncture against chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Evid Based Complement Alternat Med *2020*: 8875433, 2020. PMID: 33224260. DOI: 10.1155/2020/8875433

7 Brozou V, Vadalouca A and Zis P: Pain in platin-induced neuropathies: a systematic review and meta-analysis. Pain Ther *7(1)*: 105-119, 2018. PMID: 29196945. DOI: 10.1007/s40122-017-0092-3

8 Girach A, Julian TH, Varrassi G, Paladini A, Vadalouka A and Zis P: Quality of life in painful peripheral neuropathies: a systematic review. Pain Res Manag *2019*: 2091960, 2019. PMID: 31249636. DOI: 10.1155/2019/2091960

9 Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL and American Society of Clinical Oncology: Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol *32(18)*: 1941-1967, 2014. PMID: 24733808. DOI: 10.1200/JCO.2013.54.0914

10 Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G and Zis P: Pharmacological management of painful peripheral neuropathies: a systematic review. Pain Ther *10(1)*: 55-68, 2021. PMID: 33145709. DOI: 10.1007/s40122-020-00210-3

11 Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G and Zis P: Non-pharmacological management of painful peripheral neuropathies: a systematic review. Adv Ther *37(10)*: 4096-4106, 2020. PMID: 32809209. DOI: 10.1007/s12325-020-01462-3

12 SF | Chemotherapy Induced Polyneuropathy Non Pharmacological Management, Registrations [Internet]. Available at: https://osf.io/c6b35/registrations [Last accessed on November 20, 2022]

13 Cashin AG and McAuley JH: Clinimetrics: Physiotherapy evidence database (PEDro) scale. J Physiother *66(1)*: 59, 2020. PMID: 31521549. DOI: 10.1016/j.jphys.2019.08.005

14 PEDro scale [Internet]. PEDro. Available at: https://staging-pedro.neura.edu.au/english/resources/pedro-scale/ [Last accessed on November 20, 2022]

15 RevMan [Internet]. Available at: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman [Last accessed on August 23, 2021]

16 Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ *327(7414)*: 557-560, 2003. PMID: 12958120. DOI: 10.1136/bmj.327.7414.557

17 Bao T, Zhi I, Baser R, Hooper M, Chen C, Piulson L, Li QS, Galantino ML, Blinder V, Robson M, Seidman A, Panageas KS and Mao JJ: Yoga for chemotherapy-induced peripheral neuropathy and fall risk: a randomized controlled trial. JNCI Cancer Spectr *4(6)*: pkaa048, 2020. PMID: 33225208. DOI: 10.1093/jncics/pkaa048

18 Bao T, Baser R, Chen C, Weitzman M, Zhang YL, Seluzicki C, Li QS, Piulson L and Zhi WI: Health-related quality of life in cancer survivors with chemotherapy-induced peripheral neuropathy: a randomized clinical trial. Oncologist *26(11)*: e2070-e2078, 2021. PMID: 34390283. DOI: 10.1002/onco.13933

19 D'Alessandro EG, Nebuloni Nagy DR, de Brito CMM, Almeida EPM, Battistella LR and Cecatto RB: Acupuncture for chemotherapy-induced peripheral neuropathy: a randomised controlled pilot study. BMJ Support Palliat Care *12(1)*: 64-72, 2022. PMID: 31256014. DOI: 10.1136/bmjspcare-2018-001542

20 Iravani S, Kazemi Motlagh AH, Emami Razavi SZ, Shahi F, Wang J, Hou L, Sun W, Afshari Fard MR, Aghili M, Karimi M, Rezaeizadeh H and Zhao B: Effectiveness of acupuncture treatment on chemotherapy-induced peripheral neuropathy: a pilot, randomized, assessor-blinded, controlled trial. Pain Res Manag *2020*: 2504674, 2020. PMID: 32676134. DOI: 10.1155/2020/2504674

21 Lu W, Giobbie-Hurder A, Freedman RA, Shin IH, Lin NU, Partridge AH, Rosenthal DS and Ligibel JA: Acupuncture for chemotherapy-induced peripheral neuropathy in breast cancer survivors: a randomized controlled pilot trial. Oncologist *25(4)*: 310-318, 2020. PMID: 32297442. DOI: 10.1634/theoncologist.2019-0489

