# Evidence-based Guidelines for Lung Cancer Palliation

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Department of Health Research
Directorate General of Health Services

**Ministry of Health and Family Welfare**

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# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| **6MWD** | 6 - Minute Walking Distance |
| **6MWD** | 6 - Minute Walking Distance |
| **ALB** | Albumin |
| **ALK** | Anaplastic Lymphoma Kinase |
| **BMI** | Body Mass Index |
| **CBT** | Cognitive Behavioural Theory |
| **CNS** | Central Nervous System |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CPET** | Cardiopulmonary exercise testing |
| **CPT** | Chest Physical Therapy |
| **CRT** | Conventional resistance training |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EGFR** | Epidermal Growth Factor Receptor |
| **EORTC** | European Organization for Research and Treatment of Cancer |
| **ERAS** | Enhanced Recovery After Surgery |
| **FACT G** | Functional Assessment of Cancer Therapy – General |
| **FACT L** | Functional Assessment of Cancer Therapy – Lung |
| **FEV** | Forced Expiratory Volume |
| **FVC** | Forced Vital Capacity |
| **GDG** | Guideline Development Group |
| **GOLD** | Global Initiative for Chronic Obstructive Lung Disease |
| **GRADE** | Grading of Recommendations, Assessment, Development and Evaluations |
| **HADS A** | Hospital Anxiety and Depression Scale - Anxiety |
| **HADS D** | Hospital Anxiety and Depression Scale - Depression |
| **HIIT** | High-Intensity Interval Training |
| **IARC** | International Agency for Research on Cancer |
| **ICER** | Incremental Cost-Effectiveness Ratio |
| **IMT** | Inspiratory Muscle Training |
| **IPT** | Intensive Physical Therapy |

| | |
|---|---|
| **LMIC** | Low- and Middle-Income Countries |
| **MCID** | Minimal Clinically Important Difference |
| **MDASI** | M. D. Anderson Symptom Inventory |
| **MID** | Minimal Important Difference |
| **NPR** | Non-Pulmonary Rehabilitation |
| **NSCLC** | Non-Small Cell Lung Cancer |
| **OMD** | Oligometastatic Disease |
| **PEF** | Peak Expiratory Flow |
| **PET** | Positron Emission Tomography |
| **PFS** | Progression Free Survival |
| **PFT** | Pulmonary Functional Tests |
| **PHET** | Preoperative Home-based Exercise Training |
| **PHQ** | Patient Health Questionnaire |
| **PICO** | Population, Intervention, Comparison, Outcome |
| **PPC** | Postoperative Pulmonary Complications |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **PROSE** | Patient-Reported Outcomes and Symptoms |
| **PRP** | Pulmonary rehabilitation programme |
| **QALY** | Quality-Adjusted Life Year |
| **QLQ** | Quality of Life Questionnaire |
| **QOL** | Quality of Life |
| **RECIST** | Response Evaluation Criteria in Solid Tumors |
| **RMET** | Respiratory Muscle Endurance Training |
| **ROB** | Risk of Bias |
| **SMD** | Standardized Mean Difference |
| **TOI** | Trial Outcome Index |

# EXECUTIVE SUMMARY

**Background & Rationale:**

Lung cancer remains a major global health burden, ranking among the leading causes of cancer-related mortality and profoundly affecting patient quality of life and healthcare systems. According to the latest Global Burden of Disease (GBD) estimates, lung malignancies contribute disproportionately to cancer deaths worldwide, in both high-income and resource-limited settings. Palliative care plays an indispensable role in alleviating physical symptoms, addressing psychosocial distress, and upholding patient dignity. Although interventions, such as advanced symptom management, early integration of psychosocial support, and multidisciplinary care pathways have enhanced comfort and well-being, many patients still endure significant physical and emotional burdens that require systematic, evidence-based attention. This guideline seeks to synthesize the current evidence base and provide methodologically sound recommendations for the palliative management of lung cancer.

**Target Audience:**

These guidelines are designed to inform a wide range of stakeholders, including policy makers, clinical practitioners specializing in palliative care, program managers, and health care administrators. The primary clinical audience comprises oncologists, pulmonologists, thoracic surgeons, radiation oncologists, psychologists, and members of multidisciplinary oncology teams at secondary and tertiary care hospitals, dealing with palliative care. Academic researchers and implementation scientists engaged in translational studies and clinical trials will benefit from the consolidated review of current best practices as well as the identification of key research gaps and prioritized questions to guide future studies.

**Guideline Development Method:**

The guideline was developed using standard methodology as described by international agencies like the WHO and NICE. This involved the creation of a steering group, a guideline development group and systematic review teams. Briefly, the process involved: (i) Identifying priority review questions (PICOs), (ii) Evidence synthesis by systematic review & meta-analysis, (iii) Review of evidence profiles and grading the certainty of evidence (iv) Formulation of recommendations using the Evidence to Decision (EtD) framework (v) Drafting the guideline (vi) External review and (vii) Dissemination of guidelines. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the certainty of evidence for each review question. The evidence generated was analyzed by the GDG to make judgments and formulate recommendations based on the EtD Framework in the GRADEpro GDT software. This included assessment of the effects (benefits to harms ratio) of the intervention, values and preferences of the patients, resource required, cost effectiveness, acceptability, feasibility of intervention and equity considerations. In brief, the GDG members examined the evidence made judgements on the EtD framework for each disease condition and formulated the wording of the final recommendations. This was followed by external peer review before the final release of guidelines.

## Summary of Recommendations

| Key Question | Recommendation | Rationale/Justification |
|---|---|---|
| **For patients with lung cancer, does early integration of palliative care with standard oncological care compared to standard oncological care alone, improve patient outcomes?** | Early integration of palliative care with standard oncological care is **_recommended_** as compared to standard oncological care alone for patients with lung cancer.<br><br>Strength: Strong<br><br>Certainty of evidence: Very low | The evidence showed moderate desirable effects, along with acceptability, feasibility, and cost-effectiveness probably favouring the early integration of palliative care. Despite very low certainty of evidence, the panel judged that the benefits clearly outweigh minimal harms. Given strong patient values and preferences for early supportive care, a strong recommendation was issued, while recognizing the need to address moderate resource requirements and potential equity concerns during implementation. |
| **In patients with advanced lung cancer experiencing dyspnoea, how effective is multimodal treatment interventions compared to drug therapy alone in terms of improvement in dyspnoea?** | Multi-modal treatment is **_recommended_** as compared to drug therapy alone for treatment of dyspnoea in patients with advanced lung cancer.<br><br>Strength: Strong<br><br>Certainty of evidence: Very low | The evidence showed moderate desirable effects with negligible additional costs, and cost-effectiveness probably favouring the use of multimodal interventions. The panel judged that the benefits outweigh minimal harms, supporting a strong recommendation. |
| **For patients with newly diagnosed lung cancer, how efficacious is multi-modal approach to managing the symptom-cluster of insomnia, fatigue and depression, compare with psycho-social/ psychotherapeutic care alone?** | Multimodal Approach of treatment is **_recommended_** in comparison to treatment with Psychotherapeutic Care alone for patients with lung cancer.<br><br>Strength: Strong<br><br>Certainty of Evidence: Very low | The evidence showed moderate desirable effects with trivial harms, alongside acceptability, feasibility, and cost-effectiveness probably favouring multimodal approach in managing the symptom cluster. The anticipated benefits outweigh potential downsides, supporting a strong recommendation. |

# GUIDELINE DEVELOPMENT PROCESS

## Introduction:

A new process has been established in the MoHFW wherein one comprehensive evidence-based guideline has been jointly developed by DoHFW, DGHS and DHR using a rigorous and robust scientific process to bring clarity among stakeholders i.e. patients, clinicians, and the society in general. The generation of such evidence included collation of evidence from SR and MA of existing literature on well-defined review questions (PICOs). Finally, the evidence obtained from SR & MA was graded for its certainty using the GRADE Approach. This grading was done to assess the certainty of evidence and formulate recommendations using the EtD framework. Such rigorously developed evidence-based guidelines have the potential to address the research to policy gap by translating the best available evidence of any healthcare intervention into practice (Figure 1).

### Steps of Guideline development



**Figure 1:** Guideline Development Process - Adopted from NICE, WHO

## Rationale/Scope:

Lung cancer often progresses rapidly to advanced stages, leaving patients with high symptom burden and a critical need for timely palliative support. There is a need to establish standardized guidance to enable consistent, effective, patient-centered and evidence-based palliative care across all levels of the health system. Realizing that therapeutic applications need to be based on rational and ethical premises, these guidelines aim to summarize the evidence available on the efficacy of lung cancer palliative care to guide informed decisions.

These guidelines aim to promote the responsible, safe, equitable, and effective delivery of lung cancer palliative care.

## Contributors:

The following groups contributed to the development of guidelines (List Annexure 1):

## Steering Group:

This group was jointly chaired by the Secretary, DHR & DG, ICMR and DGHS in overseeing the entire process of guideline development. The steering group identified priority disease conditions, helped in the formulation of GDG, reviewed the declaration of interest of members, reviewed the draft guidelines and managed the guideline publication and dissemination.

## Guideline Development Group:

This group was constituted to formulate review questions relevant for the guidelines for conducting systematic reviews for addressing the question, decide on the critical outcomes and formulate recommendations based upon evidence generated by the systematic review teams. It is a multi-disciplinary group composed of methodologists, medical oncologists, surgical oncologists, radiation oncologists, health economist, person with lived experience as well as patient group representatives. Potential members of the GDG were identified and approved by the Steering Group based on requisite technical skills and diverse perspectives needed for the formulation of the guidelines. These members were free from any conflict of interest in order to formulate unbiased recommendations. The subject experts and methodologists provided critical inputs on the formulation of review questions in the PICO format. After completion of the systematic reviews, the evidence profiles were reviewed by the DHR secretariat and guideline methodologists with the help of subject matter experts. Finally, the GDG examined and interpreted the whole body of evidence and made judgements in the meeting using GRADEpro EtD framework.

## Systematic Review Teams:

These teams were commissioned to review and evaluate all available evidence in the form of randomized controlled trials (RCTs). The certainty of this evidence was assessed by the established GRADE criteria on the basis of risk of bias, imprecision, inconsistency, indirectness and publication bias.

## External Reviewers:

Relevant subject experts were identified to review the final guideline document and comment upon the clarity of the recommendations, validity of the justification provided for each recommendation and the completeness of evidence.

## DHR Secretariat:

The DHR Secretariat provided overall technical, methodological, and administrative coordination throughout the guideline development process. The Secretariat facilitated the establishment and functioning of the Guideline Development Group (GDG), and Systematic Review teams; coordinated meetings and communications among all stakeholder groups; and ensured adherence to the approved guideline development methodology and timelines. The Secretariat also monitored conduct of the systematic review process to ensure fidelity to approved protocols and internationally accepted reporting and methodological standards which included verification of PICO alignment, eligibility criteria, search strategy validation, duplicate screening and data-

extraction processes, prespecified statistical and sensitivity analyses, risk-of-bias assessments, and complete audit trails for protocols, amendments, correspondence, datasets, analysis scripts and final outputs. The Secretariat conducted a structured technical review of the evidence profiles received from the systematic review teams, verified the appropriate application of the GRADE and Evidence to Decision (EtD) frameworks in collaboration with guideline methodologists, and ensured systematic documentation of decisions at each stage of the guideline development process. The Secretariat also monitored timelines and key milestones, maintained and managed declarations of interest and conflicts (including procedures for their identification, management, and documentation), coordinated external and independent methodological peer review, and supported the finalisation of guideline recommendations.

## Declaration of Interests:

Conflicts of interest (COIs) do not automatically preclude participation in guideline development, but they must be identified, transparently disclosed, and actively managed to minimise bias. A COI is any set of circumstances that creates a risk that professional judgement about a primary interest could be unduly influenced by a secondary interest; secondary interests may be financial or non-financial and include any interest that could be affected by a guideline recommendation. All potential GDG members completed a Declaration of Interests form adapted from WHO[1], and these declarations were reviewed by the Steering Group and managed appropriately. A summary of the Declaration of Interests (DoIs) and how they were managed is provided in Annexure.

## Defining the Scope and Key Questions:

The Steering Group convened to define the full scope of the lung cancer guidelines, covering the entire continuum of care, from prevention and screening to diagnosis, treatment, and palliative care. Based on these priorities, the Guideline Development Group (GDG) formulated a total of 30 PICO-formatted review questions to guide the evidence synthesis process. These included 4 questions on prevention, 3 on screening, 8 on diagnosis, 12 on treatment, and 3 on palliation. Each question was developed with careful consideration of the Population, Intervention, Comparator, and Outcomes, ensuring alignment with the most pressing clinical and public health needs. The GDG emphasized relevance to patient priorities and feasibility within the Indian healthcare context, laying the foundation for evidence-based and context-specific recommendations.

## Systematic Reviews:

Commissioning of Systematic Reviews: Once the review questions were identified, the ICMR-DHR secretariat floated an Expression of Interest inviting experts in the field from all over the country to conduct systematic reviews and meta-analysis. Out of a total of 152 applications received, 30 teams were selected. Criteria for evaluation included methodology expertise, subject expertise, quality of systematic reviews published, database access, strength of team and conflict of interests, if any. The systematic reviews in PICO format as finalized by the GDG. All the teams were provided with the methods provided oversight, including technical assessment and feedback on each systematic review protocol. The data extraction was checked to ensure uniformity and transparency in the entire process of guideline development.

## Literature Search Strategy:

To maintain a uniform methodology, all the systematic review teams were instructed to design literature searches on the following databases: PubMed, Embase, Scopus, and Cochrane CENTRAL. Only randomized controlled trials were included in the systematic reviews of treatment and palliation related reviews. No grey literature was included. However, hand-searching of references of relevant review articles was done. Non-English articles were excluded only if translation was not possible. Subgroup analyses (if mentioned apriori in the protocol) was done wherever needed.

In addition, few criteria precluded the trial from being included in the final body of evidence in the evidence to decision framework. They were as follows:

- Flawed process of random sequence generation and/or concealment of allocation
- More than 30% deviated from allocated intervention post-randomization

Therefore, the systematic review teams were asked to do a meta-analysis excluding such trials and the evidence produced thereafter was presented to the GDG.

## Data Extraction Methods:

Data extraction was conducted by the systematic review teams and reviewed by the ICMR-DHR secretariat and the methodologists. The teams were advised to use plot digitizer wherever feasible, if values were not available in text. Imputations and assumptions were best to be avoided. All methodological queries were resolved with the help of guideline methodologists and the teams were also advised to refer to the *Cochrane Handbook for Systematic Reviews of Interventions* to resolve any methodological queries[2]. While doing meta-analysis, the use of standardized mean difference (SMD) was to be minimized, as it is easier to compare mean difference (MD) with the minimal clinically important difference (MCID).

## Risk of Bias Assessment:

Risk of bias for each study outcome was assessed using the Revised Cochrane Risk of Bias-2 tool. For assessment, the following terms of reference were agreed upon by the GDG and provided to all the systematic review teams:

- Use only the ROB-2 Tool for assessment of the risk of bias of RCTs and mention the reasons for the risk of bias judgments for all the domains of the ROB-2 Tool.
- The downgrading of evidence due to the risk of bias judgment should be decided by the following criteria:
  i. If ≥ 2/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as not serious in the GRADE Table.
  ii. If 1/3rd–2/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as serious in the GRADE Table.
  iii. If < 1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as very serious in the GRADE Table.

The teams were asked to review the RCTs with extreme results in the pooled analysis cautiously, to search for any major methodological discrepancy.

The progress of the systematic review teams was monitored monthly and queries were resolved by the secretariat after discussion with the methodologists.

**Determination of Minimal Clinically Important Difference (MCID):**

The minimal clinically important difference (MCID) is defined as the smallest change in any outcome that is considered as clinically meaningful or important by the patient and the health care providers. It is the difference at which a large set of clinicians will be willing to change their practice for this benefit and the certainty of evidence is rated in relation to this threshold.

In this guideline, the GDG determined the MCID for each critical outcome based on their clinical expertise and the expected impact of the intervention. This included considerations such as the potential for meaningful improvement in patient outcomes, the relevance and magnitude of benefit, and whether the anticipated change would influence treatment decisions. The certainty of evidence for each outcome was assessed in relation to the established MCID thresholds, ensuring that recommendations were both evidence-based and clinically significant.

