Evidence-based Guidelines for Lung Cancer Treatment

Department of Health Research
&
Directorate General of Health Services

Ministry of Health and Family Welfare

Government of India

DISCLAIMER

The Evidence-based Guidelines for Lung Cancer Palliation published by the MoHFW/DHR-DGHS provide recommendations made after careful consideration of the available evidence. This evidence has been synthesized by collation of systematic reviews (SR) and meta-analysis (MA) of exisitng studies on well defined review questions on the subject matter. The guideline reflects the best avaialble data according to the study inclusion criteria set by the guideline development group. Considerable care has been taken to ensure that the information contained in the guidelines is accurate, evidence-based and up-to-date at the time of publication. However, there is a possbility that new studies may have been published too late during the development process or after publication and are not incorporated into the guideline.

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जगत प्रकाश नड्डा
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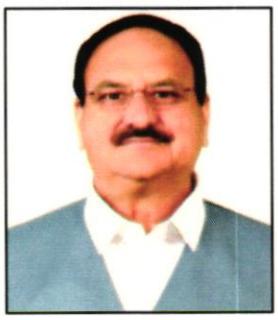
सत्यमेव जयते

मंत्री
स्वास्थ्य एवं परिवार कल्याण
व रसायन एवं उर्वरक
भारत सरकार

Minister
Health & Family Welfare
and Chemicals & Fertilizers
Government of India



MESSAGE

In recent years, lung cancer has emerged as a major public health challenge, contributing significantly to morbidity and mortality across the country. It remains one of the leading causes of cancer-related deaths, imposing a substantial burden on individuals, families and the healthcare system. Late-stage diagnosis, complex treatment pathways and high symptom burden underscore the urgent need for standardized, evidence-based approaches to care.

I am happy that Ministry of Health & Family Welfare has developed evidence-based guidelines on Lung Cancer Treatment and Palliative Care to provide comprehensive guidance on disease-directed therapies and integrated supportive and palliative care across the course of illness. These guidelines emphasise a patient-centred approach, early integration of palliative care, multidisciplinary management and rational use of healthcare resources. The recommendations are based on rigorous appraisal of scientific evidence and expert consensus, ensuring clinical relevance and feasibility within our health system.

These guidelines will serve as a valuable resource for clinicians, programme managers and policymakers in strengthening service delivery and improving patient outcomes. It reinforces our commitment to expanding access to evidence-based treatment and comprehensive palliative care for people affected by lung cancer.

The Government of India remains steadfast in its commitment to addressing the growing burden of cancer in the country. I am confident that these guidelines will support healthcare professionals across the country in delivering compassionate, effective and evidence-based care to people affected by lung cancer.

(Jagat Prakash Nadda)

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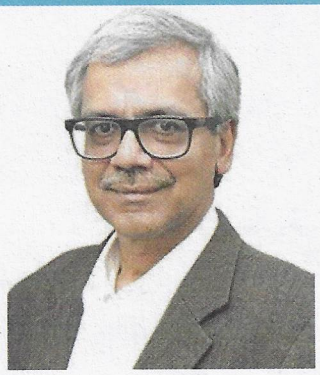
MESSAGE



In the face of India's rising burden of lung cancer, the development of robust, evidence-based treatment guidelines has never been more critical. Lung cancer remains one of the leading causes of cancer-related mortality in our country, and its complex care pathways demand a clear, unified approach that integrates the latest scientific advances with real-world clinical practice.

These Evidence-based guidelines for the treatment of lung Cancer have been crafted to support clinicians, researchers, and policymakers by offering transparent, practical recommendations for treatment ensuring that every patient benefits from the most effective, scientifically validated interventions available today.

As we strive to improve outcomes and quality of life for those affected by lung cancer, it is imperative that we balance rapid innovation with patient safety and ethical rigor. We congratulate and thank all members of the Steering Group, Guideline Development Group, systematic review teams, and contributing experts for their dedication and meticulous work. Under the visionary leadership of the Ministry of Health & Family Welfare and with the unwavering support of the Department of Health Research and DGHS, we are confident that these guidelines will serve as a cornerstone for excellence in lung cancer care nationwide.

