Original Article

Prioritizing Chinese Medicine Clinical Research Questions in Cancer Palliative Care: International Delphi Survey

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Abstract

Context. Chinese medicine modalities, including acupuncture and Chinese herbal medicine (CHM), have been used as palliative interventions among cancer patients. More research should be conducted to confirm their effectiveness.

Objectives. The objective of this study was to prioritize Chinese medicine clinical research questions for cancer palliative care.

Methods. Twelve international experts, including physicians, Chinese medicine practitioners, nurses, and clinical research methodologists ($n = 3$ from each category), from Asia, North America, Australia, and Europe participated in a two-round Delphi survey for prioritizing 29 research questions identified from existing systematic reviews. The experts were asked to 1) rate clinical importance of answering the questions on a nine-point Likert scale; 2) provide qualitative comments on their ratings; and 3) suggest outcome measurement approaches.

Results. Eight research priorities reached positive consensus after the two-round Delphi survey. Six of the priorities focused on acupuncture and related therapies, of which median ratings on importance ranged from 7.0 to 8.0 (interquartile range: 1.00 to 2.50), and the percentage agreement ranged from 75.0% to 91.7%. The remaining two priorities related to CHM, with median ratings ranged from 7.0 to 8.0 (interquartile range: 1.00 to 1.50) and percentage agreement ranged from 75.0% to 83.3%. Neither positive nor negative consensus was established among the remaining 21 questions.

Conclusion. The findings will inform rational allocation of scarce research funding for evaluating the effectiveness of Chinese medicine for cancer palliative care, especially on acupuncture and related therapies. Further research on herb safety and herb-drug interaction should be performed before conducting international trials on CHM. J Pain Symptom Manage 2019;58:1002–1014.

Key Words

Palliative care, Delphi technique, integrative medicine, research priorities

Introduction

Cancer is one of the major disease burdens globally, accounting for an estimated 18.1 million new cases and 9.6 million deaths in 2018.[1] It is also a leading cause of death worldwide, with about 16.7% of the global deaths attributable to cancer.[2] The International Agency for Research of Cancer predicts that there will be approximately 29.5 million new cancer

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cases and 16.5 million cancer deaths worldwide by 2040.[3] Rising cancer incidence and the continual improvement in cancer treatment has led to an increase in the number of cancer patients requiring timely palliative care.[4]

According to the World Health Organization, palliative care is defined as "total care" that focuses on enhancing patients' quality of life and relieving their suffering.[5] There is debate about the duration and timing of initiating cancer palliative care, with some opinions suggesting that it should be constrained to the last six months of life.[6,7] However, the United States' National Comprehensive Cancer Network (NCCN) recommends that palliative care should be provided across the whole disease trajectory,[8] beginning once a patient is diagnosed with cancer. Common symptoms among palliative cancer patients include, but are not limited to, fatigue, pain, neuropathy, and insomnia.[9] The conventional pharmaceutical treatments available for these symptoms, however, are of limited effectiveness, which restricts their clinical use.[10] It is also challenging for patients and health care professionals to make clinical decisions on palliative chemotherapy and radiotherapy due to the need to balance the potential clinical benefits and side effects.[11]

Practiced among Chinese population for thousands of years, Chinese medicine has been used as a supportive intervention for cancer patients.[12] Its popularity in cancer palliative care is increasing internationally.[13] The potential role of Chinese medicine modalities, including Chinese herbal medicine (CHM) as well as acupuncture and related modalities, such as manual acupuncture, electroacupuncture, and acupressure, in addressing the unmet needs in cancer palliative care has gained substantial interest recently. Existing overviews of systematic reviews (SRs)[14–16] and SRs[17,18] have shown that some Chinese medicine modalities had promising effect for managing cancer-related fatigue, chemotherapy-induced nausea, and vomiting, as well as improving quality of life among palliative cancer patients. Nevertheless, methodological limitations among existing clinical trials cast uncertainty on their effectiveness.[17,18] With scarce research funding,[19] it is important to identify clinical research priorities where effectiveness of promising Chinese medicine interventions for cancer palliative care needs to be confirmed before dissemination and implementation. As such, the aim of this study was to prioritize Chinese medicine clinical research questions for cancer palliative care using a two-round Delphi survey.

Method

The use of Delphi survey is an iterative process that collects the expertise and opinions from various stakeholders via series of survey until consensus is established.[20] This approach has been previously used in identifying research priorities in cancer care[21] and oncology research.[19,22] In this study, the Delphi survey was used to facilitate the prioritization of research questions related to Chinese medicine modalities in cancer palliative care, including CHM as well as acupuncture and related modalities. It promoted the interaction of a diverse stakeholder group with international cancer palliative care background, while managing their different opinions in a structured manner.[23] Ethics approval was obtained from the Survey and Behavioural Research Ethics Committee, The Chinese University of Hong Kong (reference no.: 023-17) on 2 February 2017.

This study is reported in accordance to the reporting standard for Conducting and Reporting of Delphi Studies (CREDES).[24] It is composed of four parts, as follows:

Part 1: Preparation of the List of Research Questions on Chinese Medicine for Cancer Palliative Care Before the Conduction of Delphi Survey

In this study, research needs to refer to knowledge gaps and methodological issues that limit health care decision making among health care professionals, patients, and other stakeholders.[25] Research needs were first identified from three existing overviews of SRs[14–16] and two SRs[17,18] on Chinese medicine interventions for cancer palliative care. These syntheses summarized clinical evidence from a total of 74 SRs and 88 randomized controlled trials. Authors of these syntheses were asked to provide feedback and specify potential research needs. These needs were translated into research questions using the PICO (patients, interventions, comparisons and outcomes) framework,[26] which ensured the inclusion of essential components within the clinical research questions.

Individual qualitative interviews were then conducted among Chinese ($n = 8$) and international ($n = 4$) experts to collect comments and suggestions for further amendment on these potential research questions. The experts included conventionally trained physicians ($n = 3$), Chinese medicine practitioners ($n = 3$), nurses ($n = 3$), and clinical research methodologists ($n = 3$) with practical experience in cancer palliative care. A final list of Chinese medicine clinical research questions for cancer palliative care was generated for the Round 1 Delphi survey.

Part 2: Sampling of Experts for the Delphi Survey

Purposive sampling strategy was used to identify a balanced number of international experts with 1) biomedicine, 2) Chinese medicine, 3) nursing, and 4) clinical research methodology background, with direct experiences in cancer palliative care service or research. To ensure a balance of perspectives, three experts from each of the four disciplines were sampled. The total number of experts was limited to 12 as the smaller sample size allowed us to ensure a

high response rate across the surveys.[27] All experts' identities were protected to ensure confidentiality and independence of judgments.