**Grading of the Certainty of the Evidence:**

The GRADE approach was used to assess the certainty of evidence using the GRADEpro GDT software (https://www.gradepro.org/). At baseline RCTs start with high certainty of evidence and this certainty can be downgraded based on pre-defined criteria like the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Publication bias was evaluated using funnel plots if the number of studies for a particular meta-analysis was more than 10. If the studies were less than 10, Egger's test was used for evaluation. The systematic review teams completed their reviews and shared the evidence profiles with the guideline secretariat. The secretariat then reviewed the evidence profiles, with the help of guideline methodologist and any discrepancies in the review were resolved through discussion with the systematic review teams. The table below highlights the significance of the certainty of evidence as per GRADE[3]:

| Certainty level | Significance |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| Very Low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

**Drafting of Recommendations using Evidence to Decision Frameworks:**

The DHR secretariat prepared the draft EtD frameworks. The EtD Framework available on the GRADEpro GDT software was used to draft recommendations. It consists of a set of criteria that determine the strength and direction of a recommendation to bring about transparency in the formulation of recommendations. These criteria include the certainty of evidence, the balance

between benefits and harms, the acceptability and feasibility of the intervention, patient values and preferences, equity considerations, resource use and cost effectiveness. Prior to drafting recommendations, all the GDG members were apprised of this framework and every criterion was explained in detail. The secretariat presented these frameworks along with a review of evidence profile and forest plots provided by the systematic review teams to the GDG.

## Formulation of Recommendations:

The GDG members were asked to make judgments on each of the domain of the EtD framework based on the evidence presented to them. Judgments on the desirable and undesirable effects were made on the basis of the systematic reviews and meta-analysis. Review of literature/research evidence as well as the experience of the GDG members was used to inform the discussion. Patient values and preferences, resource use and cost effectiveness, acceptability and feasibility of the intervention along with equity considerations. Wherever research evidence unavailable, the option of the GDG was recorded in additional considerations. The entire body of evidence was put into the GRADE EtD framework for drafting the final recommendation for each review question.

Detailed deliberations and the rationale for each judgment were recorded explicitly in the "Additional Considerations" column of GRADEpro GDT using the PanelVoice feature to ensure transparency. Voting was convened only when differences of opinion arose, with each domain discussed thoroughly until consensus (≥75% agreement) was achieved. Following domain-level resolution, a final vote determined the strength and direction of each recommendation. Throughout this process, the GDG also identified evidence gaps and highlighted priority areas for future research.
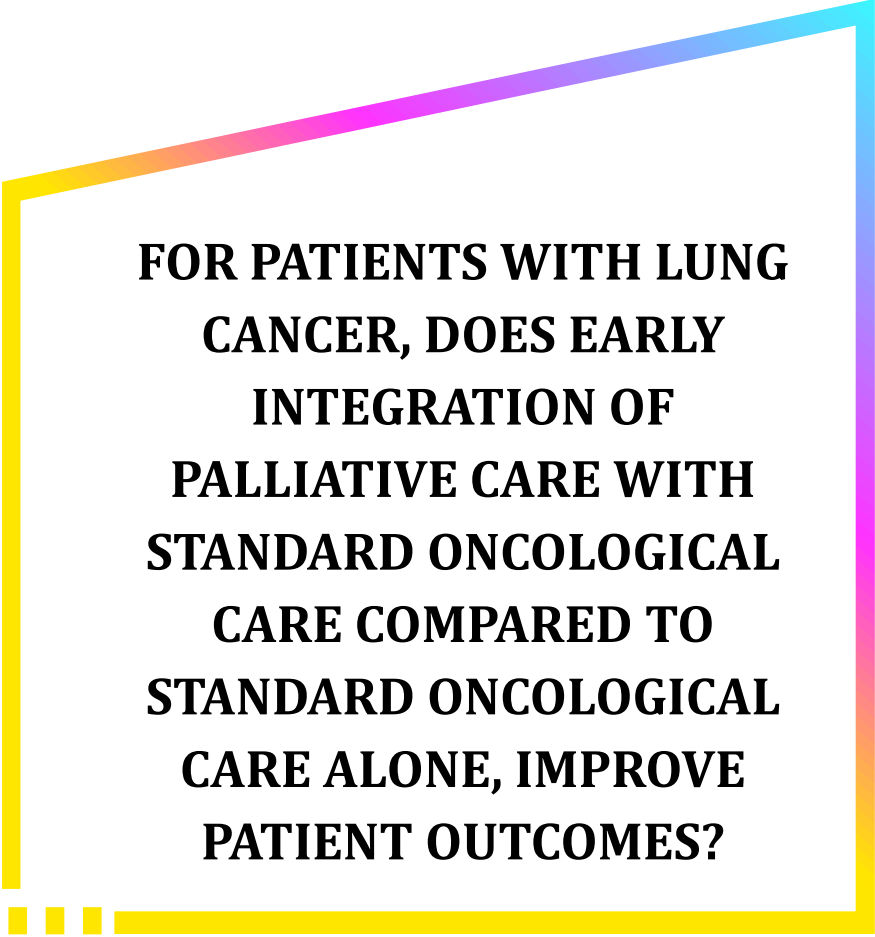
## Strength of Recommendations:

The strength of each recommendation reflects the GDG's confidence in the balance between an intervention's benefits and harms for the intended patient population, as well as considerations of resource use, equity, feasibility, and acceptability[4]. When the GDG was highly confident that desirable effects clearly outweighed undesirable effects and that the intervention was affordable, equitable, feasible, and acceptable, a strong recommendation was issued. Conversely, if uncertainty remained around the balance of benefits and harms, or if concerns arose regarding costs, implementation feasibility, equity, or stakeholder acceptability, a conditional recommendation was made. Conditional recommendations signal that clinicians should tailor decisions to individual patient circumstances, preferences, and local context.

## Document Preparation and Peer Review:

After the completion of the ETD meetings, the ICMR-DHR secretariat prepared a draft of the guideline document to accurately reflect the deliberations and decisions taken by the GDG. This draft was reviewed by the guideline methodologists followed by the external review group. The external reviewers were requested to comment upon the clarity of the recommendations so that there is no ambiguity about the decision among the end-users, validity of the justification provided for each recommendation, accuracy and completeness of the evidence (randomized controlled trials only). The steering group carefully evaluated the input of the GDG members and the comments by the external reviewers. Revisions to the draft document were done as needed, to correct for any factual errors and the document was finalized, thereafter.

# REFERENCES

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# FOR PATIENTS WITH LUNG CANCER, DOES EARLY INTEGRATION OF PALLIATIVE CARE WITH STANDARD ONCOLOGICAL CARE COMPARED TO STANDARD ONCOLOGICAL CARE ALONE, IMPROVE PATIENT OUTCOMES?

## Background

Palliative care is one of the treatment modalities for cancer treatment. It is applicable throughout the cancer continuum from diagnosis to end of life. Most often, it is initiated once curative treatment isn't feasible or death is anticipated. The advantages of early palliative care (EPC) referral are timely assessment and treatment of physical and psychological symptoms, effective coping, improved communication and support for decision making and discussion of end-of-life preferences. Lung cancer is the most common cancer worldwide. It often presents in advanced and metastatic stages and is associated with significant symptoms like pain, dyspnoea, fatigue, and anorexia. Early palliative care in solid cancers has been shown to enhance the quality of life and symptom burden based on several randomised trials. The trials are heterogeneous, involving advanced incurable cancers across sites (head and neck, gastrointestinal and lung), with some showing benefit while others showing no impact of palliative care.

A meta-analysis on EPC among all cancers by Gautama et al. showed improved quality of life but no effect on mood or symptom control with palliative care. The trials have combined the outcomes for many or all cancers, and hence, it is difficult to estimate the effect of palliative care on individual cancers, particularly lung cancer. Temel et al. was the earliest randomised trial showing the benefit of palliative care in improving symptom control, mood and quality of life. This systematic review and meta-analysis aimed to comprehensively review all available evidence that has examined the effect of early integration of palliative care with standard oncological care compared to standard oncological care alone for lung cancer patients on symptom control, quality of life and survival. The secondary outcomes are to compare documented advance care plans, aggressive interventions in the last month of life and the cost of palliative care and oncological care with oncological care alone.

## Recommendations

Early integration of palliative care with standard oncological care is ___**recommended**___ as compared to standard oncological care alone for patients with lung cancer

**Strength:** Strong
**Certainty of evidence:** Very low

## Rationale/Justification

The evidence showed moderate desirable effects, along with acceptability, feasibility, and cost-effectiveness probably favouring the early integration of palliative care. Despite very low certainty of evidence, the panel judged that the benefits clearly outweigh minimal harms. Given strong patient values and preferences for early supportive care, a strong recommendation was issued, while recognizing the need to address moderate resource requirements and potential equity concerns during implementation.

**Key Question**

For patients with lung cancer, does early integration of palliative care with standard oncological care compared to standard oncological care alone, improve patient outcomes?

**Included Studies**

A total of 3273 records from electronic databases were identified till date. Of the 3273 articles, 741 duplicate articles were removed. Further 2467 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 13 articles. After application of inclusion and exclusion criteria, 7 articles were selected for systematic review.

**Population and Study Characteristics**

All the studies included patients diagnosed with lung cancer. The review includes adults of all ages and gender. Eligible studies are those that evaluate the effect of early integration of palliative care with standard oncological care compared to standard oncological care alone, in improving patient outcomes.

Subgroups:

    a. Stage (Early-stage vs Advanced Stage)
    b. Age
    c. Comorbidities
    d. Symptoms

Eligible studies reported on at least one of the following treatment outcomes:

1. Symptom burden control (7 studies)
2. Quality of life (7 studies)
3. Overall survival (3 studies)
4. Documented advance care-plan (2 studies)
5. Aggressive interventions in last month of patients' life [emergency visits/ ICU utilization/oncological intervention] (No studies)
6. Cost (one study)

**Intervention**

Standard oncological care with early integration of palliative care

*Subgroup*: 1. Within 8 weeks of diagnosis of lung cancer vs later

       2. Various components of palliative care

**Comparator**

Standard oncological care without early integration of palliative care patients undergoing treatment for lung cancer.

**Outcome**

Different outcomes were evaluated and included the following critical and important outcomes:

1. Symptom burden control (*Critical outcome*)
2. Quality of life (*Critical outcome*)
3. Overall survival (*Critical outcome*)
4. Documented advance care-plan (*Important outcome*)
5. Aggressive interventions in last month of patients' life [emergency visits/ ICU utilization/oncological intervention] (*Important outcome*)
6. Cost (*Important outcome*)

**Duration of Follow up**

**Critical Outcome reviewed and their MCID**

| Sr. No | Critical outcome reviewed | What does it measure | MCID decided by GDG |
|---|---|---|---|
| 1 | Overall Survival | OS (Proportion of people who have survived at a particular time point) | 10% at any point of time |
| | | OS (Proportion increase in median survival) | 3 months for advanced stage 6 months for early stage |
| 2 | Symptom burden control | Difference in mean symptom score between intervention and standard of care | 20% |
| 3 | Quality of Life | Quality of life (difference in the mean scores of QoL) | FACT L: 10% difference FACT G: 10% difference EORTC QLQ 30: 10% difference |

**PICO provided by GDG**

| Framework | Description |
|---|---|
| Population | Patients with lung cancer<br>Subgroups:<br>     1. Stage (Early-stage vs Advanced stage)<br>     2. Age<br>     3. Comorbidities<br>     4. Symptoms |
| Intervention | Standard oncological care with early integration of palliative care<br>***Subgroup***: 1. within 8 weeks of diagnosis of lung cancer vs later<br>          2. Various components of palliative care |
| Comparator | Standard oncological care without early integration of palliative care |
| Outcome | Symptom burden control (*Critical outcome*)<br>Quality of life (*Critical outcome*)<br>Overall survival (*Critical outcome*)<br>Documented advance care-plan (*Important outcome*)<br>Aggressive interventions in last month of patients' life [emergency visits/ ICU utilization/oncological intervention] (*Important outcome*)<br>Cost (*Important outcome*) |

## Risk of Bias Assessment

### Symptom Burden Control

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Temel et al 2010 | - | + | - | - | + | - |
| Temel et al 2017 | + | - | + | - | + | - |
| Krug et al 2021 | + | + | + | - | + | - |
| Reinke et al 2022 | + | + | + | - | X | X |
| Chen et al 2023 | - | + | X | - | + | X |
| Dutta et al 2024 | X | + | X | X | + | X |
| Allende et al 2024 | - | + | X | X | + | X |

### Quality of life

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Temel et al 2010 | - | + | - | - | + | - |
| Temel et al 2017 | + | - | + | - | + | - |
| Krug et al 2021 | + | + | + | - | + | - |
| Reinke et al 2022 | + | + | + | - | X | X |
| Chen et al 2023 | - | + | X | - | + | X |
| Dutta et al 2024 | X | + | X | X | + | X |
| Allende et al 2024 | - | + | X | X | + | X |

### Overall Survival

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Temel et al 2010 | - | + | + | + | + | - |
| Chen et al 2023 | - | + | - | + | + | - |
| Allende et al 2024 | - | + | + | + | + | - |

### Documented Advance Care-Plan

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Temel et al 2010 | - | + | + | + | + | - |
| Reinke et al 2022 | + | + | + | + | + | + |

### Cost

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Temel et al 2010 and Greer et al 2012 | - | + | + | + | + | - |

| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

| | |
|---|---|
| + | Low risk |
| - | Some concerns |
| X | High risk |

**Desirable Effects**

**1. Symptom Burden**

1.1 HADS Anxiety

Evidence shows no statistically significant or clinically meaningful difference between integrated palliative care and cancer care alone for HADS Anxiety. The analysis of studies comparing early integration of palliative care along with standard of care versus standard oncological care alone yielded a mean difference of 0.09 lower (95% CI: 2.26 lower to 2.07 higher). Substantial heterogeneity was observed across the studies. The evidence suggests that the addition of palliative care to cancer treatment does not produce a consistent benefit and that variability in study results limits the certainty of the evidence.

**Figure 1.1** - Forest plot: Symptom Burden HADS Anxiety



1.2 HADS Depression

Evidence shows a significant and clinically meaningful benefit of integrating palliative care with cancer treatment in improving the assessed outcome. The analysis of two studies demonstrated a mean difference of 2.01 lower (95% CI: 2.46 lower to 1.56 lower), indicating a substantial reduction in the outcome score in favor of the intervention group. The score ranges from 0 to 14. Higher scores suggest high symptom burden. Higher scores were observed in patients receiving cancer care, suggesting better symptom control with the addition of palliative care.

**Figure 1.2** - Forest plot: Symptom Burden - HADS Depression

## 1.3 Edmonton Symptom Assessment Scale (ESAS)

Evidence shows a significant and clinically meaningful benefit of integrating palliative care with cancer treatment in improving the assessed outcome. The analysis of two studies demonstrated a mean difference of 2.01 lower (95% CI: 2.46 lower to 1.56 lower), indicating a substantial reduction in the outcome score in favor of the intervention group. The score ranges from 0 to 60. Higher scores were observed in patients receiving cancer care, suggesting better symptom control with the addition of palliative care.