22 Molassiotis A, Suen LKP, Cheng HL, Mok TSK, Lee SCY, Wang CH, Lee P, Leung H, Chan V, Lau TKH and Yeo W: A randomized assessor-blinded wait-list-controlled trial to assess the effectiveness of acupuncture in the management of chemotherapy-induced peripheral neuropathy. Integr Cancer Ther *18*: 1534735419836501, 2019. PMID: 30905173. DOI: 10.1177/1534735419836501

23 Saraboon C and Siriphorn A: Effects of foam pad balance exercises on cancer patients undergoing chemotherapy: A randomized control trial. J Bodyw Mov Ther *28*: 164-171, 2021. PMID: 34776136. DOI: 10.1016/j.jbmt.2021.07.013

24 Dhawan S, Andrews R, Kumar L, Wadhwa S and Shukla G: A randomized controlled trial to assess the effectiveness of muscle strengthening and balancing exercises on chemotherapy-induced peripheral neuropathic pain and quality of life among cancer patients. Cancer Nurs *43(4)*: 269-280, 2020. PMID: 30888982. DOI: 10.1097/NCC.0000000000000693

25 Han X, Wang L, Shi H, Zheng G, He J, Wu W, Shi J, Wei G, Zheng W, Sun J, Huang H and Cai Z: Acupuncture combined with methylcobalamin for the treatment of chemotherapy-induced peripheral neuropathy in patients with multiple myeloma. BMC Cancer *17(1)*: 40, 2017. PMID: 28068938. DOI: 10.1186/s12885-016-3037-z

26 Cleeland CS and Ryan KM: Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap *23(2)*: 129-138, 1994. PMID: 8080219.

27 Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, Sherman KJ, Witt CM, Linde K and Acupuncture Trialists' Collaboration: Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med *172(19)*: 1444-1453, 2012. PMID: 22965186. DOI: 10.1001/archinternmed.2012.3654

28 Yuan QL, Wang P, Liu L, Sun F, Cai YS, Wu WT, Ye ML, Ma JT, Xu BB and Zhang YG: Acupuncture for musculoskeletal pain: A meta-analysis and meta-regression of sham-controlled randomized clinical trials. Sci Rep *6*: 30675, 2016. PMID: 27471137. DOI: 10.1038/srep30675

29 Belavy DL, Van Oosterwijck J, Clarkson M, Dhondt E, Mundell NL, Miller CT and Owen PJ: Pain sensitivity is reduced by exercise training: Evidence from a systematic review and meta-analysis. Neurosci Biobehav Rev *120*: 100-108, 2021. PMID: 33253748. DOI: 10.1016/j.neubiorev.2020.11.012

30 Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA and Smith BH: Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database Syst Rev *4(4)*: CD011279, 2017. PMID: 28436583. DOI: 10.1002/14651858.CD011279.pub3

31 Ferro Moura Franco K, Lenoir D, Dos Santos Franco YR, Jandre Reis FJ, Nunes Cabral CM and Meeus M: Prescription of exercises for the treatment of chronic pain along the continuum of nociplastic pain: A systematic review with meta-analysis. Eur J Pain *25(1)*: 51-70, 2021. PMID: 32976664. DOI: 10.1002/ejp.1666

32 Li K, Giustini D and Seely D: A systematic review of acupuncture for chemotherapy-induced peripheral neuropathy. Curr Oncol *26(2)*: e147-e154, 2019. PMID: 31043820. DOI: 10.3747/co.26.4261

33 FACT-GOG-NTX [Internet]. FACIT Group. Available at: https://www.facit.org/measures/FACT-GOG-NTX [Last accessed on September 3, 2021]

34 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB and de Haes JC: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst *85(5)*: 365-376, 1993. PMID: 8433390. DOI: 10.1093/jnci/85.5.365

35 ECOG Performance Status [Internet]. ECOG-ACRIN. Available at: https://ecog-acrin.org/resources/ecog-performance-status [Last accessed on September 3, 2021]

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