Part 3: Delphi Survey Data Collection

Potential experts were initially contacted via e-mail in September 2018 and provided with the research aims and details of the Delphi survey as well as the written informed consent forms. Experts who agreed to join the study were invited to return their signed informed consent. The Round 1 survey, including questions on demographic and professional information, as well as a list of potential research questions, was sent by e-mail to the participating experts. The experts were then asked to rate the clinical importance of each question on a nine-point Likert scale,[28] ranging from "not important at all" to "of highest importance." They were also invited to provide qualitative comments on why such a rating was given and were offered the opportunity to revise existing research questions or propose new questions, if they chose to. Finally, they were requested to suggest outcome measures for each question. The elicitation of anonymous qualitative comments allowed experts to express their judgments independently, in an iterative fashion, as the same process was repeated in the Round 2 Delphi survey.[29]

Part 4: Delphi Survey Data Analysis

Quantitative ratings in Round 1 were analyzed to decide whether positive or negative consensus was reached. For each research question, the median rating for clinical importance was calculated as it is more robust to outliers when compared to mean values.[27,30] Interquartile range (IQR) of ratings were also calculated to demonstrate magnitude of disagreement among experts.[27,30] The agreement on the clinical importance was expressed as a percentage. Considering the agreement standard adopted in existing Delphi surveys,[31,32] the cutoff level of consensus was set at 75%. Hence, a research question would reach positive consensus as a priority if ≥75% of international experts rated 7 to 9 on the nine-point Likert scale, whereas negative consensus would be achieved when ≥75% rated 1 to 3 on the nine-point Likert scale. Research questions that attained positive consensus in Round 1 were considered as a research priority and qualitative comments on each question were summarized and presented. For questions without consensus, qualitative comments were used to guide amendments and were subjected to further evaluation in Round 2.

In Round 2, the same panel of international experts was invited to assess 1) research questions that reached neither positive nor negative consensus and 2) new research questions suggested in the Round 1. The Round 2 survey package for each question included 1) respondents' own ratings in the Round 1; 2) median ratings with IQRs and percentage agreement; and 3) anonymous qualitative comments from each expert. Data collection and data analysis similar to Round 1 were performed. A list of international experts endorsed research priorities were generated at the end of Round 2, which included all questions reaching positive consensus across both rounds.

Table 1
Demographic Data of Participants in Two-Round Delphi Survey ($N = 12$)

Demographics	Values
Gender, *n* (%)	
Male	8 (66.7)
Female	4 (33.3)
Age, *n* (%)	
31–45	4 (33.3)
46–60	6 (50.0)
61 or above	2 (16.6)
Profession, *n* (%)	
Physician	3 (25.0)
CMP	3 (25.0)
Nurse	3 (25.0)
Clinical research methodologist	3 (25.0)
Countries of work, *n* (%)	
Asia	5 (41.7)
North America	4 (33.3)
Australia	2 (16.6)
Europe	1 (8.3)
Work setting, *n* (%)	
Hospitals only	1 (8.3)
Academic institutions only	4 (33.3)
Academic institutions and hospitals	6 (50.0)
Academic institutions, hospitals, and private outpatient practice	1 (8.3)
Mean years of professional experience in cancer palliative care	10.75

CMP = Chinese medicine practitioner.

Results

Participants

Twelve experts in cancer palliative care recruited internationally agreed to participate in this two-round Delphi survey. The response rates of completing both rounds of questionnaires were 100%. Of these 12 experts, 66.7% of the respondents were male and half of them were aged 46 to 60 years. The experts consisted of conventionally trained physicians (25.0%), Chinese medicine practitioners (25.0%), nurses (25.0%) and clinical research methodologists (25.0%). Approximately 40% were from Asia, followed by 33.3% from North America, 16.6% from Australia (16.6%), and 8.3% from Europe. The majority of experts worked in both academic institutions and hospitals (50.0%), or at academic institutions only (33.3%). The mean years of their professional experience in cancer palliative care was 10.75 years (Table 1).

Research Priorities Identified in Delphi Survey Round 1

A list of 25 research questions on Chinese medicine for cancer palliative care was generated in Round 1 of the Delphi survey, based on expert feedback. In this round, only one research question achieved positive consensus as a priority: addition of manual acupuncture on top of opioids for reducing pain among palliative cancer adult patients. The median rating for clinical importance was 8.0 (IQR: 1.75) on the nine-point Likert scale, with a percentage agreement of 83.3% (Table 2). The remaining 24 research questions reached neither positive nor negative consensus.

Research Priorities Identified in Delphi Survey Round 2

A total of 26 research questions, including 22 questions listed in the original Delphi survey Round 1, plus four new questions proposed by experts in Round 1, were presented in the Delphi survey Round 2 for rating. Seven research questions reached positive consensus as priorities in this round. Among these seven priorities, five were on the evaluation of acupuncture and related therapies for relieving xerostomia, fatigue, insomnia, anxiety, paresthesia, and dysesthesia. The median rating for clinical importance ranged from 7.0 to 8.0 (IQR: 1.00 to 2.50) with a percentage agreement ranging from 75.0% to 91.7% (Table 2).

The remaining two research priorities were on the assessment of CHM for reducing constipation and for improving anemia. The median rating ranged from 7.0 to 8.0 (IQR: 1.00 to 1.50), whereas the percentage agreement ranged from 75.0% to 83.3% (Table 2). The international experts also suggested one to three outcome measures for each recommended research priority. Details of the experts' qualitative comments on the priorities, as well as the suggested outcome measures, are shown in Table 3.

Research Questions Without Consensus After the Two-Round Delphi Survey

Ten of the 16 research questions related to acupuncture and related therapies for cancer palliative care did not attain positive consensus as research priorities. The median rating for clinical importance ranged from 3.5 to 7.0 (IQR: 1.00−4.25), whereas the percentage agreement ranged from 0.0% to 66.7% at the end of Round 2 (Appendix I). The agreement on the use of moxibustion (8.3%) and TENS (0.0%) were particularly low (Appendix I). According to experts' qualitative comments, the use of moxibustion in hospital settings should not be considered owing to concerns on the possible negative effect of smoke particulates on patients' health conditions. TENS were not favored owing to lack of familiarity, as well as the lack of reliable sham TENS procedure in trial design.

For the 12 research questions related to CHM, 10 questions did not reach positive consensus. The median rating ranged from 4.5 to 7.0 (IQR: 1.75−4.75), whereas the percentage agreement ranged from 33.3% to 58.3% at the end of Round 2 (Appendix I). The main reasons for not establishing positive consensus on these questions were strong concerns on CHM safety and herb-drug interactions among palliative cancer patients receiving chemotherapy.