**Figure 1.3** - Forest plot: Symptom Burden - ESAS

| Study or Subgroup | PC and Cancer Care Mean | SD | Total | Cancer Care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dutta et al 2024 | 51.84 | 0.01 | 64 | 97.64 | 2.18 | 51 | 100.0% | -45.80 [-46.40, -45.20] |
| Total (95% CI) | | | 64 | | | 51 | 100.0% | -45.80 [-46.40, -45.20] |

Heterogeneity: Not applicable
Test for overall effect: Z = 150.03 (P < 0.00001)

## 1.4 Distress Thermometer (DT)

Evidence shows no statistically significant or clinically meaningful difference between integrated palliative care and cancer care alone for Distress thermometer. The analysis of studies comparing early integration of palliative care along with standard of care versus standard oncological care alone yielded a mean difference of 0.60 lower (95% CI: 1.58 lower to 0.38 higher). The score ranges from 0 to 10. Higher scores suggest high symptom burden. Higher scores were observed in patients receiving cancer care, suggesting better symptom control with the addition of palliative care. This crosses the null line and is not significant.
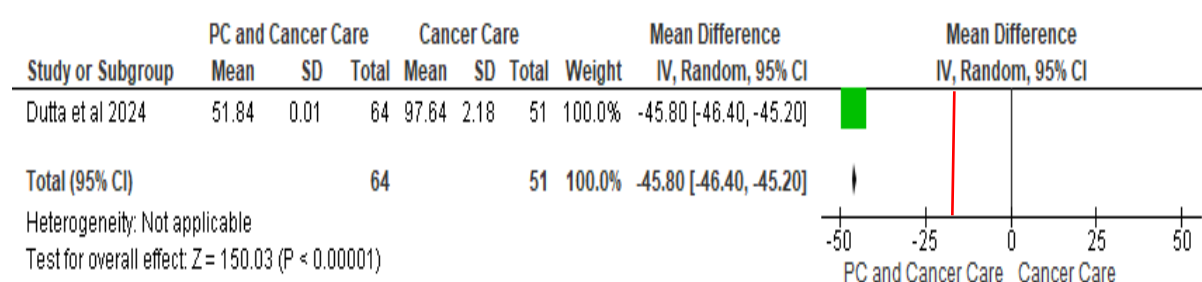
**Figure 1.4** - Forest plot: Symptom Burden - Distress Thermometer

| Study or Subgroup | PC and Cancer Care Mean | SD | Total | Cancer Care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Krug et al 2021 | 4.9 | 2.5 | 51 | 5.5 | 2.4 | 46 | 100.0% | -0.60 [-1.58, 0.38] |
| Total (95% CI) | | | 51 | | | 46 | 100.0% | -0.60 [-1.58, 0.38] |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)

**Quality of Life**

## 1.5 FACT L

Evidence shows a significant and clinically meaningful benefit of integrating palliative care with cancer treatment in improving the assessed outcome. Pooled analysis of three randomized studies showed that integrated palliative and cancer care (intervention) was favoured over cancer care alone, with patients in the intervention group achieving higher outcome scores (mean difference 6.11 points; 95% CI: 3.53 to 8.69).
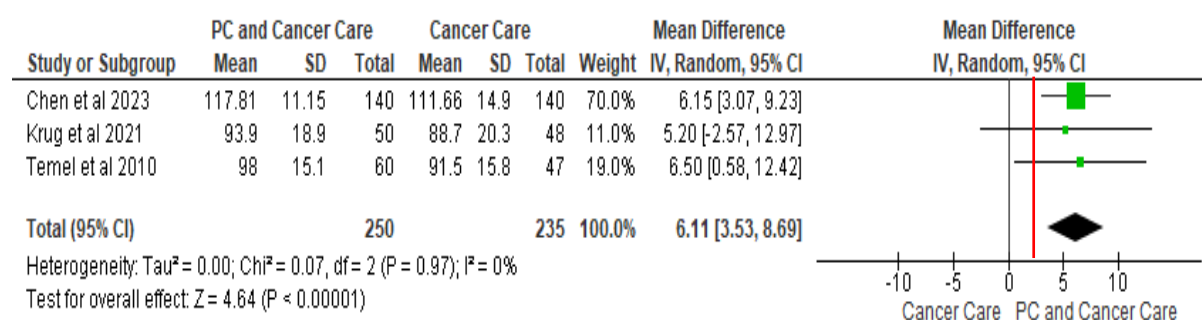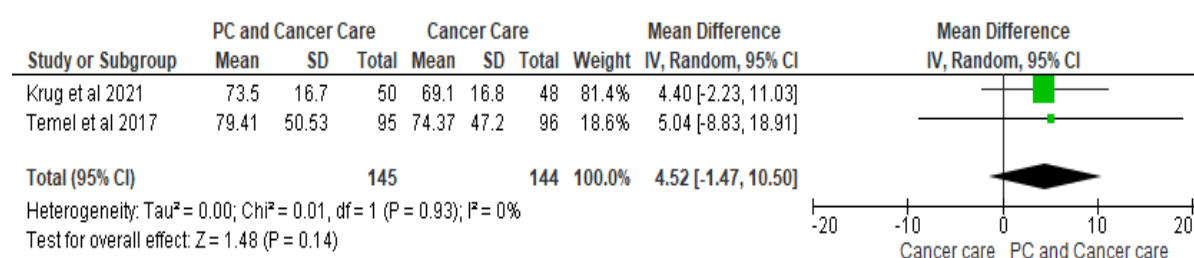
**Figure 1.5** - Forest plot: Symptom Burden - FACT L

| Study or Subgroup | PC and Cancer Care Mean | SD | Total | Cancer Care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chen et al 2023 | 117.81 | 11.15 | 140 | 111.66 | 14.9 | 140 | 70.0% | 6.15 [3.07, 9.23] |
| Krug et al 2021 | 93.9 | 18.9 | 50 | 88.7 | 20.3 | 48 | 11.0% | 5.20 [-2.57, 12.97] |
| Temel et al 2010 | 98 | 15.1 | 60 | 91.5 | 15.8 | 47 | 19.0% | 6.50 [0.58, 12.42] |
| | | | | | | | | |
| Total (95% CI) | | | 250 | | | 235 | 100.0% | 6.11 [3.53, 8.69] |

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 4.64 (P < 0.00001)

## 1.6 FACT G

Evidence shows no statistically significant or clinically meaningful difference between integrated palliative care and cancer care alone for FACT G. The analysis of studies comparing early integration of palliative care along with standard of care versus standard oncological care alone yielded a mean difference of 4.52 higher (95% CI: 1.47 lower to 10.50 higher).

**Figure 1.6** - Forest plot: Symptom Burden - FACT G

| Study or Subgroup | PC and Cancer Care Mean | SD | Total | Cancer Care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Krug et al 2021 | 73.5 | 16.7 | 50 | 69.1 | 16.8 | 48 | 81.4% | 4.40 [-2.23, 11.03] |
| Temel et al 2017 | 79.41 | 50.53 | 95 | 74.37 | 47.2 | 96 | 18.6% | 5.04 [-8.83, 18.91] |
| | | | | | | | | |
| Total (95% CI) | | | 145 | | | 144 | 100.0% | 4.52 [-1.47, 10.50] |

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

## 1.7 Trial Outcome Index (TOI)

Evidence shows a statistically significant benefit of integrating palliative care with cancer treatment in improving patient outcomes. The analysis of studies demonstrated a mean difference of 4.53 higher (95% CI: 2.23 higher to 6.83 higher; p = 0.0001) in favor of the integrated palliation approach, with low heterogeneity across studies. These findings suggest that adding palliative care to standard oncological treatment is consistently associated with improved outcomes.
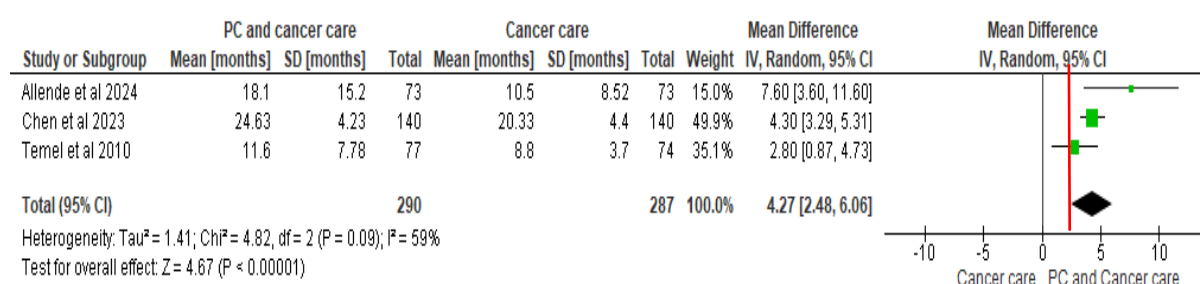
**Figure 1.7** - Forest plot: Trial Outcome Index



## 1.8 Overall Survival

Pooled analysis of three randomized studies (total n = 577) found that adding palliative care to standard cancer treatment produced a statistically significant and clinically important improvement in the outcome: mean difference 4.27 months (95% CI 2.48 to 6.06 months; Z = 4.67, p < 0.00001), favoring the integrated palliative-and-cancer-care arm. All three studies point in the same direction, but there was moderate heterogeneity (Tau$^2$ = 1.41; Chi$^2$ = 4.82, df = 2, p = 0.09; I$^2$ = 59%), so the exact magnitude of benefit varies somewhat between trials.

**Figure 1.8** - Forest plot: Overall Survival



*MCID Line in red (-)

## Undesirable Effects

The evidence did not report any undesirable effects associated with the early integration of palliative care into cancer treatment, and potential harms remain unknown, indicating a need for further research to evaluate unintended consequences.

**Table 1. Summary of Findings**

**Early Integration of Palliative Care along with Standard Oncological Care versus Standard Oncological Care alone**

**Patient or population:** Patients with Lung Cancer

**Intervention:** Palliative care with standard oncological care

**Comparison:** Standard Oncological Care

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative Effect (95% CI) | No. of Participants (Studies) | Certainty of the Evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with standard oncological care alone | Risk with Early integration of Palliative care with standard oncological care | | | | |
| HADS A | Mean score 4.33 | MD **0.09 lower** (2.26 lower to 2.07 higher) | - | 426 (2 RCTs) | ⊕◯◯◯ Very low[a,b,c] | The evidence is very uncertain about the effect of early integration of Palliative care with standard oncological care on HADS A. |
| HADS D | Mean score 5.77 | MD **2.01 lower** (2.46 lower to 1.56 lower) | - | 426 (2 RCTs) | ⊕◯◯◯ Very low[a,d] | Early integration of Palliative care with standard oncological care may reduce HADS D slightly. |
| ESAS | Mean score 97.64 | MD **45.8 lower** (46.4 lower to 45.2 lower) | - | 115 (1 RCT) | ⊕◯◯◯ Very low[a,d,e] | The evidence is very uncertain about the effect of early integration of Palliative care with standard oncological care on ESAS. |
| DT SCORE | Mean score 5.5 | MD **0.6 lower** (1.58 lower to 0.38 higher) | - | 97 (1 RCT) | ⊕⊕◯◯ Low[c,e,f] | Early integration of Palliative care with standard oncological care likely reduces DT SCORE. |
| FACT L | Mean score 97.29 | MD **6.11 higher** (3.53 higher to 8.69 higher) | - | 485 (3 RCTs) | ⊕⊕◯◯ Low[a,d] | Early integration of Palliative care with standard oncological care likely results in a large increase in FACT L. |

| | | | | | | |
|---|---|---|---|---|---|---|
| FACT G | Mean score 71.73 | MD **4.52 higher** (1.47 lower to 10.5 higher) | - | 289 (2 RCTs) | ⊕⊕◯◯ Low[a,c] | Early integration of Palliative care with standard oncological care may increase/have little to no effect on FACT G but the evidence is very uncertain. |
| Quality of life assessed with: TOI | Mean score 58.92 | MD **4.53 higher** (2.23 higher to 6.83 higher) | - | 489 (3 RCTs) | ⊕◯◯◯ Very low[a,d] | Early integration of Palliative care with standard oncological care may increase/have little to no effect on quality of life but the evidence is very uncertain.[a,c] |
| Overall survival | The median overall survival was **13.2** months | MD **4.27 months higher** (2.48 higher to 6.06 higher) | - | 577 (3 RCTs) | ⊕◯◯◯ Very low[a,d] | The evidence suggests early integration of Palliative care with standard oncological care increases overall survival. |

**CI:** Confidence Interval; **HR:** Hazard Ratio; **MD:** Mean Difference; **OR:** Odds Ratio

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Explanations*

a. *The studies included are of high risk. As per the SOP, < 1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), hence the overall risk of bias for this outcome has been downgraded by two level and is labeled as very serious in the GRADE table.*
b. *Heterogeneity is present with I2=96% and P<0.001.*
c. *Downgraded one level for imprecision as the 95% Confidence interval (CI) crosses the null effect line*
d. *Optimal Information size (OIS) is not met.*
e. *Single study was downgraded one level for inconsistency as it was inevaluable*
f. *One study had some concerns in the measurement of the outcome*

| Table 2. Evidence Profile |
| --- |

**Early Integration of Palliative Care along with Standard Oncological Care versus Standard Oncological Care alone**

**Patient or population:** Patients with Lung Cancer

**Intervention:** Palliative care with standard oncological care

**Comparison:** Standard Oncological Care

| Certainty Assessment | | | | | | | No. of Patients | | Effect | | Certainty | Importance |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. of Studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Early Integration of Palliative Care with Standard Oncological Care | Standard Oncological Care Alone | Relative (95% CI) | Absolute (95% CI) | | |
| HADS A | | | | | | | | | | | | |
| 2 | randomised trials | very serious[a] | Serious[b] | not serious | Serious[c] | none | 213 | 213 | - | MD **0.09 lower** (2.26 lower to 2.07 higher) | ⊕○○○ Very low[a,b,c] | CRITICAL |

| HADS D | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | very serious[a] | not serious | not serious | Serious[d] | none | 213 | 213 | - | MD **2.01 lower** (2.46 lower to 1.56 lower) | ⊕◯◯◯ Very low[a,d] | CRITICAL |
| ESAS | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | Serious[e] | not serious | Serious[d] | none | 64 | 51 | - | MD **45.8 lower** (46.4 lower to 45.2 lower) | ⊕◯◯◯ Very low[a,d,e] | CRITICAL |
| DT SCORE | | | | | | | | | | | | |
| 1 | randomised trials | serious[f] | Serious[e] | not serious | Serious[c] | none | 51 | 46 | - | MD **0.6 lower** (1.58 lower to 0.38 higher) | ⊕⊕◯◯ Low[c,e,f] | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **FACT L** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | Serious[d] | none | 250 | 235 | - | MD **6.11 higher** (3.53 higher to 8.69 higher) | ⊕⊕◯◯ Low[a,d] | CRITICAL |
| **FACT G** | | | | | | | | | | | | |
| 2 | randomised trials | Serious[a] | not serious | not serious | Serious[c] | none | 145 | 144 | - | MD **4.52 higher** (1.47 lower to 10.5 higher) | ⊕⊕◯◯ Low[a,c] | CRITICAL |
| **Quality of Life (Assessed with: TOI)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[a] | not serious | not serious | Serious[c] | none | 252 | 237 | - | MD **4.53 higher** (2.23 higher | ⊕◯◯◯ Very low[a,c] | CRITICAL |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | to 6.83 higher) | |
| **Overall Survival** | | | | | | | | | | | |
| 3 | randomis ed trials | very seriou sª | not serious | not serious | Seriousᵈ | none | 290 | 287 | - | MD **4.27 month s higher** (2.48 higher to 6.06 higher) | ⊕◯◯ ◯ very lowª,ᵈ | CRITICAL |

**CI:** Confidence Interval; **MD:** Mean Difference

**Explanations**

a. *The studies included are of high risk. As per the SOP, < 1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), hence the overall risk of bias for this outcome has been downgraded by two level and is labeled as very serious in the GRADE table.*
b. *Heterogeneity is present with I2=96% and P<0.001.*
c. *Downgraded one level for imprecision as the 95% Confidence interval (CI) crosses the null effect line*
d. *Optimal Information size (OIS) is not met.*
e. *Single study was downgraded one level for inconsistency as it was inevaluable*
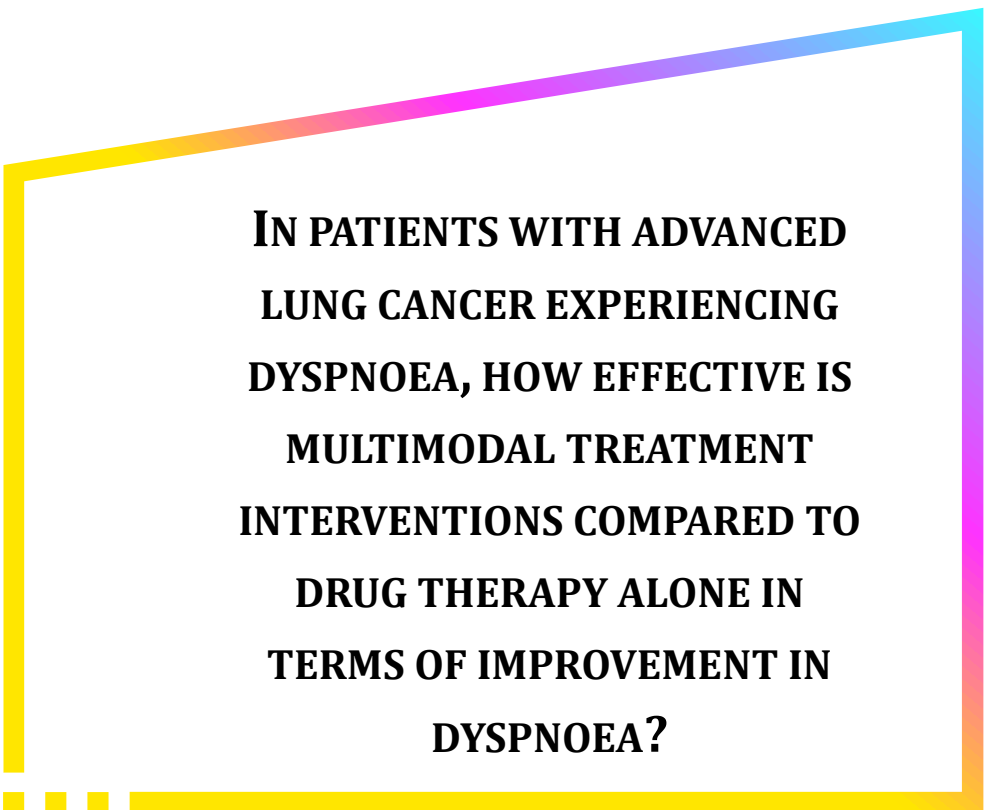f. *One study had some concerns in the measurement of the outcome*

## Summary of Judgements

| | |
|---|---|
| **Problem** | Yes |
| **Desirable Effects** | Moderate |
| **Undesirable Effects** | Don't Know |
| **Certainty of evidence** | Very Low |
| **Values** | No important uncertainty or variability |
| **Balance of effects** | Favors the intervention |
| **Resources required** | Moderate costs |
| **Certainty of evidence of required resources** | Low |
| **Cost effectiveness** | Probably favors the intervention |
| **Equity** | Probably reduced |
| **Acceptability** | Yes |
| **Feasibility** | Yes |
| **Recommendation**: Early integration of palliative care with standard oncological care is _**recommended**_ as compared to standard oncological care alone for patients with lung cancer.<br><br>**Strength**: Strong<br>**Certainty of Evidence**: Very low | |

**RESEARCH PRIORITIES:**

The GDG identified the following priority areas where further evidence is required to address the impact of early integration of palliative care alongside standard oncological care in patients with lung cancer:

- Limited availability of high-quality randomized controlled trials directly comparing early integrated palliative care plus standard oncological care versus standard oncological care alone, particularly with respect to patient-reported outcomes.