The experts recommended one to three outcome measures for each research question, even when consensus was not reached, except for two questions that evaluated 1) brain function, cognitive performance, and memory loss and 2) stomatitis. Details of experts' qualitative comments and the proposed outcome measures are shown in Appendix II.

Discussion

Summary of Findings

In this study, international experts ($n = 12$) were invited to prioritize Chinese medicine clinical research questions for cancer palliative care. After a two-round Delphi survey, eight research priorities were established with positive consensus; the remaining 21 research questions achieved neither positive nor negative consensus.

Guideline-Recommended Acupuncture Treatments Remain Research Priorities

Although the palliative care version of the NCCN clinical practice guidelines in oncology has already recommended acupuncture for reducing cancer pain[33,34] and cancer-related fatigue,[33,35] international experts in our study still suggested that more research on these topics should be conducted. A possible explanation is that the panel members may question the validity of the recommendations from clinical guidelines,[36] given the proposed methodological flaws of the trials supporting the recommendations.[37] If future trials on these priorities are funded, methodological rigor should be ensured to prevent wastage of precious funding.[38] The necessity of updating the NCCN guideline on these two recommendations should be assessed using appropriate methods of evidence update and expert consensus.[39]

As indicated by the IQR of median rating for clinical importance, the research priority related to acupressure for relieving insomnia among palliative cancer adult patients receiving chemotherapy reached the largest magnitude of disagreement among the experts. This was due to divergent opinions on whether a comparison between self-acupressure and Chinese medicine practitioner−delivered acupressure should be regarded as a priority. While some considered

Table 2
Final List of Research Priorities Generated From the Two-Round Delphi Survey

Research Questions	Delphi Round 1			Delphi Round 2		
	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)
Intervention: acupuncture and related therapies						
1) Is adding manual acupuncture on top of opioids more effective in reducing pain among palliative cancer adult patients?	8.0 (1.75)	83.3	Yes	N/A[b]		
2) Is adding manual acupuncture on top of artificial saliva more effective in reducing xerostomia among palliative cancer adult patients?	6.5 (2.00)	50.0	No	8.0 (1.75)	75.0	Yes
3) Is adding electroacupuncture on top of oral vitamin B6 (pyridoxine) supplement more effective in reducing paresthesia and dysesthesia among palliative cancer adult patients?	6.0 (2.00)	41.7	No	7.0 (1.50)	75.0	Yes
4) Is adding manual acupuncture on top of exercise more effective in reducing fatigue among palliative cancer adult patients?	7.0 (2.75)	66.7	No	8.0 (1.00)	91.7	Yes
5) Is acupressure provided by Chinese medicine practitioners more effective than self-acupressure in improving insomnia among palliative cancer adult patients receiving chemotherapy?		N/A[c]		7.0 (2.50)	75.0	Yes
6) Is adding manual acupuncture on top of conventional care more effective in reducing anxiety among palliative cancer adult patients?		N/A[c]		8.0 (1.75)	75.0	Yes
Intervention: Chinese herbal medicine (CHM)						
7) Is adding CHM[d] on top of conventional care (glycerin suppositories/lactulose syrup) more effective in reducing constipation among palliative cancer adult patients?	7.0 (2.75)	58.3	No	8.0 (1.00)	83.3	Yes
8) Is adding CHM[e] on top of conventional care (blood transfusion/erythropoiesis-stimulating agents [e.g., epoetin]) more effective in improving anemia among palliative cancer adult patients?	7.0 (2.00)	58.3	No	7.0 (1.50)	75.0	Yes

IQR = interquartile range; N/A = not applicable; CHM = Chinese herbal medicine.
[a]The cutoff level of consensus in this study was set at 75%.
[b]Not applicable because the research question has achieved positive consensus in Round 1 Delphi survey.
[c]Not applicable because the research question has been revised based on the qualitative comments of international experts in Round 1 Delphi survey.
[d]Details of CHM: a) Panax ginseng C. A. Mey. [Ren Shen人參], Astragalus mongholicus Bunge [Huang Qi黃芪], Atractylodes macrocephala Koidz. [Bai Zhu白術], Magnolia officinalis Rehder & E.H.Wilson [Cortex Magnoliae Officinalis厚朴], Citrus aurantium L. [Zhi shi枳實], Rheum palmatum L. [Da huang大黃], Paeonia lactiflora Pall. [Bai Shao白芍], Codonopsis pilosula (Franch.) Nannf. [Dang Shen黨參], Cornus officinalis Siebold & Zucc. [Shan Zhu Yu山茱萸]; b) Chengqi decoction [承氣湯類], Apricot Seed & Linum Formula [Ma Zi Ren Wan麻子仁丸].
[e]Details of CHM: a) Adjusted Angelicae Sinensis Decoction for Supplementing Blood [當歸補血湯加減]; b) Adjusted Shiquan Dabu Decoction [十全大補湯加減 (Astragalus mongholicus Bunge [Huang Qi黃芪]), Panax ginseng C. A. Mey. [Ren Shen人參], Angelica sinensis (Oliv.) Diels [Dang Gui當歸], Paeonia lactiflora Pall. [Bai Shao白芍], Atractylodes macrocephala Koidz. [Bai Zhu白術], Cibotium barometz (L.) J.Sm. [Gou Qi枸杞], Colla Corii Asini [E Jiao阿膠], Glycyrrhiza uralensis Fisch. ex DC. [Zhi Gan Cao炙甘草], Salvia miltiorrhiza Bunge [Dan Shen丹參], Panax notoginseng (Burkill) F.H.Chen [San Qi三七])].

equipping patients with self-acupressure skills as a form of patient empowerment,[40] other found this to be an invalid control for Chinese medicine practitioner–based acupressure because the two might differ greatly in terms of strength, technique, and accuracy in locating acupoints.[41] To address this comparative effectiveness research priority, which would have potential cost-saving implications, regular training on acupressure should be provided by an experienced Chinese medicine practitioner for participants before and during trial implementation, so as to ensure the fidelity of self-acupressure.[41]

Concerns Regarding Safety of Chinese Herbal Medicine and Herb-Drug Interaction

Continuous concerns over CHM safety[42] and herb-drug interaction[43] were the main reasons for not reaching positive consensus on a majority of research questions related to CHM among international experts. A recent large-scale observational study indicated that CHM was one of the leading causes of drug-induced liver injury in China, with an estimated annual incidence of 23.80 per 100,000 persons in the general population.[44] Several surveys showed that many cancer patients consumed herbal medicines, including CHM, simultaneously with chemotherapeutic agents with the hope of "boosting" treatment efficacy, or minimizing adverse effects of chemotherapy.[45,46] This may possibly induce undesirable herb-drug interactions[47] between CHM and chemotherapeutic agents. In addition, some CHMs were found to have negative pharmacokinetic interaction with chemotherapeutic agents.[47] Their coadministration might result in unanticipated toxicities[48] and multiorgan failure might happen in the worst-case scenario.[48]

It is therefore unsurprising that the two CHM research priorities identified in our study were not focused on the combined use of CHM and chemotherapy. To demystify the safety profile of CHM, and to reduce the possibility of undesirable herb-drug interactions, appropriate observational and pharmacological studies should be conducted to investigate the risk of adverse events before clinical trials.[49] With the emergence of electronic health record–based cohort or case-control studies on CHM adverse events and herb-drug interactions, it is expected that international trials on CHM will become more of interest in the future.[50]

Suggested Outcome Measures for the Identified Research Priorities

In this study, the outcome measures recommended for pain (McGill Pain Questionnaire,[51] Visual Analogue Scale,[51] and Numerical Rating Scale[51]), fatigue (Brief Fatigue Inventory,[52] and Multidimensional Fatigue Inventory[53]), anxiety (Hospital Anxiety and Depression scale[54] and State Trait Anxiety Inventory[54]), and insomnia (Pittsburgh Sleep Quality Index[55]) were concordant with the outcome measures suggested in the Person-focused Outcome Measurement System in Cancer (PROMS-Cancer Core) that were found to be relevant and feasible for cancer patients.[56] PROMS-Cancer Core was developed by interdisciplinary decision makers, clinicians, and cancer survivors in Canada, and it was used to provide guidance on the establishment of a patient-reported outcome information system for cancer.[56] However, the outcome measures proposed in our study are symptom-specific measures[57] without validation among palliative care patients.[57,58] This concurred with findings of a previous study that suggested that even experienced researchers might overlook the validity of outcome measures in palliative care populations when proposing outcome measures during research design,[59] or due to a general lack of awareness on the availability of such guidelines.[60]

To enhance comprehensiveness of assessment, future trialists may consider the use of patient-reported outcome measures that are validated in palliative care as well as being symptom-specific measures.[57,61] For example, Edmonton Symptom Assessment Scale,[62] Palliative Care Outcome Scale,[63] Memorial Symptom Assessment Scale–Short Form,[64] European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative[65] were recommended by the European Association for Palliative Care White Paper on outcome measurement.[57] Because these outcome measures are easy to administer and interpret while satisfying the criteria of a good outcome measure suggested in the Methods Of Researching End of life Care (MORECare) statement,[66] they can be integrated into research or even clinical care settings.

Next Steps for Influencing Funding Allocation

Although we have established research priorities in this study, our results were generated without direct involvement from patients as well as funding bodies. There could be mismatches among stakeholders on what should be considered priorities, and further work is needed to advance wider partnership for influencing funding decisions.[67–69] The work of James Lind Alliance (JLA) is a prime example of such partnership. JLA was established in 2004 to bring patients, carers, and health care professionals together in research priority setting partnerships (PSPs).[70] The JLA infrastructure is directly funded by the United Kingdom (UK) National Institute of Health Research (NIHR), which commission the JLA to implement PSP processes.[71] Via the NIHR–JLA partnership, priorities identified from the PSP were successfully

Table 3
Qualitative Comments and Suggested Outcome Measures on the Final List of Research Priorities

Research Questions	Qualitative Comments From Delphi Rounds 1 and 2	Suggested Outcome Measures
Intervention: acupuncture and related therapies		
1) Is adding manual acupuncture on top of opioids more effective in reducing pain among palliative cancer adult patients?	• Manual acupuncture may have a role in relieving somatic pain, but not in neuropathic pain among palliative cancer patients; • Lower dose of opioids can be administered along with manual acupuncture; • There is growing research evidence supporting the use of manual acupuncture for cancer pain, but the long-term effects of acupuncture, as well as the combined effects of acupuncture and NSAIDs for cancer pain might be further evaluated.	• McGill Pain Questionnaire[51] • Visual Analogue Scale for measuring pain intensity[51] • Numerical Rating Scale for measuring pain intensity[51]
2) Is adding manual acupuncture on top of artificial saliva more effective in reducing xerostomia among palliative cancer adult patients?	• Xerostomia is a very problematic symptom among patients with head and neck cancers and the damage to salivary glands caused by radiotherapy is significant; • Xerostomia poses lasting negative impacts on patients' dental health and thus their quality of life, so it would be great to have more treatment options for these patients; • Although some existing studies have showed that manual acupuncture could stimulate saliva secretion, further research is needed to investigate the synergic effect of acupuncture and artificial saliva for xerostomia.	• University of Michigan Xerostomia Related Quality of Life Scale (XeQOLS)[87] • Basal and citric acid primed whole salivary production (WSP)[87] • Five-item xerostomia symptom questionnaire with a Visual Analog Scale[88]
3) Is adding electroacupuncture on top of oral vitamin B6 (pyridoxine) supplement more effective in reducing paresthesia and dysesthesia among palliative cancer adult patients?	• Paresthesia and dysesthesia are important clinical problems which may negatively affect palliative cancer patients' mobility and hence their quality of life; • Patients may feel bothersome with paresthesia and dysesthesia induced by chemotherapy; • Electroacupuncture protocol can be standardized. Some existing evidence demonstrate that it is helpful for relieving these symptoms, while the effect of vitamin B6 is uncertain; • It is not easy to quantify paresthesia and dysesthesia as these symptoms are very subjective.	• Patient-reported outcome measures for paresthesia and dysesthesia
4) Is adding manual acupuncture on top of exercise more effective in reducing fatigue among palliative cancer adult patients?	• Fatigue is a distressing symptom among cancer patients, affecting both physical and mental health. It also brings negative impacts on their quality of life; • The combination of manual acupuncture and exercise may be a cost-effective treatment option for fatigue; • CHM may be more effective in tonifying qi and reducing fatigue when compared to manual acupuncture; • There is growing research evidence supporting the use of manual acupuncture for managing fatigue, but more research is needed to explore the physiological response induced by acupuncture on fatigue, as well as the effectiveness of combining acupuncture with Tai Chi or Qigong in relieving fatigue.	• Brief Fatigue Inventory (BFI)[52] • Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)[89] • Multidimensional Fatigue Inventory (MFI)[53]