- Insufficient evidence on the effect of early palliative care integration on key patient-centred outcomes, including symptom burden, quality of life, psychological distress, and functional status.

- Scarcity of evidence addressing caregiver-related outcomes, including caregiver burden, satisfaction, and psychosocial well-being, in the context of early palliative care integration.

- Paucity of health economic evaluations, including cost-effectiveness and budget impact analyses, comparing early integrated palliative care with standard oncological care alone.

**IN PATIENTS WITH ADVANCED LUNG CANCER EXPERIENCING DYSPNOEA, HOW EFFECTIVE IS MULTIMODAL TREATMENT INTERVENTIONS COMPARED TO DRUG THERAPY ALONE IN TERMS OF IMPROVEMENT IN DYSPNOEA?**

## Background

Dyspnoea, or the subjective experience of breathlessness, is a prevalent (45%) and distressing symptom among patients with advanced lung cancer, significantly impacting their quality of life (Damani et al., 2018). As the disease progresses, the physiological and psychological burden of dyspnoea intensifies, necessitating effective symptom management strategies (Hui et al., 2020). Traditional pharmacological interventions, while beneficial, may not provide adequate relief for all patients and can be accompanied by side effects (Hui et al., 2021). Consequently, there is a growing interest in multimodal interventions that combine pharmacological treatments with non-pharmacological approaches to enhance symptom relief (Zemel et al., 2021).

Multimodal interventions apart from pharmacological treatment may include a variety of strategies such as physical therapies, psychosocial support, breathing exercises, and assistive devices (Hui et al., 2021). These approaches aim to address the complex interplay of physiological, emotional, and social factors that contribute to dyspnoea in this population. For instance, incorporating physical rehabilitation can improve functional capacity and reduce respiratory distress (Jastrzębski et al., 2015, while psychological interventions can alleviate anxiety, which often exacerbates the sensation of breathlessness (Garcia et al., 2012).

Despite the theoretical benefits of multimodal strategies, the effectiveness of these interventions in managing dyspnoea in advanced lung cancer patients remains inadequately assessed. Systematic reviews and meta-analyses can provide valuable insights into the overall efficacy and safety of these interventions by synthesizing data from various studies (Hui et al., 2021). By analysing existing literature, this systematic review aims to evaluate the impact of multimodal interventions on the symptomatic management of dyspnoea in adult patients with advanced lung cancer. The findings could inform clinical practice, guiding healthcare providers in developing comprehensive care plans that address the multifaceted nature of dyspnoea and ultimately improve patient outcomes.

## Recommendations

> Multi-modal treatment is ***recommended*** as compared to drug therapy alone for treatment of dyspnoea in patients with advanced lung cancer.
>
> **Strength**: Strong
> **Certainty of Evidence**: Very low

## Rationale/Justification

The evidence showed moderate desirable effects with negligible additional costs, and cost-effectiveness probably favouring the use of multimodal interventions. The panel judged that the benefits outweigh minimal harms, supporting a strong recommendation.

## Summary of Evidence

**Key Question**

In patients with advanced lung cancer experiencing dyspnoea, how effective is multimodal treatment interventions compared to drug therapy alone in terms of improvement in dyspnoea?

**Included Studies**

A total of 1392 records from electronic databases were identified till date. Of the 1392 articles, 208 duplicate articles were removed. Further 1110 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 72 articles. After application of inclusion and exclusion criteria, 13 articles were selected for systematic review and 12 studies were included in meta-analysis.

**Population and Study Characteristics**

All the studies included patients diagnosed with advanced lung cancer. The review includes adults of all ages and gender. Eligible studies are those that evaluate the effect of multimodal treatment interventions compared to drug therapy in improving dyspnoea.

Eligible studies reported on at least one of the following treatment outcomes:

a) Improvement in dyspnoea (13 studies)
b) Performance status (5 studies)
c) Quality of life (6 studies)
d) Cost (2 studies)

**Intervention:**

**Multi-modal interventions (combination of drug and non-drug**). Drug: (opioids in dose for breathlessness, non-opioid medications (bronchodilators, corticosteroids, other analgesics, anxiolytics, laxatives, crisis medications) Nondrug: position, psycho-social support, vaccination, education on self-management (physical/occupational therapy, energy conservation techniques, hand-held fan)

**Comparator:**

**Drug therapy alone** (opioids in dose for breathlessness, non-opioid medications (bronchodilators, corticosteroids, other analgesics, anxiolytics, laxatives)

**Outcome**

Different outcomes were evaluated and included the following critical and important outcomes:

- e) Improvement in dyspnoea (*Critical outcome*)
- f) Performance status (*Critical outcome*)
- g) Quality of life (*Critical outcome*)
- h) Cost (*Important outcome*)

### Critical Outcome reviewed and their MCID

| Sr. No | Critical outcome reviewed | What does it measure | MCID decided by GDG |
|---|---|---|---|
| 1 | Improvement in dyspnoea | Difference in the mean scores | 20% |
| 2 | Performance status | Difference in mean performance status between intervention and comparator | Difference of 1 point in KPS ECOG: difference of one point higher Reaching the best possible score |
| 3 | Quality of Life | Difference in the mean scores of QoL | 10% |

### PICO

| Framework | Description |
|---|---|
| Population | Adult patients with advanced lung cancer experiencing shortness of breath |
| Intervention | **Multi-modal interventions (combination of drug and non-drug)**. Drug: (opioids in dose for breathlessness, non-opioid medications (bronchodilators, corticosteroids, other analgesics, anxiolytics, laxatives, crisis medications) Nondrug: position, psycho-social support, vaccination, education on self-management (physical/occupational therapy, energy conservation techniques, hand-held fan) |
| Comparator | **Drug therapy alone** (opioids in dose for breathlessness, non-opioid medications (bronchodilators, corticosteroids, other analgesics, anxiolytics, laxatives) |
| Outcome | Improvement in dyspnoea (*critical outcome*) Performance status (*critical outcome*) Quality of life (*Critical outcome*) Cost (*Important outcome*) |

## Risk of Bias Assessment

### Improvement in dyspnea

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Bade et al, 2021 | − | X | − | X | + | X |
| Chan et al, 2011 | − | + | + | + | + | − |
| Farquhar et al, 2014 | + | + | + | + | + | + |
| Fernandez-Rodriguez et al, 2021 | + | + | + | − | + | − |
| Fernandez-Rodriguez et al, 2024 | + | + | + | + | + | + |
| Greer et al, 2024 | + | + | + | + | + | + |
| Hwang et al, 2012 | − | + | − | + | + | − |
| Molassiotis et al, 2015 | − | + | + | − | + | − |
| Molassiotis et al, 2021 | + | − | + | − | + | − |
| Rutkowska et al, 2019 | + | − | X | − | + | X |
| Yates et al, 2020 | + | − | + | − | + | − |
| Yorke et al, 2023 | + | − | X | − | + | X |
| Yorke et al, 2015 | + | − | X | − | + | − |

### Effect on performance

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Fernandez-Rodriguez et al, 2021 | + | − | + | − | + | − |
| Fernandez-Rodriguez et al, 2024 | + | + | + | + | + | + |
| Greer et al, 2024 | + | + | + | + | + | + |
| Rutkowska et al, 2019 | − | + | − | + | − | − |
| Yates et al, 2020 | + | − | + | − | + | − |

### Quality of life

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Bade et al, 2021 | − | − | + | − | + | − |
| Farquhar et al, 2014 | + | + | − | + | + | − |
| Greer et al, 2024 | + | − | − | − | + | − |
| Hwang et al, 2012 | − | − | X | + | + | X |
| Molassiotis et al, 2015 | − | − | + | − | − | − |
| Molassiotis et al, 2021 | − | − | + | − | − | − |

### Cost

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Farquhar et al, 2014 | + | + | + | + | + | + |
| Yorke et al, 2023 | + | − | X | − | + | X |

| | |
|---|---|
| **D1** | Randomisation process |
| **D2** | Deviations from the intended interventions |
| **D3** | Missing outcome data |
| **D4** | Measurement of the outcome |
| **D5** | Selection of the reported result |

| | |
|---|---|
| + | Low risk |
| − | Some concerns |
| X | High risk |

## Desirable Effects

### Improvement in dyspnoea

Evidence shows no significant benefit of use of multi-modal treatment in reducing dyspnoea in advanced lung cancer patients in comparison to drug therapy alone. Multimodal intervention was associated with a non-significant reduction in symptom scores compared to usual care, with a pooled mean difference of 0.40 lower (95% CI: 0.95 lower to 0.14 higher; p = 0.15) based on data from 140 participants across three randomized controlled trials. While one study demonstrated a statistically significant benefit, the overall effect did not meet the threshold for statistical significance, and the presence of substantial heterogeneity ($I^2$ = 83%) warrants cautious interpretation. Multimodal interventions consistently reduced dyspnoea severity across validated scales, including the Numerical Rating Scale (pooled mean difference [MD] = 1.2 lower, 95% CI [1.8 lower, 0.6 lower]), modified Medical Research Council Dyspnoea Scale (MD = 0.33 lower, 95% CI [0.61 lower, 0.05 lower]), and Cancer Dyspnoea Scale discomfort subscale (MD = 0.59 lower, 95% CI [1.16 lower, 0.01 lower]). Nurse-led behavioural interventions (e.g., breathing techniques, posture adjustments, fan therapy) demonstrated statistically and clinically significant improvements, with sustained effects at 12 weeks.

**Figure 1.1 (a):** Forest plot: Improvement in Dyspnoea
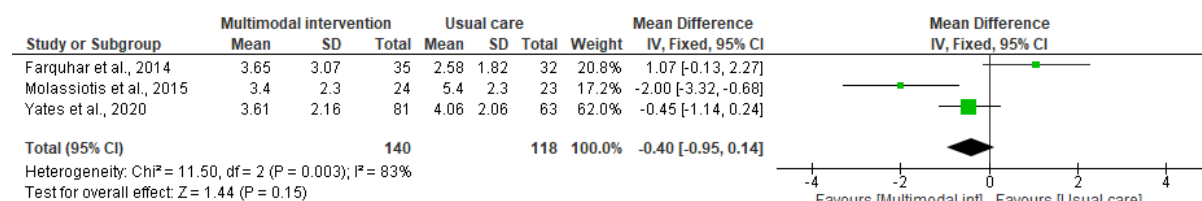
Numerical rating scale (0-10)



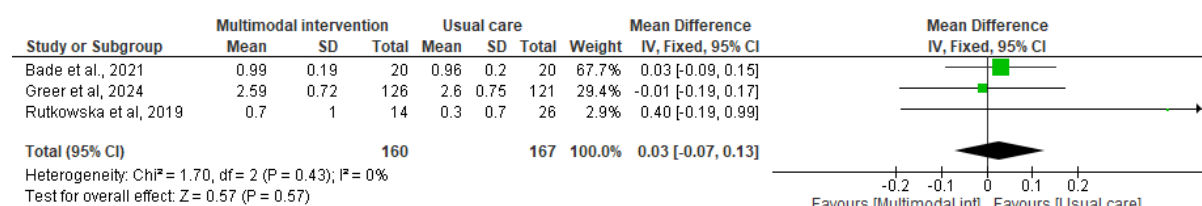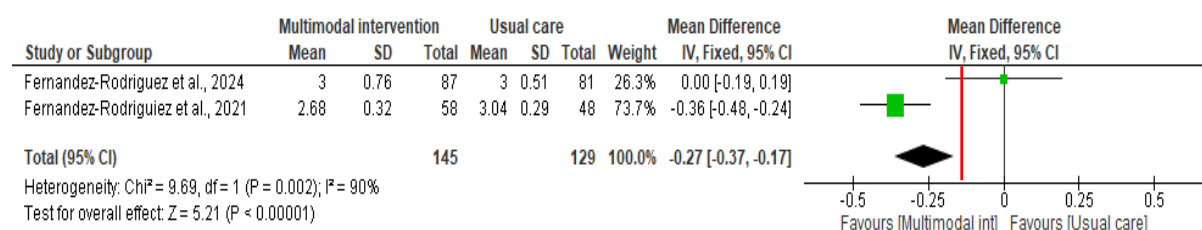**Figure 1.1 (b):** Forest plot: Modified Medical Research Council (mMRC) Scale



**Figure 1.1 (c):** Forest plot: Medical Research Council Dyspnoea Scale (MRC, 1-5)

**Figure 1.1 (d):** Forest plot: Cancer Dyspnoea Scale (CDS)

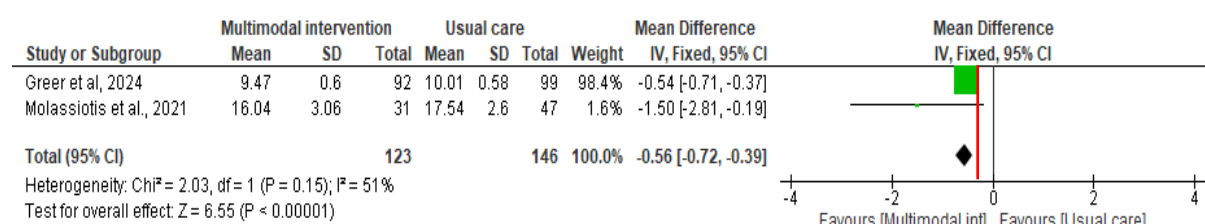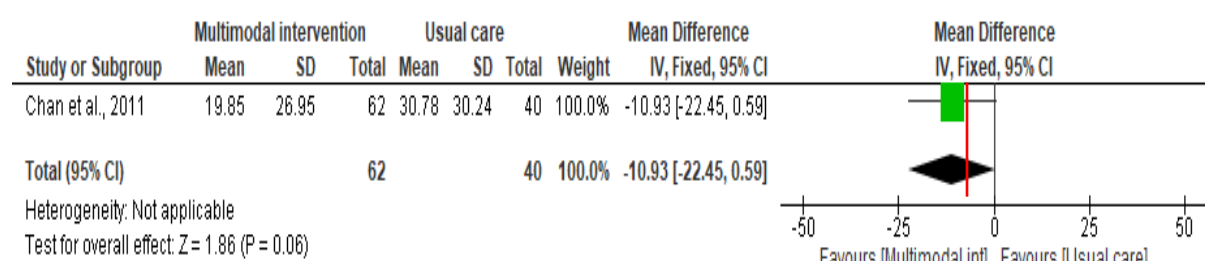| Study or Subgroup | Multimodal intervention Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Greer et al, 2024 | 9.47 | 0.6 | 92 | 10.01 | 0.58 | 99 | 98.4% | -0.54 [-0.71, -0.37] |
| Molassiotis et al., 2021 | 16.04 | 3.06 | 31 | 17.54 | 2.6 | 47 | 1.6% | -1.50 [-2.81, -0.19] |
| Total (95% CI) | | | 123 | | | 146 | 100.0% | -0.56 [-0.72, -0.39] |