5) Is acupressure provided by Chinese medicine practitioners more effective than self-acupressure in improving insomnia among palliative cancer adult patients receiving chemotherapy?	• Insomnia is a common symptom among palliative cancer patients and it causes poor quality of life; • Empowering patients and caregivers to practice acupressure would increase autonomy and independence, it is interesting to explore the differences between acupressure provided by Chinese medicine practitioners and self-acupressure; • As it is important to locate the acupoint accurately, it would be better to provide acupressure delivered by Chinese medicine practitioners; • If we are going to conduct a clinical trial to address this research question in the future, identical acupoints should be used between the two groups. Besides, we need to consider the number of acupressure training sessions and the types of teaching methods for patients or caregivers, etc.	• Pittsburgh Sleep Quality Index (PSQI)[55] • Self-reported sleep quality[90] • Patient-reported hours of sleep
6) Is adding manual acupuncture on top of conventional care more effective in reducing anxiety among palliative cancer adult patients?	• Anxiety exists as a primary and secondary manifestation in cancer palliative care. Chronic anxiety adversely impacts quality of life and affects patients' response to pain and discomfort; • Manual acupuncture may relieve anxiety by regulating emotional changes through neuromodulation and the combined use of acupuncture and conventional care may preclude the need for anti-anxiety agents; • Existing systematic reviews have shown that manual acupuncture would improve anxiety in noncancer population, further research should be conducted to explore the effectiveness of acupuncture among cancer patients.	• Beck Anxiety Inventory (BAI)[54] • Hospital Anxiety and Depression Scale (HADS)[54] • State Trait Anxiety Inventory (STAI)[54]
Intervention: Chinese herbal medicine (CHM)		
7) Is adding CHM[a] on top of conventional care (glycerin suppositories/lactulose syrup) more effective in reducing constipation among palliative cancer adult patients?	• Opioids received by the vast majority of palliative cancer patients for pain relief may cause constipation, so effective management of constipation is important; • Regular bowel movements is integral to well-being, using CHM plus conventional care may reduce patients' constipation, hence pose positive impacts on their quality of life and sense of well-being; • Many cancer patients have Spleen Qi deficiency syndrome after receiving chemotherapy or surgery, and some might have Qi stagnation or Yin deficiency. CHM that addresses these three issues might be helpful; • The CHM decoction must be mild, promoting gentle bowel movement; otherwise, it would be unsuitable for certain palliative cancer patients; • Syndrome differentiation is recommended when prescribing CHM for patients and herb-drug interaction should be considered, future studies may need to define the type of constipation among patients who should be considered for CHM treatment.	• Bristol Stool Form Scale[91] • Complete spontaneous bowel movement (CSBM)[92] • Feeling of complete evacuation[92]

(*Continued*)

Table 3
Continued

Research Questions	Qualitative Comments From Delphi Rounds 1 and 2	Suggested Outcome Measures
8) Is adding CHM[b] on top of conventional care (blood transfusion/erythropoiesis-stimulating agents [e.g., epoetin]) more effective in improving anemia among palliative cancer adult patients?	• Anemia is an important clinical problem among palliative cancer patients as there is no effective conventional therapy except blood transfusion; • CHM might help improve hematopoiesis; • Owing to the general shortage of suitable blood supply (in China) and risk associated with blood transfusions, it is important to investigate the add-on effect of CHM for anemia; • More clinical trials should be conducted to examine the use of CHM, especially the suggested CHM formula, for managing anemia. Herb-drug interaction should also be considered.	• Hemoglobin count[93] • Red blood cell (RBC) count[93] • Complete blood count (CBC)[93]

CHM = Chinese herbal medicine.
[a]Details of CHM: a) Panax ginseng C. A. Mey. [Ren Shen人參], Astragalus mongholicus Bunge [Huang Qi黃芪], Atractylodes macrocephala Koidz. [Bai Zhu白術], Magnolia officinalis Rehder & E.H.Wilson [Cortex Magnoliae Officinalis厚朴], Citrus aurantium L. [Zhi shi枳實], Rheum palmatum L. [Da huang大黃], Paeonia lactiflora Pall. [Bai Shao白芍], Codonopsis pilosula (Franch.) Nannf. [Dang Shen黨參], Cornus officinalis Siebold & Zucc. [Shan Zhu Yu山茱萸]; b) Chengqi decoction [承氣湯類], Apricot Seed & Linum Formula [Ma Zi Ren Wan麻子仁丸].
[b]Details of CHM: a) Adjusted Angelicae Sinensis Decoction for Supplementing Blood [當歸補血湯加減]; b) Adjusted Shiquan Dabu Decoction [十全大補湯加減 (Astragalus mongholicus Bunge [Huang Qi黃芪]), Panax ginseng C. A. Mey. [Ren Shen人參], Angelica sinensis (Oliv.) Diels [Dang Gui當歸], Paeonia lactiflora Pall. [Bai Shao白芍], Atractylodes macrocephala Koidz. [Bai Zhu白術], Cibotium barometz (L.) J.Sm. [Gou Qi枸杞], Colla Corii Asini [E Jiao阿膠], Glycyrrhiza uralensis Fisch. ex DC. [Zhi Gan Cao炙甘草], Salvia miltiorrhiza Bunge [Dan Shen丹參], Panax notoginseng (Burkill) F.H.Chen [San Qi三七])].

translated to research themes under the NIHR funding schemes.

For instance, Marie Curie, one of the largest charitable funders of palliative and end-of-life care research in the U.K.,[72] has been using the list of priorities generated from the JLA PSP process to inform their call for funding since 2015.[73] Marie Curie also made use of the PSP priorities for designing themes of a research conference in 2016.[73] To maximize the impact of our current findings, we will need to engage patients and funding bodies via a formal process like the JLA PSP.[70] Given the varying values and expectations from patients across different health systems, it is likely that such process would be localized and tailored by each funding body.

Pros and Cons of Prioritizing Research Based on Consensus-Based Method

Prioritizing research funding in areas with expert consensus reduces research waste,[74] and channels limited funding to research which will strengthen the evidence base where important gaps exist in current clinical practice.[75,76] Nonetheless, our approach has a limited scope, of which we solely focused on CHM as well as acupuncture and related therapies. In addition, gaps were identified from existing overviews of SRs[14–16] and SRs.[17,18] We may have missed promising other Chinese medicine interventions, and those not examined by previous SRs. For instance, a recent SR suggested that Tai chi appears to be effective in managing fatigue and improving sleep quality among cancer patients.[77] However, such finding was not included in the present study due to scope limitations. Research priorities should be updated regularly with increasingly wider scope,[74] so as to reduce the unexpected consequence of overlooking novel research questions with high potential in priority settings.[78]

Barriers to Conducting Clinical Palliative Care Research on Chinese Medicine

It is noteworthy that ethical concerns and methodological challenges are the main obstacles for conducting clinical research in palliative care.[79] Performing research in vulnerable population increases difficulties in obtaining informed consent, hence the sample size of palliative care research is usually small.[80,81] In addition, gatekeeping from ethics committee members and frontline health care professionals on the suitability of research in palliative care settings also hampers patients from participating.[80,81] Despite these concerns, a previous study indicated that patients receiving palliative care valued the opportunity to participate in research, and they regarded participation as a contribution to future patient care, even at end of life.[82] To address these barriers, it is important to involve patients and caregivers in the

ethical judgment of trial appropriateness in palliative care settings.[80,83]

On the methodological challenges, high attrition rate and missing data usually lead to insufficient sample size in palliative care research.[79] Fostering international collaborations for multicenter trials would be a key strategy for increasing sample sizes.[80] Besides, acceptability for cancer patients and physicians toward randomization and heterogeneous interventions may increase the difficulties of conducting randomized controlled trials,[79] so patient preference clinical trials might be considered.[79] In such a trial, patients with a preference for a treatment are given the opportunity to select from at least two interventions, which are then compared.[84] This type of trial is favorable, particularly when blinding of interventions is difficult.[84] For instance, this may be applied in the evaluation of CHM as it is hard to design a placebo CHM decoction that resembles the smell, taste, and color of the real CHM decoction.[85] However, a larger sample size may be needed to conduct this type of trial when many patients show the same preference.[84]

Strengths and Limitations

The experts who participated in this study were from Asia, North America, Australia, and Europe, with diversified perspectives originating from variations in health care system organization, availability of interventions, and cultural acceptability of Chinese medicine. The wide geographical coverage has ensured the international generalizability of our results.[19]

Nonetheless, because this study focused on clinical research questions identified from existing overviews of SRs[14–16] and SRs,[17,18] the scope of research priorities generated from this Delphi survey might be limited to those that have been previously evaluated. Potential research questions focusing on other Chinese medicine interventions, such as Qigong and Tuina,[86] might be included in future Delphi surveys for research priority setting.

Conclusions

We identified a list of eight Chinese medicine clinical research priorities for cancer palliative care from an international perspective via a two-round Delphi survey. This provides the research community as well as funders with insights on how scarce clinical research funding can be rationally allocated for assessing the effectiveness of Chinese medicine, particularly on acupuncture and related therapies. Research on herb safety and herb-drug interactions appears to be a prerequisite for launching international trials on CHM.

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Appendix

Appendix I

List of Research Questions Without Consensus in the Two-Round Delphi Survey

Research Questions	Delphi Round 1			Delphi Round 2		
	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)
Intervention: acupuncture and related therapies						
1) Is adding manual acupuncture on top of systemic opioids more effective in reducing dyspnea among palliative cancer adult patients?	6.0 (2.00)	41.7	No	5.0 (2.00)	41.7	No
2) Is adding manual acupuncture on top of orexigenic agents[b] more effective in reducing anorexia among palliative cancer adult patients?	6.5 (4.75)	50.0	No	6.5 (3.00)	50.0	No
3) Is adding electroacupuncture on top of neurokinin-1 receptor antagonists + serotonin-3 receptor antagonist (HT3) and/or dexamethasone more effective in reducing nausea and vomiting, as well as improving quality of life among palliative cancer adult patients?	6.5 (3.00)	50.0	No	5.5 (3.50)	41.7	No
4) Is adding manual acupuncture on top of neurokinin-1 receptor antagonists + serotonin-3 receptor antagonist (5-HT3) and/or dexamethasone more effective in reducing nausea and vomiting, as well as improving quality of life among palliative cancer adult patients?	6.5 (3.75)	50.0	No	7.0 (3.00)	66.7	No
5) Is adding manual acupuncture on top of conventional care (SSRI [antidepressants]/ clonidine/Effexor/gabapentin/hormone therapy/paroxetine [Brisdelle]) more effective in reducing hot flashes among palliative cancer adult patients?	6.5 (2.00)	50.0	No	6.5 (2.00)	50.0	No
6) Is adding manual acupuncture on top of manual lymphatic drainage more effective in reducing lymphedema among palliative cancer adult patients?	7.0 (1.75)	58.3	No	6.5 (1.75)	50.0	No
7) Is adding moxibustion on top of exercise more effective in reducing fatigue among palliative cancer adult patients?	5.0 (2.75)	24.9	No	5.0 (1.00)	8.3	No
8) Is manual acupuncture more effective than sham acupuncture in improving quality of life and reducing hot flashes among palliative cancer adult patients?	6.0 (4.75)	25.0	No	6.0 (4.25)	41.7	No
9) Is TENS more effective than sham TENS in reducing pain among palliative cancer adult patients?	4.0 (3.75)	8.3	No	3.5 (3.75)	0.0	No
10) Is acupressure more effective than sham acupressure in improving insomnia among palliative cancer adult patients undergoing chemotherapy?	6.5 (3.50)	50.0	No	N/A[c]		

(*Continued*)

Appendix I
Continued

Research Questions	Delphi Round 1			Delphi Round 2		
	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)	Median (IQR)	Agreement (%)	Consensus[a] (Yes/No)
Intervention: Chinese herbal medicine (CHM)						
11) Is using CHM effective in improving quality of life among palliative cancer adult patients receiving chemotherapy?	7.0 (2.75)	58.3	No	7.0 (3.00)	58.3	No
12) Is adding CHM on top of orexigenic agents[b] more effective in reducing anorexia among palliative cancer adult patients?	6.0 (4.75)	33.3	No	6.5 (3.50)	50.0	No
13) Is using CHM on top of progesterone analogs effective in reducing anorexia among palliative cancer adult patients receiving chemotherapy?	4.5 (5.50)	41.7	No	4.5 (4.75)	41.7	No
14) Is adding CHM on top of conventional care (granulocyte colony-stimulating factor [G-CSF]/granulocyte macrophage colony-stimulating factor [GM-CSF]/interleukin 3 [IL3]) more effective in improving leukopenia among palliative cancer adult patients?	6.0 (3.00)	41.7	No	6.5 (2.00)	50.0	No
15) Is adding CHM on top of conventional care (interleukin 3 [IL3]/platelet transfusion) more effective in improving thrombocytopenia among palliative cancer adult patients?	6.0 (2.75)	41.7	No	6.0 (1.75)	41.7	No
16) Is adding CHM on top of conventional care (compression bandaging and manual lymphatic drainage) more effective in reducing limbs edema among palliative cancer adult patients?	5.5 (3.75)	41.7	No	5.0 (2.75)	33.3	No
17) Is adding CHM on top of conventional care more effective in improving brain function, cognitive performance, and memory loss among palliative cancer patients with malignant brain tumors?	6.5 (4.75)	50.0	No	6.5 (1.75)	50.0	No
18) Is adding CHM on top of loperamide more effective in reducing diarrhea and stomatitis among palliative cancer adult patients?	6.5 (3.50)	50.0	No	N/A[c]		
19) Is adding CHM on top of loperamide more effective in reducing diarrhea among palliative cancer adult patients?	N/A[d]			7.0 (3.00)	58.3	No
20) Is adding CHM on top of loperamide more effective in reducing stomatitis among palliative cancer adult patients?	N/A[d]			5.5 (4.75)	41.7	No
Intervention: acupuncture and related therapies plus CHM						
21) Is adding moxibustion on top of CHM more effective in improving quality of life among palliative cancer adult patients?	5.0 (2.75)	25.0	No	4.0 (1.75)	16.7	No