Heterogeneity: Chi² = 2.03, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 6.55 (P < 0.00001)



**Figure 1.1 (e):** Forest plot: 100mm visual analogue scale

| Study or Subgroup | Multimodal intervention Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chan et al., 2011 | 19.85 | 26.95 | 62 | 30.78 | 30.24 | 40 | 100.0% | -10.93 [-22.45, 0.59] |
| Total (95% CI) | | | 62 | | | 40 | 100.0% | -10.93 [-22.45, 0.59] |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)

**Figure 1.1 (f):** Forest plot: Dyspnea-12

| Study or Subgroup | Multimodal intervention Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Yorke et al., 2022 | 11.45 | 10.72 | 67 | 14.35 | 10.63 | 87 | 100.0% | -2.90 [-6.30, 0.50] |
| Total (95% CI) | | | 67 | | | 87 | 100.0% | -2.90 [-6.30, 0.50] |

Heterogeneity: Not applicable
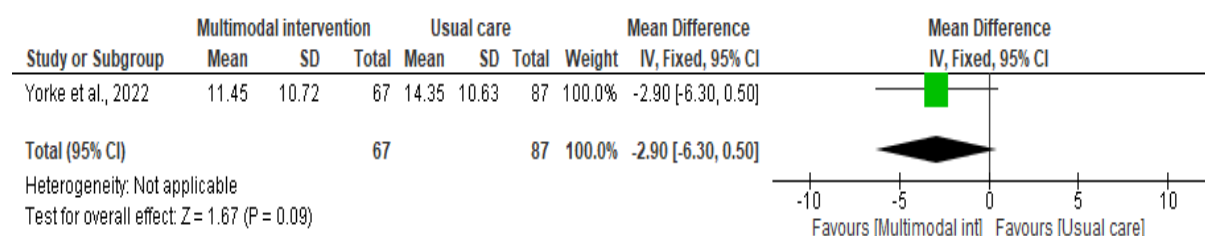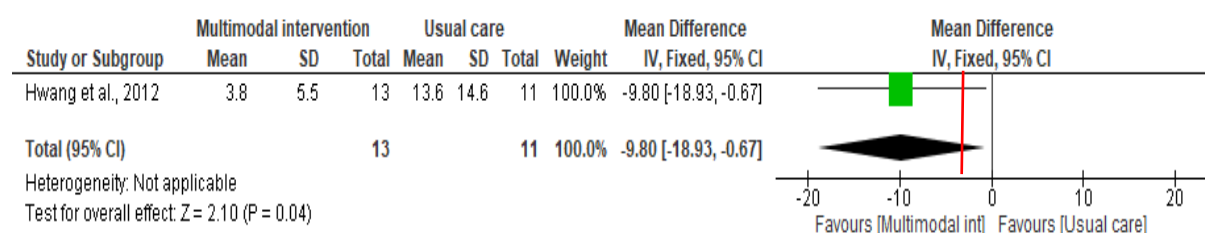Test for overall effect: Z = 1.67 (P = 0.09)



**Figure 1.1 (g):** Forest plot: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-LC-13, Chinese language version) - Dyspnea subscale

| Study or Subgroup | Multimodal intervention Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hwang et al., 2012 | 3.8 | 5.5 | 13 | 13.6 | 14.6 | 11 | 100.0% | -9.80 [-18.93, -0.67] |
| Total (95% CI) | | | 13 | | | 11 | 100.0% | -9.80 [-18.93, -0.67] |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)

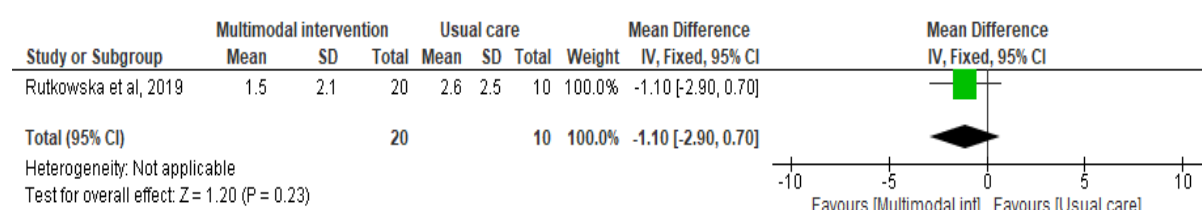**Figure 1.1 (h):** Forest plot: Borg scale



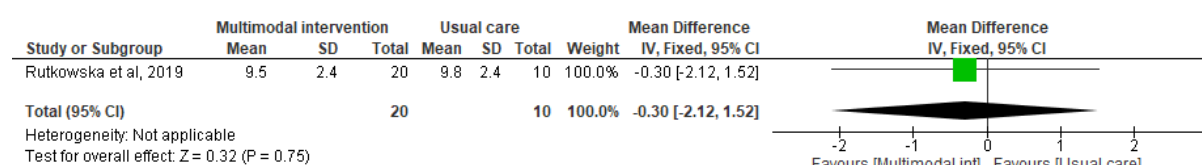**Figure 1.1 (i):** Forest plot: Baseline dyspnoea index
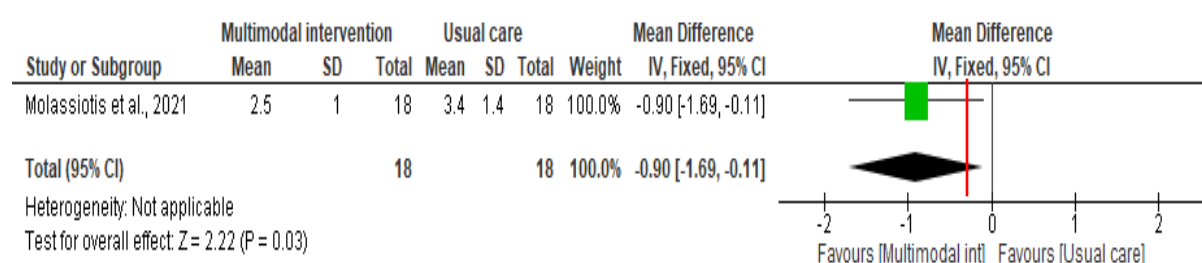


**Figure 1.1 (j):** Forest plot: Modified Borg scale



*(-) Red line shows MCID given by GDG

## Effect on Performance Status

The evidence shows that the 6-minute walk test (6MWT) showed a mean difference of 41 higher (95% CI: 43.98 lower to 125.98 higher), which was not statistically significant (p = 0.34), indicating no clear benefit of multimodal intervention on walking endurance. In contrast, plot for percentage of time immobile in actinography shows a significant reduction in immobility time measured via actigraphy, favoring multimodal intervention with a mean difference of 1.62 higher (95% CI: 1.21 higher to 2.03 higher; p < 0.00001). For the Godin-Shephard questionnaire indicate a modest yet statistically significant improvement in leisure-time physical activity with a mean difference of 0.75 higher (95% CI: 0.62 higher to 0.89 higher; p < 0.00001), albeit with high heterogeneity ($I^2$ = 98%). However, plot 3.2(d) reflects a non-significant difference in physical activity (mean difference = 1.10 higher; 95% CI: 3.29 lower to 5.49 higher; p = 0.62). Furthermore, the evidence demonstrates a strong and statistically significant improvement in functional independence as measured by the Barthel Index (mean difference = 29.92 higher; 95% CI: 16.20 higher to 25.64 higher; p < 0.00001), showcasing the potential of multimodal interventions in enhancing activities of daily living.

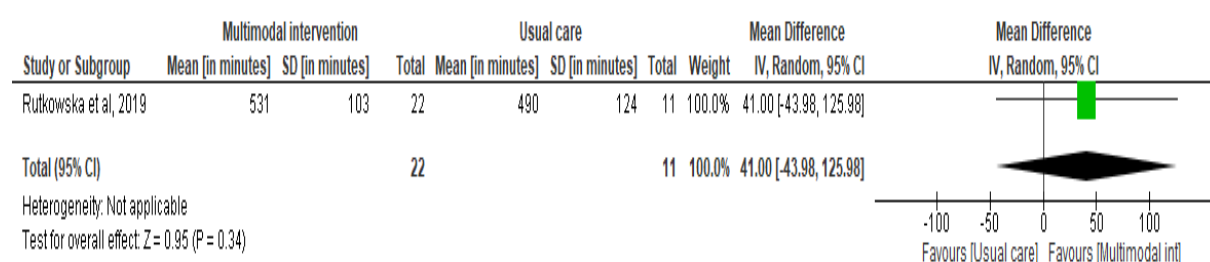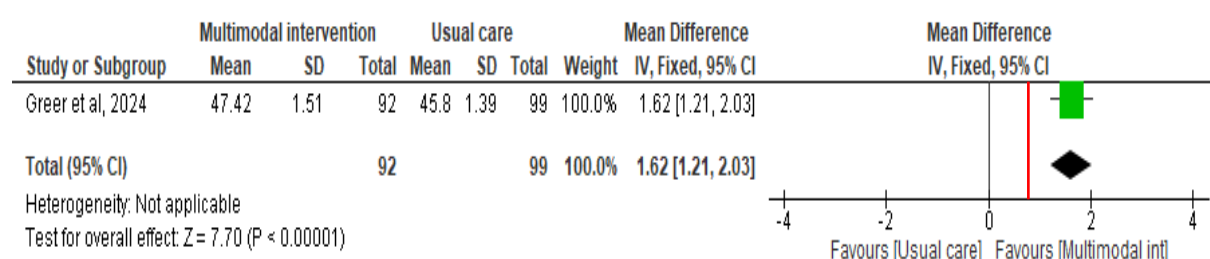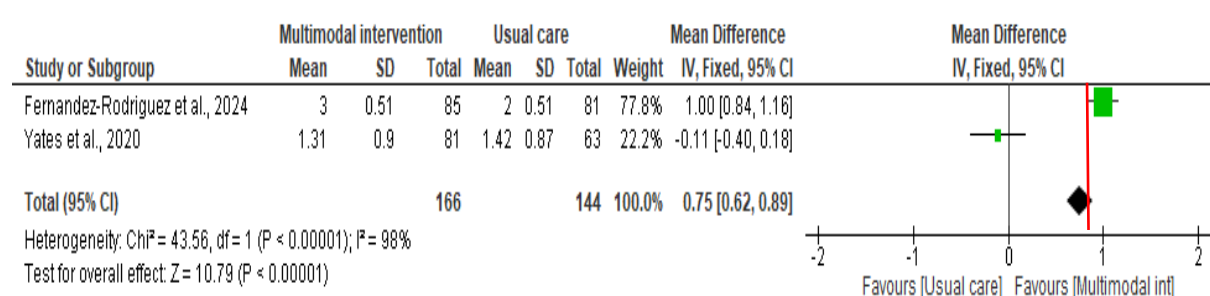**Figure 1.2 (a):** Forest Plot - 6MWT in minutes



**Figure 1.2 (b):** Forest Plot - Percentage of time immobile in actigraphy



*(-) Red line shows MCID given by GDG

**Figure 1.2 (c):** Forest Plot - ECOG score



*(-) Red line shows MCID given by GDG

**Figure 1.2 (d):** Forest Plot - Godin-Shephard Leisure Time Physical Activity Questionnaire
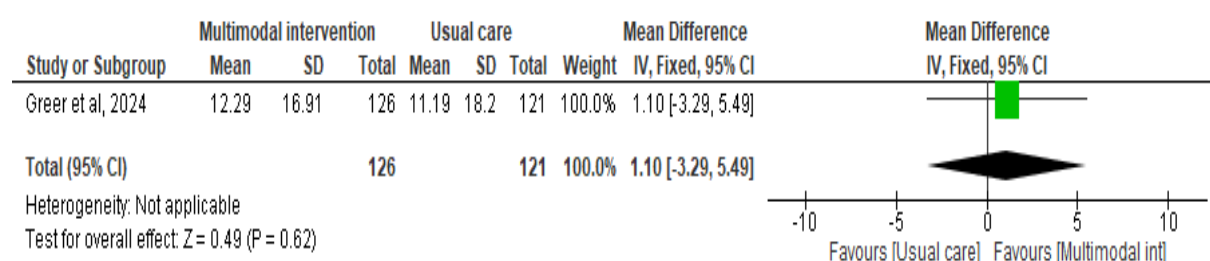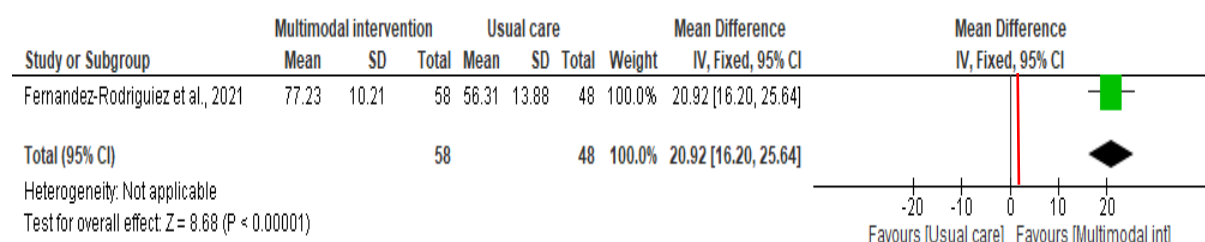
**Figure 1.2 (e):** Forest Plot - Barthel Index



| Study or Subgroup | Multimodal intervention Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Fernandez-Rodriguez et al., 2021 | 77.23 | 10.21 | 58 | 56.31 | 13.88 | 48 | 100.0% | 20.92 [16.20, 25.64] |
| Total (95% CI) | | | 58 | | | 48 | 100.0% | 20.92 [16.20, 25.64] |

Heterogeneity: Not applicable
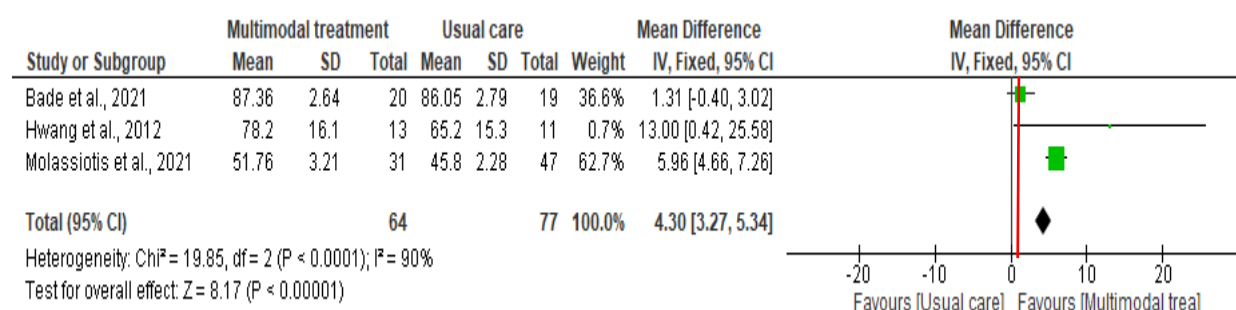Test for overall effect: Z = 8.68 (P < 0.00001)

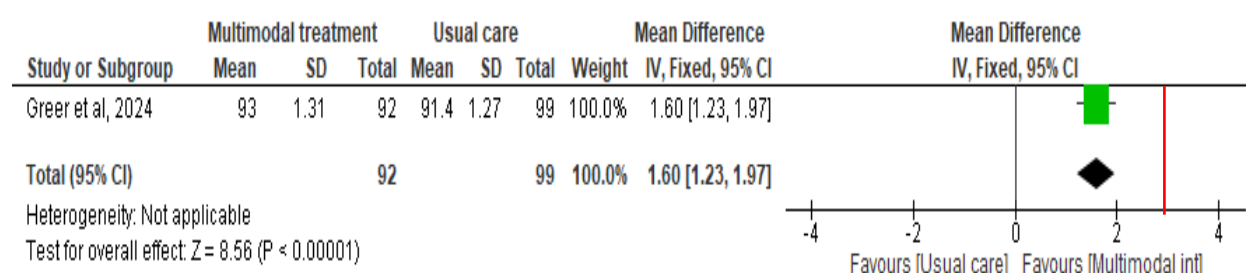*(-) Red line shows MCID given by GDG

## Quality of Life

The evidence for EORTC-QLQ-C30 Global Health Status indicates a statistically significant improvement with multimodal intervention over usual care, with a mean difference of 4.30 higher [3.27 higher, 5.34 higher], although substantial heterogeneity is observed ($I^2$ = 90%). FACT-L scores also favor the multimodal intervention, showing a significant improvement in Quality-of-Life scores with a mean difference of 1.60 higher [1.23 higher, 1.97 higher], with no heterogeneity. In contrast, the Chronic Respiratory Questionnaire Mastery domain did not demonstrate a significant difference between groups, with a mean difference of 0.09 higher [0.58 lower, 0.76 higher], indicating no substantial improvement. The Chronic Respiratory Disease Questionnaire-short form fatigue scores, however, reflect a significant reduction in fatigue in the multimodal intervention group, with a mean difference of 2.00 higher [0.61 higher, 3.39 higher], suggesting a beneficial effect. These findings collectively suggest that multimodal interventions have a positive impact on general and disease-specific quality of life domains, although effectiveness may vary across different outcome measures.