IQR = interquartile range; N/A = not applicable; TENS = transcutaneous electrical nerve stimulation; CHM = Chinese herbal medicine.
[a]The cutoff level of consensus in this study was set at 75%.
[b]In Canada, practitioners are able to select from a variety of pharmaceutical agents: corticosteroid (short term)/progestational agents (e.g., megestrol acetate)/metoclopramide (for nausea and vomiting)/omega 3 (less common)/Dronabinol (less common).
[c]Not applicable since the research question was revised and not included in Round 2 Delphi survey.
[d]Not applicable since the research question was newly added in Round 2 Delphi survey.

Appendix II

Qualitative Comments and Suggested Outcome Measures of the Research Questions Without Consensus in the Two-Round Delphi Survey

Research Questions	Qualitative Comments in Delphi Rounds 1 and 2	Suggested Outcome Measures
Intervention: acupuncture and related therapies		
1) Is adding manual acupuncture on top of systemic opioids more effective in reducing dyspnea among palliative cancer adult patients?	• The acceptability of manual acupuncture for reducing dyspnea is uncertain; • Manual acupuncture is not suitable for reducing all kinds of dyspnea; • Dyspnea is a very distressing symptom for patients; • Manual acupuncture may modulate the autonomic nervous system but its effectiveness in reducing dyspnea is uncertain.	• Pulmonary function test • Change in dose of opioids • Quality of life
2) Is adding manual acupuncture on top of orexigenic agents[a] more effective in reducing anorexia among palliative cancer adult patients?	• It is important to compare the effectiveness of manual acupuncture with orexigenic agents in reducing anorexia, instead of the add-on effect of acupuncture, among palliative cancer adult patients; • Currently, pharmacological treatments are not so effective in reducing anorexia and manual acupuncture is commonly used; • Manual acupuncture is useful to address the side effects of orexigenic agents.	• Change in appetite • Change in weight
3) Is adding electroacupuncture on top of neurokinin-1 receptor antagonists + serotonin-3 receptor antagonist (5-HT3) and/or dexamethasone more effective in reducing nausea and vomiting, as well as improving quality of life among palliative cancer adult patients?	• Targeting the right emetic receptor with commonly used medications can usually manage nausea and vomiting; • Long-term use of dexamethasone is detrimental to immune function, muscle, and cortisol; • Nausea and vomiting significantly impact quality of life; • The current antiemetics can better control the gastrointestinal tract to reduce vomiting, and electroacupuncture has no obvious advantage when compared with antiemetic.	• Complete response to vomiting—no emesis or use of rescue medication[1] • Four-point Likert scale (0, no symptoms; 3, severe) on nausea and anorexia[1] • European Organization for Research and Treatment of Cancer QLQ-C30 version 3 questionnaire for measuring quality of life[1]
4) Is adding manual acupuncture on top of neurokinin-1 receptor antagonists + serotonin-3 receptor antagonist (5-HT3) and/or dexamethasone more effective in reducing nausea and vomiting, as well as improving quality of life among palliative cancer adult patients?	• The combined approach of manual acupuncture and antiemetics can be used when nausea and vomiting is not well controlled; • Manual acupuncture would require manipulation and it is difficult to standardize across different practitioners; • The current antiemetics can better manage nausea and vomiting, and manual acupuncture has no obvious advantage when compared with antiemetic; • Quality of life is concerned among palliative cancer patients and any modalities should be tried.	• Complete response to vomiting—no emesis or use of rescue medication[1] • Four-point Likert scale (0, no symptoms; 3, severe) on nausea and anorexia[1] • European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30[1]
5) Is adding manual acupuncture on top of conventional care (SSRI [antidepressants]/clonidine/Effexor/gabapentin/hormone therapy/paroxetine [Brisdelle]) more effective in reducing hot flashes among palliative cancer adult patients?	• This is an important research question as vasomotor symptoms, for example, hot flashes, can be extremely distressing for patients receiving cancer treatments; • Hot flashes negatively impact quality of life; • Antidepressants have myriad side effects and perhaps the dosage could be markedly decreased when combined with acupuncture.	• Hot flashes score at the end of treatment[2] • Hot flashes composite score (HFCS)[3] • Greene Climacteric and Menopause Quality of Life Scale[2]
6) Is adding manual acupuncture on top of manual lymphatic drainage more effective in reducing lymphedema among palliative cancer adult patients?	• Lymphedema is difficult to manage, and it might bring potential complications;	• Circumferential measurement (CM) • Bioelectrical impedance spectrometry (BIS) • Diagnostic ultrasound (US)