**Figure 1.3 (a):** Forest Plot - EORTC-QLQ-C30 - Global Health Status



| Study or Subgroup | Multimodal treatment Mean | SD | Total | Usual care Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bade et al., 2021 | 87.36 | 2.64 | 20 | 86.05 | 2.79 | 19 | 36.6% | 1.31 [-0.40, 3.02] |
| Hwang et al., 2012 | 78.2 | 16.1 | 13 | 65.2 | 15.3 | 11 | 0.7% | 13.00 [0.42, 25.58] |
| Molassiotis et al., 2021 | 51.76 | 3.21 | 31 | 45.8 | 2.28 | 47 | 62.7% | 5.96 [4.66, 7.26] |
| Total (95% CI) | | | 64 | | | 77 | 100.0% | 4.30 [3.27, 5.34] |

Heterogeneity: Chi² = 19.85, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 8.17 (P < 0.00001)

*(-) Red line shows MCID given by GDG

**Figure 1.3 (b):** Forest Plot - FACT L



*(-) Red line shows MCID given by GDG

Figure 1.3 (c): Forest Plot - Chronic Respiratory Questionnaire Mastery



**Figure 1.3 (d):** Forest Plot - Chronic Respiratory Disease Questionnaire-Short Form Fatigue Scores



*(-) Red line shows MCID given by GDG

## Undesirable Effects

The evidence did not report any undesirable effects associated with multimodal interventions in the treatment of dyspnoea in patients with advanced lung cancer, and potential harms remain unknown, indicating a need for further research to evaluate unintended consequences.

## Table 1: Summary of Findings

**Multimodal intervention compared to Usual care for management of dyspnoea**

**Patient or population:** Advanced lung cancer patients with dyspnoea
**Intervention:** Multi-modal intervention (drug and non-drug)
**Comparison:** Standard of Care

| Outcomes | Anticipated Absolute Effects* (95% CI) | | Relative Effect (95% CI) | No. of Participants (studies) | Certainty of the Evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with Usual care | Risk with Multimodal Intervention | | | |
| **Improvement in Dyspnoea** | | | | | |
| **Numerical rating scale (0-10)** | Mean Score 4.01 | MD 0.4 lower (0.95 lower to 0.14 higher) | - | 258 (3 RCTs) | ⊕◯◯◯ Very low[a,b,c] |
| **Modified Medical Research Council (mMRC) Scale** | Mean Score 1.28 | MD 0.03 higher (0.07 lower to 0.13 higher) | - | 327 (3 RCTs) | ⊕◯◯◯ Very Low[a,c] |
| **Medical Research Council Dyspnoea Scale (MRC, 1-5)** | Mean Score 3.02 | MD 0.27 lower (0.37 lower to 0.17 lower) | - | 274 (2 RCTs) | ⊕◯◯◯ Very Low[a,b,d] |
| **Cancer Dyspnea scale (CDS)** | Mean Score 13.77 | MD 0.56 lower (0.72 lower to 0.39 lower) | - | 269 (2 RCTs) | ⊕⊕⊕◯ Moderate[d] |
| **100mm visual analogue scale** | Mean Score 30.78 | MD 10.93 lower (22.45 lower to 0.59 higher) | - | 102 (1 RCT) | ⊕◯◯◯ Very Low[,e,f,c] |
| **Dyspnea-12** | Mean score 14.35 | MD 2.9 lower (6.3 lower to 0.5 higher) | - | 154 (1 RCT) | ⊕◯◯◯ Very Low[a,f,c] |

| | | | | | |
|---|---|---|---|---|---|
| **European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-LC-13, Chinese language version) - Dyspnea subscale** | Mean score 13.6 | MD 9.8 lower (18.93 lower to 0.67 lower) | - | 24 (1 RCT) | ⊕◯◯◯ Very Low[e,f,c] |
| **Borg scale** | Mean score 2.6 | MD 1.1 lower (2.9 lower to 0.7 higher) | - | 30 (1 RCT) | ⊕◯◯◯ Very Low[a,f,c] |
| **Baseline Dyspnea Index** | Mean score 9.8 | MD 0.3 lower (2.12 lower to 1.52 higher) | - | 30 (1 RCT) | ⊕◯◯◯ Very Low[a,f,c] |
| **Modified Borg scale** | Mean score 3.4 | MD 0.9 lower (1.69 lower to 0.11 lower) | - | 36 (1 RCT) | ⊕◯◯◯ Very Low[e,f,g] |
| **Effect on Performance Status** | | | | | |
| **6MWT in minutes** | Mean score 490 | MD 41 higher (43.98 lower to 125.98 higher) | - | 33 (1 RCT) | ⊕◯◯◯ Very Low[a,f,c] |
| **Actigraphy (percent time immobile)** | Mean score 45.8 | MD 1.62 higher (1.21 higher to 2.03 higher) | - | 191 (1 RCT) | ⊕⊕◯◯ Low[f,d] |
| **ECOG** | Mean score 1.71 | MD 0.75 higher (0.62 higher to 0.89 higher) | - | 310 (2 RCTs) | ⊕⊕◯◯ Low[b,g] |
| **Godin-Shephard Leisure Time Physical Activity Questionnaire** | Mean score 11.19 | MD 1.1 higher (3.29 lower to 5.49 higher) | - | 247 (1 RCT) | ⊕⊕◯◯ Low[f,c] |
| **Barthel index** | Mean score 56.31 | MD 20.92 higher (16.2 higher to 25.64 higher) | - | 106 (1 RCT) | ⊕◯◯◯ Very low[e,f,d] |
| **Quality of Life** | | | | | |
| **EORTC-QLQ-C30 - Global health status** | Mean score 65.68 | MD 4.3 higher (3.27 higher to 5.34 higher) | - | 141 (3 RCTs) | ⊕◯◯◯ Very Low[a,b,d] |

| | | | | | |
|---|---|---|---|---|---|
| **FACT-L** | Mean score 91.4 | MD 1.6 higher (1.23 higher to 1.97 higher) | - | 191 (1 RCT) | ⊕⊕◯◯ Low[f,d] |
| **Chronic Respiratory Questionnaire Mastery** | Mean score 4.72 | MD 0.09 higher (0.58 lower to 0.76 higher) | - | 54 (1 RCT) | ⊕◯◯◯ Very low[e,f,c] |
| **Chronic Respiratory Disease Questionnaire-short form fatigue scores** | Mean score 6.8 | MD 2 higher (0.61 higher to 3.39 higher) | - | 34 (1 RCT) | ⊕◯◯◯ Very Low[e,f,,d] |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk difference** of the intervention (and its 95% CI).

**CI:** Confidence Interval, **MD:** Mean Difference

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations:**

a. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
b. *High heterogeneity is present with significant I².*
c. Downgraded one level for imprecision as the 95% CI crossed the null effect line
d. *Small sample size, Optimal Information size (OIS) is not met.*
e. *Some concerns were identified in the study included for this outcome*
f. Single study was downgraded one level for inconsistency as it was inevaluable
g. *Confidence interval (CI) crosses the Minimal clinically important (MCID) line*

**Table 2: Evidence Profile Table**

**Multimodal intervention compared to Usual care for management of dyspnoea**

**Patient or population:** Advanced lung cancer patients with dyspnoea
**Intervention:** Multi-modal intervention (drug and non-drug)
**Comparison:** Standard of Care

| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Multimodal intervention | Standard of Care | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Certainty Assessment** | | | | | | | **No. of Patients** | | **Effect** | | | |
| **Improvement in Dyspnoea** | | | | | | | | | | | | |
| **Numerical rating scale (0-10)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[a] | serious[b] | not serious | serious[c] | none | 140 | 118 | - | MD **0.4 lower** (0.95 lower to 0.14 higher) | ⊕○○○ Very low[a,b,c] | CRITICAL |
| **Modified Medical Research Council (mMRC) Scale** | | | | | | | | | | | | |
| 3 | randomised trials | Very serious[a] | not serious | not serious | Serious[c] | none | 160 | 167 | - | MD **0.03 higher** (0.07 lower to 0.13 higher) | ⊕○○○ Very Low[a,c] | CRITICAL |
| **Medical Research Council Dyspnea Scale (MRC, 1-5)** | | | | | | | | | | | | |
| 2 | randomised trials | Very serious[a] | Serious[b] | not serious | Serious[d] | none | 145 | 129 | - | MD **0.27 lower** (0.37 lower to 0.17 lower) | ⊕○○○ Very Low[a,b,d] | CRITICAL |
| **Cancer Dyspnea scale (CDS)** | | | | | | | | | | | | |

| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | № col1 | № col2 | col3 | Effect | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | Not serious | not serious | not serious | Serious[d] | none | 123 | 146 | - | MD **0.56 lower** (0.72 lower to 0.39 lower) | ⊕⊕⊕◯ Moderate[d] | CRITICAL |
| **100mm visual analogue scale** | | | | | | | | | | | | |
| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | Serious[c] | none | 62 | 40 | - | MD **10.93 lower** (22.45 lower to 0.59 higher) | ⊕◯◯◯ Very Low[e,f,c] | CRITICAL |
| **Dyspnea-12** | | | | | | | | | | | | |
| 1 | randomised trials | Very serious[a] | inevaluable[f] | not serious | Serious[c] | none | 67 | 87 | - | MD **2.9 lower** (6.3 lower to 0.5 higher) | ⊕◯◯◯ Very Low[a,f,c] | CRITICAL |
| **European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-LC-13, Chinese language version) - Dyspnea subscale** | | | | | | | | | | | | |
| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | Serious[c] | none | 13 | 11 | - | MD **9.8 lower** (18.93 lower to 0.67 lower) | ⊕◯◯◯ Very Low[e,f,c] | CRITICAL |
| **Borg scale** | | | | | | | | | | | | |
| 1 | randomised trials | Very serious[a] | Inevaluable[f] | not serious | Serious[c] | none | 20 | 10 | - | MD **1.1 lower** (2.9 lower to 0.7 higher) | ⊕◯◯◯ Very Low[a,f,c] | CRITICAL |
| **Baseline Dyspnea Index** | | | | | | | | | | | | |
| 1 | randomised trials | Very serious[a] | Inevaluable[f] | not serious | Serious[c] | none | 20 | 10 | - | MD **0.3 lower** (2.12 lower to 1.52 higher) | ⊕◯◯◯ Very Low[a,f,c] | CRITICAL |
| **Modified Borg scale** | | | | | | | | | | | | |

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other | n1 | n2 | - | Absolute (MD) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | Serious[g] | none | 18 | 18 | - | MD **0.9 lower** (1.69 lower to 0.11 lower) | ⊕◯◯◯ Very Low[e,f,g] | CRITICAL |

**Effect on Performance Status**

**6MWT in minutes**

| 1 | randomised trials | Very serious[a] | Inevaluable[f] | not serious | Serious[c] | none | 22 | 11 | - | MD **41 higher** (43.98 lower to 125.98 higher) | ⊕◯◯◯ Very Low[a,f,c] | CRITICAL |

**Actigraphy (percent time immobile)**

| 1 | randomised trials | Not serious | Inevaluable[f] | not serious | serious[d] | none | 92 | 99 | - | MD **1.62 higher** (1.21 higher to 2.03 higher) | ⊕⊕◯◯ Low[f,d] | CRITICAL |

**ECOG**

| 2 | randomised trials | not serious | Serious[b] | not serious | Serious[g] | none | 166 | 144 | - | MD **0.75 higher** (0.62 higher to 0.89 higher) | ⊕⊕◯◯ Low[b,g] | CRITICAL |

**Godin-Shephard Leisure Time Physical Activity Questionnaire**

| 1 | randomised trials | not serious | Inevaluable[f] | not serious | Serious[c] | none | 126 | 121 | - | MD **1.1 higher** (3.29 lower to 5.49 higher) | ⊕⊕◯◯ Low[f,c] | CRITICAL |

**Barthel index**

| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | serious[d] | none | 58 | 48 | - | MD **20.92 higher** (16.2 higher to 25.64 higher) | ⊕◯◯◯ Very low[e,f,d] | CRITICAL |

## EORTC-QLQ-C30 - Global health status

| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | very serious[a] | Serious[b] | not serious | Serious[d] | none | 64 | 77 | - | MD **4.3 higher** (3.27 higher to 5.34 higher) | ⊕◯◯◯ Very Low[a,b,d] | CRITICAL |

## FACT-L

| 1 | randomised trials | Not serious | Inevaluable[f] | not serious | Serious[d] | none | 92 | 99 | - | MD **1.6 higher** (1.23 higher to 1.97 higher) | ⊕⊕◯◯ Low[f,d] | CRITICAL |

## Chronic Respiratory Questionnaire Mastery

| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | serious[c] | none | 28 | 26 | - | MD **0.09 higher** (0.58 lower to 0.76 higher) | ⊕◯◯◯ Very low[e,f,c] | CRITICAL |

## Chronic Respiratory Disease Questionnaire-short form fatigue scores

| 1 | randomised trials | Serious[e] | Inevaluable[f] | not serious | Serious[d] | none | 16 | 18 | - | MD **2 higher** (0.61 higher to 3.39 higher) | ⊕◯◯◯ Very Low[e,f,,d] | CRITICAL |