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Appendix II
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Research Questions	Qualitative Comments in Delphi Rounds 1 and 2	Suggested Outcome Measures
	• Cancer-related lymphedema is not easy to quantify, so it might not be easy to conduct research on this research question; • There might be secondary infection and ulcerations among palliative cancer patients with lymphedema undergoing manual acupuncture.	
7) Is adding moxibustion on top of exercise more effective in reducing fatigue among palliative cancer adult patients?	• Moxibustion can produce smoke particulates and may negatively affect patients' health conditions; • The dose and quality of moxa are main concerns when performing moxibustion; • Moxibustion may improve immune function among palliative cancer patients.	• Brief Fatigue Inventory (BFI)[4] • Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Scale[5] • Multidimensional Assessment of Fatigue (MAF) Scale[6]
8) Is manual acupuncture more effective than sham acupuncture in improving quality of life and reducing hot flashes among palliative cancer adult patients?	• Hot flashes and quality of life are important clinical issue among palliative cancer patients; • There are uncertainties that manual acupuncture is more effective than sham acupuncture in improving quality of life and reducing hot flashes; • Sham control is ethically problematic and it should not be performed.	• Hot flashes score at the end of treatment[2] • Hot flashes composite score (HFCS)[3] • Greene Climacteric and Menopause Quality of Life Scale[2]
9) Is TENS more effective than sham TENS in reducing pain among palliative cancer adult patients?	• Sham TENS may be easily identified by the participants; • It is more difficult to develop appropriate sham control as insomnia is a psychiatric symptom that might be relieved by sham control; • The use of manual acupuncture is preferred over TENS for pain relief.	• McGill Pain Questionnaire[7] • Visual Analogue Scale for measuring pain intensity[7] • Numerical Rating Scale for measuring pain intensity[7]
10) Is acupressure more effective than sham acupressure in improving insomnia among palliative cancer adult patients undergoing chemotherapy?	Qualitative comments in Round 1[b]: • Sham acupressure is not good for cancer patients and it is more difficult to developing appropriate sham control; • From patients' perspective, the self-acupressure may be easy to use intervention and worth to test the efficacy; • Insomnia is an important issue among palliative cancer patients.	Suggested outcome measures in Round 1[b]: • Pittsburgh Sleep Quality Index (PSQI)[8]
Intervention: Chinese herbal medicine (CHM)		
11) Is using CHM effective in improving quality of life among palliative cancer adult patients receiving chemotherapy?	• Compositions of CHM are big safety issue especially when combining with chemotherapy, so herb-drug interaction should be considered; • Quality of life is ravaged by chemotherapy; • The severity of cancer should be considered as some patients cannot swallow or digest CHM well.	• Short-Form 36 Health Survey Questionnaire (SF-36)[9] • European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30[10] • World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF)[11]
12) Is adding CHM on top of orexigenic agents[a] more effective in reducing anorexia among palliative cancer adult patients?	• Current orexigenic agents are not particularly effective, so it would be good to have interventions which show improvement in anorexia; • CHM can effectively improve loss of appetite; • It might not be easy for palliative cancer patients with anorexia to take CHM.	• Change in appetite • Change in weight

13) Is using CHM on top of progesterone analogs effective in reducing anorexia among palliative cancer adult patients receiving chemotherapy?	• Progesterone analogs should not be used as the weight gain is water but not lean body mass; • Compositions of CHM are big safety issue in combination with chemotherapy and progesterone analogs, so it is necessary to investigate the cross-interactions between the pharmaceutical treatments before examining the effect of this complex intervention; • Palliative cancer patients with anorexia may not be able to take CHM.	• Change in appetite • Change in weight
14) Is adding CHM on top of conventional care (granulocyte colony-stimulating factor [G-CSF]/granulocyte macrophage colony stimulating factor [GM-CSF]/interleukin 3 [IL3]) more effective in improving leukopenia among palliative cancer adult patients?	• G-CSF is not suitable for all cancer patients; • Herb-drug interaction should be considered; • The effectiveness of CHM for improving leukopenia among palliative cancer adult patients is doubted.	• Change in neutrophil counts • Change in total white blood cell count • Common Terminology Criteria for Adverse Events[12]
15) Is adding CHM on top of conventional care (interleukin 3 [IL3]/platelet transfusion) more effective in improving thrombocytopenia among palliative cancer adult patients?	• There is no effective pharmacological therapy for chemotherapy-induced thrombocytopenia so far; • Thrombocytopenia is a significant clinical concern among palliative cancer patients; • Herb-drug interaction should be considered.	• Change in hematologic indices • Complete blood count (CBC)[13] • Common Terminology Criteria for Adverse Events[12]
16) Is adding CHM on top of conventional care (compression bandaging and manual lymphatic drainage) more effective in reducing limbs edema among palliative cancer adult patients?	• Limbs edema is a common problem among palliative cancer patients; however, compression bandaging and manual lymphatic drainage only offer some relief; • The use of compression bandaging is usually very difficult for most patients to manage alone; • Manual acupuncture should be investigated over CHM for managing limbs edema.	• Patient-reported outcome measures for limbs edema
17) Is adding CHM on top of conventional care more effective in improving brain function, cognitive performance, and memory loss among palliative cancer patients with malignant brain tumors?	• Neurodegeneration problem is less considered among palliative cancer patients; • The safety of CHM should be considered and whether the CHM can pass the blood-brain barrier; • Conventional care, for example, dexamethasone, might bring significant side effects with personality changes, violence, and distress on patients, so it would be helpful to have other modalities to improve their cognitive function.	• No suggestion was provided by experts.
18) Is adding CHM on top of loperamide more effective in reducing diarrhea and stomatitis among palliative cancer adult patients?	Qualitative comments in Round 1[b]: • The research question should be rephrased to two new research questions which targeted specifically to the addition of CHM on top of loperamide for diarrhea and stomatitis, respectively; Diarrhea and stomatitis are distressing symptoms among palliative cancer patients.	Suggested outcome measures in Round 1[b]: For diarrhea: number of bowel movements per day
19) Is adding CHM on top of loperamide more effective in reducing diarrhea among palliative cancer adult patients?	• Loperamide is effective in relieving diarrhea; • Herb-drug interaction remains a major concern; • Manual acupuncture should be investigated over CHM for managing diarrhea.	• Gastrointestinal Symptom Rating Scale (GSRS)[14] • Patient-reported outcomes for change in frequency and volume of diarrhea
20) Is adding CHM on top of loperamide more effective in reducing stomatitis among palliative cancer adult patients?	• Patients experiencing stomatitis may not tolerate CHM; • Conventional therapies are usually not effective for stomatitis;	• No suggestion was provided by experts.

(*Continued*)

Appendix II
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Research Questions	Qualitative Comments in Delphi Rounds 1 and 2	Suggested Outcome Measures
	• Syndrome differentiation is recommended for prescribing CHM for patients with stomatitis and the cause/pathology of the stomatitis should be considered.	
Intervention: acupuncture and related therapies plus CHM 21) Is adding moxibustion on top of CHM more effective in improving quality of life among palliative cancer adult patients?	• Moxibustion increases concerns over ventilation of smoke particulates in hospital settings and patients' health conditions; • It might be difficult to monitor the dose and quality of moxa; • Safety of CHM is an important issue in palliative cancer care.	• European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30[10] • World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF)[11] • Functional Assessment of Cancer Therapy–General (FACT-G)[15]

CHM = Chinese herbal medicine.
[a]In Canada, practitioners are able to select from a variety of pharmaceutical agents: corticosteroid (short-term)/progestational agents (e.g., megestrol acetate)/metoclopramide (for nausea and vomiting)/omega 3 (less common)/Dronabinol (les common).
[b]The research question was revised and not included in Round 2 Delphi survey.

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