**CI:** Confidence Interval

**Explanations:**

a. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
b. *High heterogeneity is present with significant $I^2$.*
c. Downgraded one level for imprecision as the 95% CI crossed the null effect line
d. *Small sample size, Optimal Information size (OIS) is not met.*
e. *Some concerns were identified in the study included for this outcome*
f. Single study was downgraded one level for inconsistency as it was inevaluable
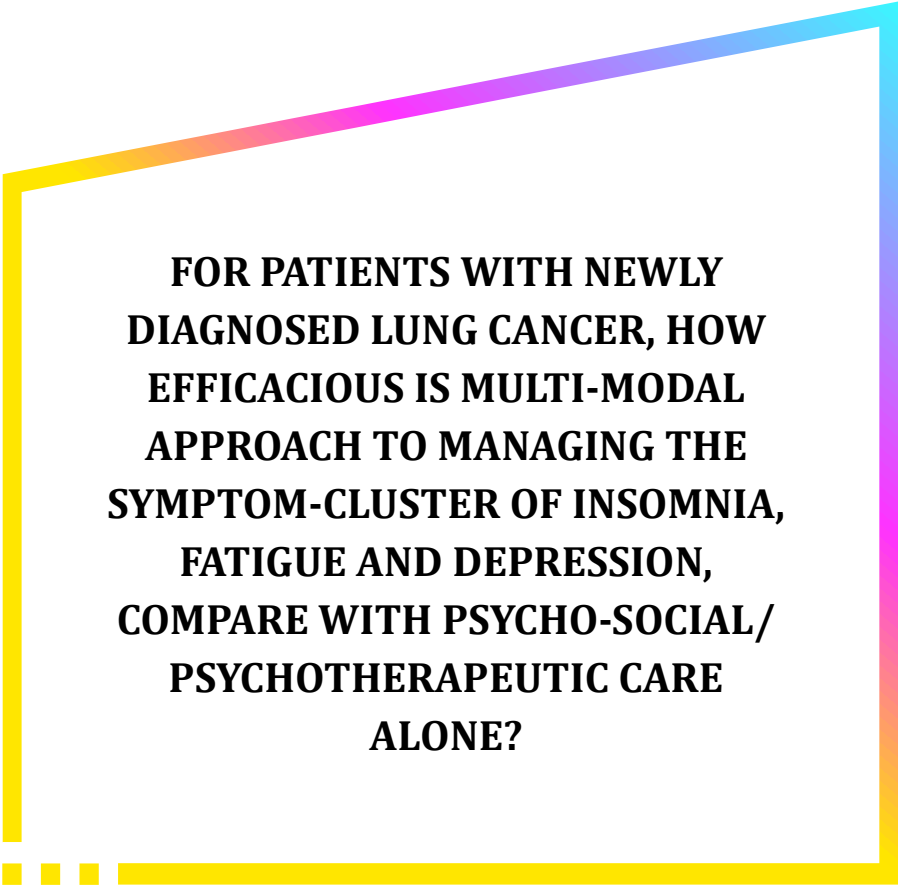g. *Confidence interval (CI) crosses the Minimal clinically important (MCID) line*

| Problem | Yes |
|---|---|
| **Desirable Effects** | Moderate |
| **Undesirable Effects** | Don't Know |
| **Certainty of evidence** | Very Low |
| **Values** | No important uncertainty or variability |
| **Balance of effects** | Probably Favors the intervention |
| **Resources required** | Negligible costs and savings |
| **Certainty of evidence of required resources** | Very Low |
| **Cost effectiveness** | Probably Favors the intervention |
| **Equity** | Probably reduced |
| **Acceptability** | Yes |
| **Feasibility** | Probably Yes |
| **Recommendations:** Multi-modal treatment* is ___recommended___ as compared to drug therapy alone for treatment of dyspnoea in patients with advanced lung cancer.<br><br>**Strength**: Strong<br>**Certainty of evidence**: Very low | |

*In this guideline, multimodal treatment for dyspnoea in patients with advanced lung cancer refers to the planned and concurrent delivery of standard pharmacological management alongside one or more structured non-pharmacological interventions, implemented as a coordinated package rather than as isolated or ad-hoc measures. Pharmacological therapy includes usual care with opioids, bronchodilators, corticosteroids, or oxygen therapy where clinically indicated. Non-pharmacological components include breathing retraining and pacing techniques, graded physical activity or pulmonary rehabilitation, posture optimisation, psychoeducational and behavioural support for symptom coping, and simple airflow interventions such as handheld fan use. These components are delivered by trained nurses or a multidisciplinary team, individually tailored to patient needs and disease stage, and may be provided in inpatient, outpatient, or home-based settings with scheduled follow-up. The emphasis of the multimodal approach is on coordinated implementation, patient education, and reinforcement over time, rather than reliance on pharmacological treatment alone.

## RESEARCH PRIORITIES:

The GDG identified the following priority areas and limitations in the existing evidence related to the management of dyspnoea in patients with advanced lung cancer:

- Limited high-quality randomized controlled trials directly comparing multimodal dyspnoea management interventions (combining non-pharmacological, behavioural, and supportive strategies) with pharmacological therapy alone.
- Lack of studies employing a homogeneous and clearly defined comparator, with most available trials using "usual care" as the comparator rather than drug therapy alone, thereby limiting the ability to isolate the incremental benefit of multimodal interventions.
- Insufficient evidence on the added benefit of non-pharmacological components when used alongside standard drug therapy, including opioids, bronchodilators, and oxygen where indicated.
- Lack of health economic evaluations comparing multimodal interventions with drug therapy alone, including cost-effectiveness and impact on health-care utilisation.

**FOR PATIENTS WITH NEWLY DIAGNOSED LUNG CANCER, HOW EFFICACIOUS IS MULTI-MODAL APPROACH TO MANAGING THE SYMPTOM-CLUSTER OF INSOMNIA, FATIGUE AND DEPRESSION, COMPARE WITH PSYCHO-SOCIAL/ PSYCHOTHERAPEUTIC CARE ALONE?**

## Background

Multiple treatment approaches are available for patients with lung cancer including chemotherapy, radiotherapy, immunotherapy, and surgery. Additionally, most patients with lung cancer receive psychotherapeutic or psychosocial or supportive care, which can range from very structured approaches to simple educational strategies. Furthermore, patients could receive additional medications for specific symptom management including opioids, steroids, cough medications, antidepressants, etc. The symptom cluster of insomnia, fatigue, and depression are sometimes assessed and treated using these psychotherapeutic or psychosocial approaches or medications. Such multi-modal treatment approaches frequently also have a psychotherapy component that could help not only in symptom reduction but also improve quality of life of the patients. However, whether such multi-modal approaches including assessment and treatment are better than routine psychotherapeutic care alone for these symptom clusters has not been systematically studied. Therefore, this systematic review was aimed to comprehensively review all available evidence that has examined the effect of multimodal treatment approaches for newly diagnosed lung cancer patients on the symptom cluster of insomnia, fatigue, and depression, compared to psychotherapeutic care alone. Additionally, we intended to compare the quality of life, cost of treatment, and treatment adherence in those receiving multimodal treatment and psychotherapeutic care alone.

## Recommendations

> Multimodal Approach of treatment is ***recommended*** in comparison to treatment with Psychotherapeutic Care alone for patients with lung cancer.
>
> **Strength**: Strong
> **Certainty of Evidence**: Very low

## Rationale/Justification

The evidence showed moderate desirable effects with trivial harms, alongside acceptability, feasibility, and cost-effectiveness probably favouring multimodal approach in managing the symptom cluster. The anticipated benefits outweigh potential downsides, supporting a strong recommendation.

## Summary of Evidence

**Key Question**

For patients with newly diagnosed lung cancer, how efficacious is multi-modal approach to managing the symptom-cluster of insomnia, fatigue and depression, compared with psycho-social/ psychotherapeutic care alone?

**Included Studies**

A total of 5303 records from electronic databases were identified till date. Of the 5303 articles, 843 duplicate articles were removed. Further 4183 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 274 articles. After application of inclusion and exclusion criteria, 15 articles were selected for systematic review and 10 studies were included in meta-analysis.

**Population and Study Characteristics**

All the studies included patients diagnosed with lung cancer undergoing psychotherapeutic care treatment for lung cancer using multimodal approach. The review includes adults of all ages and genders. Eligible studies are those that evaluate multi-modal interventions for psychotherapeutic care as a part of palliative care services for treatment of lung cancer. Studies also included a comparison group receiving psychotherapeutic care alone.

Eligible studies reported on at least one of the following **outcomes**:

- **Improvement in symptom** (10 studies)
- **Quality of life** (4 studies)
- Treatment adherence/compliance (10 studies)
- **Cost** (No studies)

**Intervention**

The intervention included multi-modal approach with clinical assessment and reversing the reversible (drugs, disease-conditions) and psychotherapeutic care (communication, counselling, expression therapies, sleep hygiene, problem solving, education) for treatment of patients with lung cancer.

**Comparator**

Psychotherapeutic care alone which includes communication, counselling, expression therapies, sleep hygiene, problem solving, education.

**Outcome**

Different outcomes were evaluated and included the following critical and important outcomes:
   a) Improvement in symptom score (Critical outcome)
   b) Quality of life (Critical outcome)
   c) Cost (Important outcome)
   d) Treatment adherence/compliance (important outcome)

## Critical Outcome reviewed and their MCID

| Sr. No | Critical Outcome Reviewed | What does it measure | MCID decided by GDG |
|---|---|---|---|
| 1 | Improvement in symptom score | Difference in the mean scores | 20% difference |
| 2 | Quality of Life | Difference in the mean scores of QoL | 10% improvement |

## PICO

| Framework | Description |
|---|---|
| Population | Patients with newly diagnosed lung cancer |
| Intervention | Multi-modal approach<br><br>Clinical assessment and reversing the reversibles (drugs, disease-conditions) and psychotherapeutic care (communication, counselling, expression therapies, sleep hygiene, problem solving, education) |
| Comparator | Psychotherapeutic care alone (communication, counselling, expression therapies, sleep hygiene, problem solving, education) |
| Outcome | a. Improvement in symptom score (*critical outcome*)<br>b. Quality of life (*Critical outcome*)<br>c. Cost (*Important outcome*)<br>d. Treatment adherence/compliance (Important outcome) |

## Risk of Bias Assessment

### Improvement in Symptom Score

#### Improvement in INSOMNIA

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Tan et al, 2019 | + | X | - | + | + | X |

#### Fatigue (PFS)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Chan et al, 2011 | - | + | X | + | + | X |

#### Fatigue (MDASI)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Tan et al, 2019 | + | X | - | + | + | X |

#### Fatigue (EORTC QLQ-C30)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Walker et al, 2014 | + | + | + | + | + | + |

#### Depression (HADS)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Huang et al, 2018 | - | X | X | + | + | X |
| Lu et al, 2024a | + | + | + | + | + | + |
| Lu et al, 2024b | + | + | + | + | + | + |
| Schellekens et al, 2017 | - | + | + | + | + | - |
| Yates et al, 2020 | + | + | - | + | + | - |

#### Depression (PHQ4)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Krug et al, 2021 | + | X | - | X | + | X |

#### Depression (PHQ9)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Xiao et al, 2022 | + | + | X | + | + | X |

| | |
|---|---|
| D1 | Randomisation Process |
| D2 | Deviations from the Intended Interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

| | |
|---|---|
| + | Low risk |
| - | Some concerns |
| X | High risk |

## Depression (MDASI) tan

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Tan et al, 2019 | + | X | - | + | + | X |

## Depression (MDASI)

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Walker et al, 2014 | + | + | + | + | + | + |

## Quality of Life

## QOL FACT-L

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Huang et al, 2018 | - | X | X | + | + | X |

## SEIQoL

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Krug et al, 2014 | + | X | - | X | + | X |

## EORTC QLQ-C30

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Schellekens et al, 2017 | - | + | + | + | + | - |
| Walker et al, 2014 | + | + | + | + | + | + |

## Adherence drop out rate

| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Chen et al, 2011 | - | + | X | + | + | X |
| Huang et al, 2018 | - | X | X | + | + | X |
| Krug et al, 2021 | + | X | - | X | + | X |
| Lu et al, 2024a | + | + | + | + | + | + |
| Lu et al, 2024b | + | + | + | + | + | + |
| Schellekens et al, 2017 | - | + | + | + | + | - |
| Tan et al, 2019 | + | X | - | + | + | X |
| Walker et al, 2014 | + | + | + | + | + | + |
| Xiao et al, 2022 | + | + | X | + | + | X |
| Yates et al, 2020 | + | + | - | + | + | - |

## Desirable Effects

Total 12 studies were included for meta-analysis that examined the cluster of symptoms (insomnia, fatigue, and depression) comparing multimodal approaches with usual psychotherapeutic or psychosocial care. Change in insomnia was found to be higher with multimodal approach (MD 1.08, 95% CI 0.14, 2.02). Fatigue was examined using three different scales; there was no difference between the approaches on PFS, whereas the other two studies showed multimodal approaches are better. Depression was better with multimodal approaches in 4 RCTs using HADS scores (MD 1.10, 95% CI 0.18, 2.02). Similar findings were seen with PHQ-9 scores, MDASI, and SCL-20, whereas the findings on PHQ-4 was not significantly different. All studies showed that QoL scores were better following multimodal approaches. However, dropout rates were not different between the different approaches.

### Improvement in Symptom Score

**Figure 1.1 (a):** Forest plot: Insomnia



*(-) Red line shows MCID given by GDG
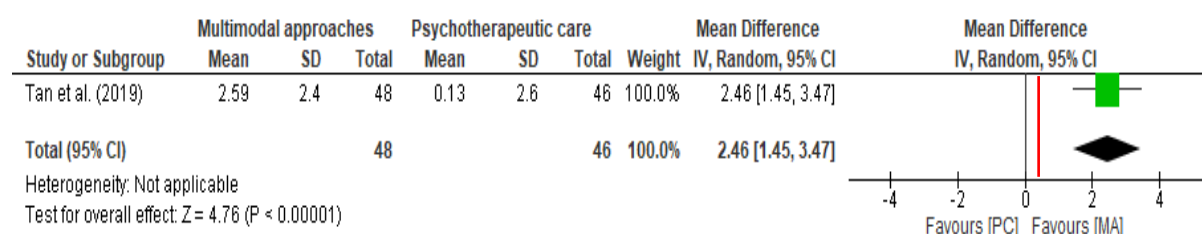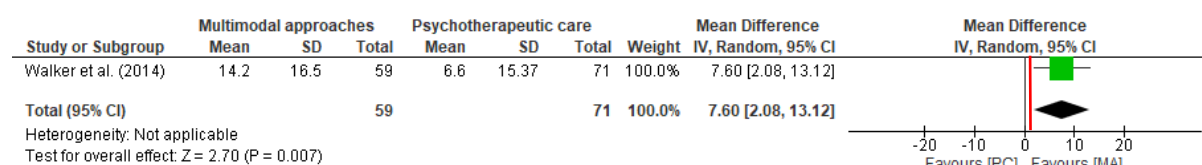
**Figure 1.1 (b):** Forest plot: Fatigue – PFS



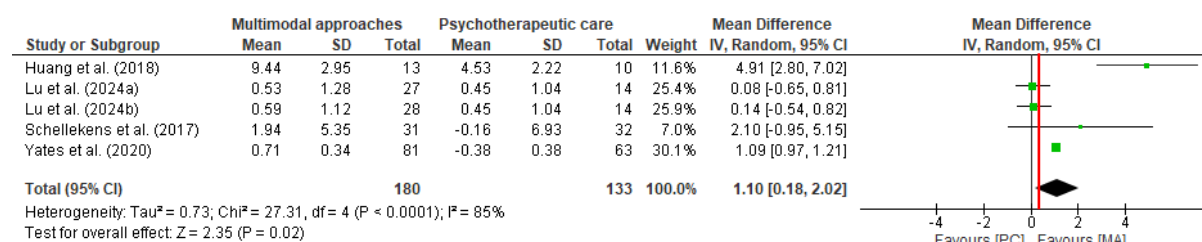**Figure 1.1 (c):** Forest plot: Fatigue - MDASI



*(-) Red line shows MCID given by GDG

**Figure 1.1 (d):** Forest plot: Fatigue - EORTC QLQ-C30



*(-) Red line shows MCID given by GDG

**Figure 1.1 (e):** Forest plot: Depression - HADS



*(-) Red line shows MCID given by GDG

**Figure 1.1 (f):** Forest plot: Depression PHQ-4
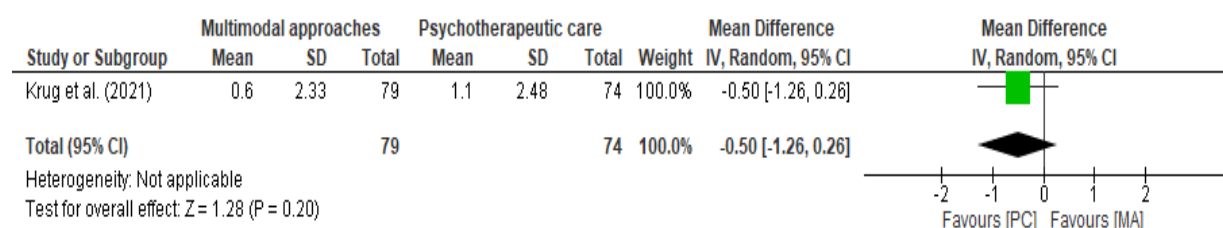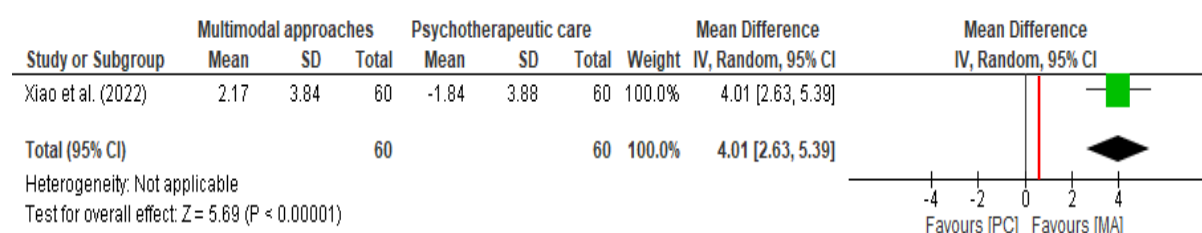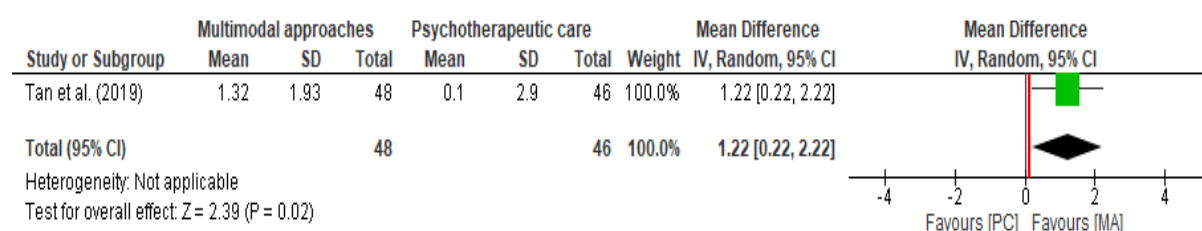


**Figure 1.1 (g):** Forest plot: Depression PHQ-9
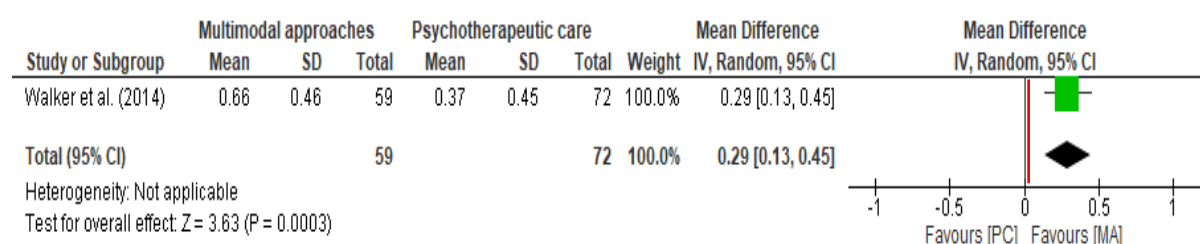


*(-) Red line shows MCID given by GDG

**Figure 1.1 (h):** Forest plot: Depression MDASI



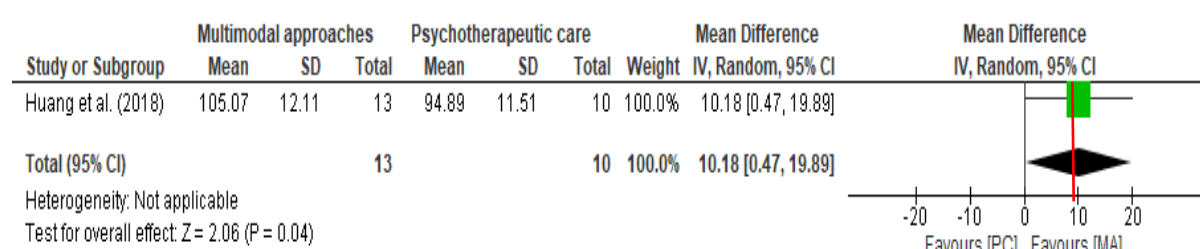*(-) Red line shows MCID given by GDG

**Figure 1.1 (i):** Forest plot: Depression SCL-20



*(-) Red line shows MCID given by GDG

## Quality of Life

**Figure 1.2 (a):** Forest Plot: QoL - FACT L



*(-) Red line shows MCID given by GDG

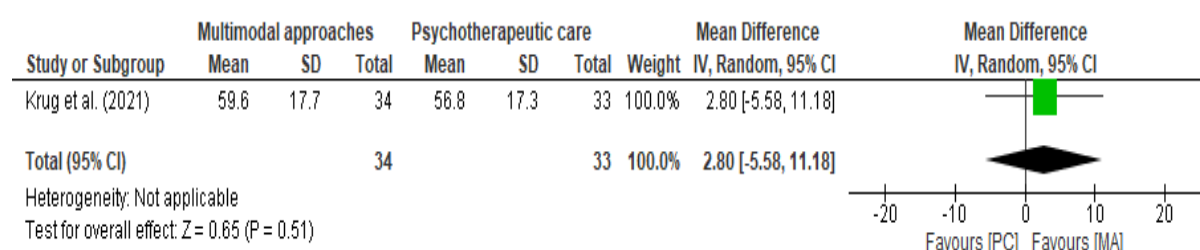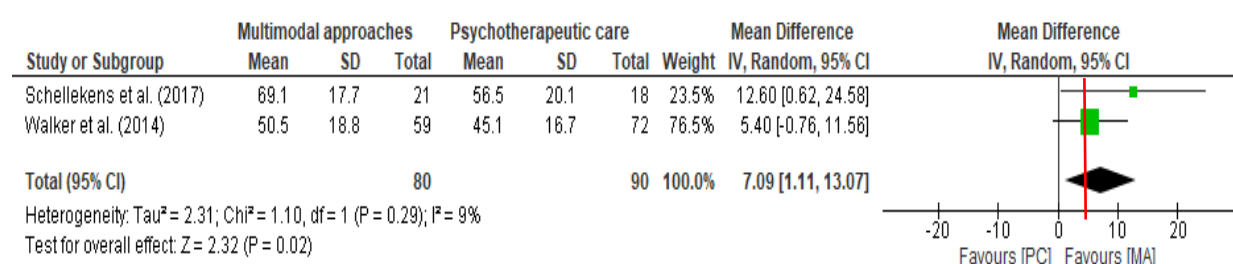**Figure 1.2 (b):** Forest Plot:  QoL – SEIQoL



**Figure 1.2 (c):** Forest Plot: QoL EORTC QLQ-C30



*(-) Red line shows MCID given by GDG

## Undesirable Effects

The evidence did not report any undesirable effects associated with the multimodal approach of treatment, and potential harms remain unknown.

## Table 1: Summary of Findings

**Multimodal approaches compared to psychotherapeutic care alone for newly diagnosed cases with lung cancer**

**Patient or population:** Patients with Lung Cancer
**Intervention:** Multi-modal intervention (drug and non-drug)
**Comparison:** Psychotherapy alone

| Outcomes | Anticipated absolute effects[*] (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with Psychotherapeutic Care Alone | Risk with Multimodal intervention | | | | |
| **Improvement in Symptom Score** | | | | | | |
| Insomnia assessed with: MDASI | The mean insomnia was **0.09** | MD **1.08 higher** (0.14 higher to 2.02 higher) | - | 94 (1 RCT) | ⊕◯◯◯ Very Low[a,b,c] | Lower insomnia with multimodal approaches |
| Fatigue assessed with: PFS | The mean fatigue was **0.45** | MD **0.09 higher** (0.62 lower to 0.8 higher) | - | 140 (1 RCT) | ⊕◯◯◯ Very Low[a,b,d] | |
| Fatigue assessed with: MDASI | The mean fatigue was **0.13** | MD **2.46 higher** (1.45 higher to 3.47 higher) | - | 94 (1 RCT) | ⊕◯◯◯ Very Low[a,b,c] | Fatigue is less with multimodal approaches |
| Fatigue assessed with: QLQ-C30 | The mean fatigue was **6.6** | MD **7.6 higher** (2.08 higher to 13.12 higher) | - | 130 (1 RCT) | ⊕⊕◯◯ Low[b,e] | Fatigue is less with multimodal approaches |

| | | | | | | |
|---|---|---|---|---|---|---|
| Depression assessed with: HADS | The mean depression was **0.98** | **1.01 higher** (0.18 higher to 2.02 higher) | - | 313 (5 RCTs) | ⊕◯◯◯ Very low[f,g,c] | Lower depression with multimodal approaches |
| Depression assessed with: PHQ-4 | The mean depression was **1.1** | MD **0.5 lower** (1.26 lower to 0.26 higher) | - | 153 (1 RCT) | ⊕◯◯◯ Very Low[a, b, d] | |
| Depression assessed with: PHQ-9 | The mean depression was **-1.84** | MD **4.01 higher** (2.63 higher to 5.39 higher) | - | 120 (1 RCT) | ⊕◯◯◯ Very Low[a,b,e] | Lower depression with multimodal approaches |
| Depression assessed with: MDASI | The mean depression was **0.1** | MD **1.22 higher** (0.22 higher to 2.22 higher) | - | 94 (1 RCT) | ⊕◯◯◯ Very Low[a,b,e] | Lower depression with multimodal approaches |
| Depression assessed with: SCL-20 | The mean depression was **0.37** | **0.29 higher** (0.13 higher to 0.45 higher) | - | 131 (1 RCT) | ⊕⊕◯◯ Low[b,e] | Lower depression with multimodal approaches |
| **Quality of Life** | | | | | | |
| Quality of Life assessed with: FACT-L | The mean quality of Life was **94.89** | MD **10.18 higher** (0.47 higher to 19.89 higher) | - | 23 (1 RCT) | ⊕◯◯◯ Very Low[a,b,c] | Higher QoL with multimodal approaches |
| Quality of Life assessed with: SEIQoL | The mean quality of Life was **56.8** | MD **2.8 higher** (5.58 lower to 11.18 higher) | - | 67 (1 RCT) | ⊕◯◯◯ Very Low[a,b,d] | |
| Quality of life assessed with: QLQ-C30 | The mean quality of Life was **50.8** | MD **7.09 higher** (1.11 higher to 13.07 higher) | - | 170 (2 RCTs) | ⊕⊕⊕◯ moderate[c] | Higher QoL in those receiving multimodal approaches |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk difference** of the intervention (and its 95% CI).
**CI:** Confidence Interval

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Explanations*

   a.  *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
   b.  *Single study was downgraded one level for inconsistency as it was inevaluable*
   c.  *Downgraded one level for imprecision as the 95% CI crossed the MCID*
   d.  *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
   e.  *Optimal Information Size (OIS) not met*
   f.  *Downgraded one level for risk of bias as less than 2/3rd studies (by weight) were at low risk of bias*
   g.  *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with i2 of 85%*

**Table 2: Evidence Profile Table**

**Multimodal approaches compared to psychotherapeutic care alone for newly diagnosed cases with lung cancer**

**Patient or population:** Patients with Lung Cancer
**Intervention:** Multi-modal intervention (drug and non-drug)
**Comparison:** Psychotherapy alone

| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Multimodal intervention | Standard of Care | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Certainty Assessment** | | **No. of Patients** | | **Effect** | | | |
| **Improvement in Symptom Score** | | | | | | | | | | | | |
| **Insomnia (assessed with: MDASI)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a,] | inevaluable[b] | not serious | serious[c] | none | 48 | 46 | - | MD **1.08 higher** (0.14 higher to 2.02 higher) | ⊕◯◯◯ Very Low[a,b,c] | CRITICAL |
| **Fatigue (assessed with: PFS)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[d] | none | 70 | 70 | - | MD **0.09 higher** (0.62 lower to 0.8 higher) | ⊕◯◯◯ Very Low[a,b,d] | CRITICAL |
| **Fatigue (assessed with: MDASI)** | | | | | | | | | | | | |

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[a,] | inevaluable[b] | not serious | serious[c] | none | 48 | 46 | - | MD **2.46 higher** (1.45 higher to 3.47 higher) | ⊕◯◯◯ Very Low[a,b,c] | CRITICAL |

**Fatigue (assessed with: QLQ-C30)**

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | not serious | inevaluable[b] | not serious | serious[e] | none | 59 | 71 | - | MD **7.6 higher** (2.08 higher to 13.12 higher) | ⊕⊕◯◯ Low[b,e] | CRITICAL |

**Depression (assessed with: HADS)**

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | randomised trials | serious[f] | serious[g] | not serious | serious[c] | none | 180 | 133 | - | **1.01 higher** (0.18 higher to 2.02 higher) | ⊕◯◯◯ Very low[f,g,c] | CRITICAL |

**Depression (assessed with: PHQ-4)**

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[d] | none | 79 | 74 | - | MD **0.5 lower** (1.26 lower to 0.26 higher) | ⊕◯◯◯ Very Low[a,b,d] | CRITICAL |

**Depression (assessed with: PHQ-9)**

| № | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[e] | none | 60 | 60 | - | MD **4.01 higher** (2.63 higher to 5.39 higher) | ⊕◯◯◯ Very Low[a,b,e] | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Depression (assessed with: MDASI)** | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[e] | none | 48 | 46 | - | MD **1.22 higher** (0.22 higher to 2.22 higher) | ⊕◯◯◯ Very Low[a,b,e] | CRITICAL |
| **Depression (assessed with: SCL-20)** | | | | | | | | | | | |
| 1 | randomised trials | not serious | inevaluable[b] | not serious | serious[e] | none | 59 | 72 | - | **0.29 higher** (0.13 higher to 0.45 higher) | ⊕⊕◯◯ Low[b,e] | CRITICAL |
| **Quality of Life** | | | | | | | | | | | |
| **Quality of Life (assessed with: FACT-L)** | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[c] | none | 13 | 10 | - | MD **10.18 higher** (0.47 higher to 19.89 higher) | ⊕◯◯◯ Very Low[a,b,c] | CRITICAL |
| **Quality of Life (assessed with: SEIQoL)** | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | inevaluable[b] | not serious | serious[d] | none | 34 | 33 | - | MD **2.8 higher** (5.58 lower to 11.18 higher) | ⊕◯◯◯ Very Low[a,b,d] | CRITICAL |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality of life (assessed with: QLQ-C30)** | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious[c] | none | 80 | 90 | - | MD **7.09 higher** (1.11 higher to 13.07 higher) | ⊕⊕⊕◯ moderate[c] | CRITICAL |

**CI**: Confidence Interval

***Explanations***

a. Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias
b. Single study was downgraded one level for inconsistency as it was inevaluable
c. Downgraded one level for imprecision as the 95% CI crossed the MCID
d. Downgraded one level for imprecision as the 95% CI crossed the null effect line
e. Optimal Information Size (OIS) not met
f. Downgraded one level for risk of bias as less than 2/3rd studies (by weight) were at low risk of bias
g. Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with $i^2$ of 85%

## Summary of Judgements

| | |
|---|---|
| **Problem** | Yes |
| **Desirable Effects** | Moderate |
| **Undesirable Effects** | Trivial |
| **Certainty of evidence** | Very Low |
| **Values** | No important uncertainty or variability |
| **Balance of effects** | Probably Favors the intervention |
| **Resources required** | Moderate costs |
| **Certainty of evidence of required resources** | Low |
| **Cost effectiveness** | Probably Favors the intervention |
| **Equity** | Probably reduced |
| **Acceptability** | Yes |
| **Feasibility** | Yes |
| **Recommendations:** Multimodal Approach of treatment is recommended in comparison to treatment with Psychotherapeutic Care alone for patients with lung cancer.<br><br>**Strength**: Strong<br>**Certainty of Evidence:** Very low | |

## Research Priorities:

The GDG identified the following priority evidence gaps relevant to the question of whether a multi-modal intervention is superior to psychosocial/psychotherapeutic care alone for managing the symptom cluster of insomnia, fatigue, and depression in patients with newly diagnosed lung cancer:

1. Limited availability of high-quality randomized controlled trials evaluating multi-modal interventions that simultaneously target insomnia, fatigue, and depression in patients with newly diagnosed lung cancer.

2. Heterogeneity in the components, intensity, and duration of multi-modal interventions (e.g. pharmacological, behavioural, exercise-based, psychoeducational, and supportive care elements), limiting comparability across studies.

3. Insufficient comparative evidence directly contrasting multi-modal symptom management strategies with psychosocial or psychotherapeutic care alone, particularly in early phases following diagnosis.

4. Short duration of follow-up in existing studies, providing limited evidence on the sustainability of symptom control, relapse, or long-term mental health outcomes.

5. Limited data on the feasibility, acceptability, and resource requirements of delivering multi-modal interventions within routine oncology and palliative care pathways, especially in public-sector and resource-constrained settings.

6. Scarcity of health economic evaluations assessing the cost-effectiveness of multi-modal approaches compared with psychosocial or psychotherapeutic care alone.

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