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CONTENTS

Acknowledgement

Abbreviation & Acronyms

Executive Summary

I. **Guideline Development Process** 1-8

Introduction

Rationale

Target Audience

Contributors

Management of Conflict of Interest

Defining the Scope and Key Questions

Systematic review methods

GRADing of the certainty of evidence

Drafting of Evidence to Decision Frameworks

Formulation of recommendations EtD

Strength of Recommendations

Document preparation and peer review

II. **Recommendations**

S. No	Recommendations	Pg. No.
01	In patients planned for lung cancer surgery, does prehabilitation improve perioperative outcomes over standard of care?	9
02	In Patients with Operable Non-Small Cell Lung Cancer, Does Neoadjuvant Chemotherapy With/Without Immunotherapy Followed by Surgery as Compare to Upfront Surgery Followed by Adjuvant Chemotherapy With/Without Immunotherapy Improve Overall Survival?	25
03	Effectiveness of Stereotactic Body Radiation Therapy Versus Lobectomy/Segmentectomy Among Patients with Non - Small Cell Lung Cancer	35
04	In patients with operable non-small cell lung cancer (NSCLC), does systematic mediastinal lymph node dissection improve overall survival compared to mediastinal lymph nodal sampling?	57
05	In Patients Diagnosed with Early-Stage Non-Small Cell Lung Cancer (NSCLC) Harbouring an EGFR Mutation, Does the Addition of Adjuvant TKI Therapy, Either Alone or In Combination Improve Overall Survival Compared to Chemotherapy Alone?	79
06	In Completely Resected NSCLC, Does the Addition of Postoperative Radiotherapy to Standard Therapy Improve Survival Compared to Standard Therapy Alone?	99

07	In patients with oligometastatic non-small cell lung cancer (NSCLC), what is the comparative effectiveness of radical local treatment of the primary & metastatic sites compared to systemic therapy alone?	115
08	In Patients with Advanced NSCLC Harbouring Sensitizing Epidermal Growth Factor Receptor (EGFR) Mutations, How Effective Are 2nd And 3rd Generation Tyrosine Kinase Inhibitors (TKI) In Comparison to First Generation TKI With or Without Chemotherapy/Antiangiogenic Agents?	129
09	In Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) And No Oncogenic Driver Alteration, Does Immunotherapy Either Alone or In Combination Improve Overall Survival as Compared to Chemotherapy Alone?	143
10	Should Individualized Dosing Regimen Vs. Standard Fixed Full Dose Indefinite Dosing Schedule Be Used for Patients with NSCLC, Eligible for Immune Checkpoint Inhibitors?	161
11	In patients with Small Cell Lung Cancer (SCLC), what is the comparative effectiveness of Prophylactic Cranial Irradiation (PCI) as compared to patients who did not receive PCI)?	173
12	In limited stage small cell lung cancer (SCLC), what would be the most effective timing and fractionation of radiation with concurrent chemotherapy that could significantly impact patient outcome?	185

ACKNOWLEDGEMENTS

Lung cancer represents a significant and growing public health challenge in India, with rising incidence and mortality rates that underscore the urgent need for standardized, evidence-based management guidelines. In response to this pressing need, the Ministry of Health & Family Welfare envisioned one comprehensive guideline for the entire country based on the best available evidence.

The secretariat gratefully acknowledges the Steering Group for their leadership and strategic oversight throughout the guideline process. We extend our heartfelt appreciation to the members of the Guideline Development Group, whose expertise and dedication were instrumental in formulating the recommendations contained herein. We also acknowledge their commitment in attending multiple extended meetings to review and refine the evidence profiles and to participate fully in the Evidence-to-Decision process. We are indebted to our methodologist Prof. Joseph Mathew for his invaluable guidance and rigorous methodological support. Our sincere thanks also go to the systematic review teams, whose meticulous evidence syntheses provided the foundation for every recommendation.

We are profoundly grateful to Dr. Rajiv Bahl, Secretary, Department of Health Research and Director General, ICMR, whose steadfast guidance, visionary leadership, and relentless advocacy have been pivotal at every stage of this guideline's development. We also extend our sincere gratitude to Ms. Anu Nagar, Additional Secretary, Department of Health Research, for her exemplary administrative coordination and assistance throughout the process.

The constant support of the Centre for Evidence-Based Guidelines is deeply valued, and we greatly appreciate the logistical and administrative contributions of the Department of Health Research and the Delivery Division of ICMR staff.

ABBREVIATIONS

Abbreviation	Full Form
AJC	American Joint Committee
CALGB	Cancer and Leukaemia Group B
COMP	chemotherapy regimen name; appears as COMP in trials
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ES	Extensive Stage
HR	Hazard Ratio
ITT	Intention To Treat
LS	Limited Stage
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OR	Odds Ratio
OS	Overall Survival
PCI	Prophylactic Cranial Irradiation
PICO	Population, Intervention, Comparison, Outcome
PMC	PubMed Central
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RAD/rd/Gy	radiation dose units appear, e.g., rad and Gy
RD	Risk Difference
RCT	Randomized Controlled Trial
RTOG	Radiation Therapy Oncology Group
RR	Risk Ratio
SCLC	Small Cell Lung Cancer
SD	Stable Disease
AJC	American Joint Committee
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RTOG	Radiation Therapy Oncology Group
RR	Risk Ratio
SCLC	Small Cell Lung Cancer
SD	Stable Disease
ALK	Anaplastic Lymphoma Kinase
CNS	Central Nervous System
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FACT G	Functional Assessment of Cancer Therapy – General
FACT L	Functional Assessment of Cancer Therapy – Lung Cancer
GDG	Guideline Development Group
GLOBOCAN	Global Cancer Observatory
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HADS A	Hospital Anxiety and Depression Scale - Anxiety
HADS D	Hospital Anxiety and Depression Scale - Anxiety
ICER	Incremental Cost-Effectiveness Ratio
JAMA	Journal of the American Medical Association
MCID	Minimal Clinically Important Difference
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute

NIH	National Institutes of Health
NSCLC	Non-Small Cell Lung Cancer
OMD	Oligometastatic Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PICO	Population, Intervention, Comparison, Outcome
PMC	PubMed Central
PMCID	PubMed Central Identifier
PMID	PubMed Identifier
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSE	Patient-Reported Outcomes and Symptoms
QALY	Quality-Adjusted Life Year
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumors
ROB	Risk of Bias
SABR	Stereotactic Ablative Body Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SITC	Society for Immunotherapy of Cancer
SMD	Standardized Mean Difference
SRS	Stereotactic Radiosurgery
TOI	Trial Outcome Index
VAS	Visual Analogue Scale

EXECUTIVE SUMMARY

Background & Rationale:

Lung cancer poses a growing public health challenge in India, accounting for a significant proportion of cancer-related morbidity and mortality. As per the latest Global Burden of Disease (GBD) estimates, lung cancer is among the leading causes of cancer deaths in the country. In recent years, the clinical landscape of lung cancer has evolved rapidly, with advancements in molecular diagnostics, targeted therapies, and immunotherapy significantly altering treatment paradigms. However, in the Indian setting, this progress has been accompanied by considerable variation in clinical practices, inconsistent access to diagnostics and newer therapies, and challenges in integrating emerging evidence into routine care, especially in public and resource-constrained healthcare systems.

These disparities highlight the urgent need for standardized, contextually appropriate, and evidence-informed treatment guidelines. Such guidance is essential not only to streamline clinical decision-making but also to ensure equitable access to quality care across India's diverse healthcare settings.

Target Audience:

These guidelines are designed to inform a wide range of stakeholders, including clinical practitioners, program managers, policymakers, and healthcare administrators. The primary clinical audience; oncologists, pulmonologists, thoracic surgeons, radiation oncologists, palliative specialists, pathologists, and radiologists-will find practical, evidence-based recommendations for patient management. Academic researchers and educators engaged in translational studies, clinical trials, and workforce training will benefit from a consolidated review of current best practices and from identification of key research gaps and prioritized research questions to guide future studies.

Guideline Development Methodology:

The guideline was developed using standard methodology as described by international agencies such as the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE). This involved the establishment of a steering group, a Guideline Development Group (GDG), and multiple evidence synthesis (systematic review) teams. Briefly, the process included conducting a scoping exercise to define the objectives, scope, and target population of the guideline; identifying priority review questions (PICOs); undertaking evidence synthesis through systematic reviews and meta-analyses; reviewing evidence profiles and grading the certainty of evidence; formulating recommendations using the Evidence-to-Decision (EtD) framework; drafting the guideline; conducting external review; and disseminating the 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 analysed by the GDG to make judgements and formulate recommendations using the EtD framework within the GRADEpro GDT software. This included assessment of intervention effects (balance between benefits and harms), values and preferences of those affected, resources required, cost-effectiveness, acceptability, feasibility of the intervention, and equity considerations. The GDG examined the evidence, made judgements for each disease condition, and finalized the wording of the recommendations. This was followed by external peer review, after which the draft guidelines were placed on the Department of Health Research (DHR) website for public consultation prior to final release.

Summary of Recommendations

Key Question	Recommendation	Rationale/Justification
In patients planned for lung cancer surgery, does prehabilitation improve perioperative outcomes over standard of care?	Prehabilitation is ***recommended*** for patients planned to undergo lung cancer surgery. **Strength:** Strong **Certainty of Evidence**: Very low	The evidence showed moderate desirable effects with trivial harms, alongside cost-effectiveness favouring the prehabilitation, increased equity, acceptability, and feasibility supporting a strong recommendation despite very low certainty of evidence
In patients with operable non-small cell lung cancer, does neoadjuvant chemotherapy with/without immunotherapy followed by surgery as compared to upfront surgery followed by adjuvant chemotherapy with/without immunotherapy improve overall survival?	For patients with operable non-small cell lung cancer (NSCLC), either neoadjuvant chemotherapy with or without immunotherapy followed by surgery, or upfront surgery followed by adjuvant chemotherapy with or without immunotherapy, is ***recommended***. **Strength:** Conditional **Certainty of evidence:** Very low	The evidence showed trivial desirable effects and trivial undesirable effects with low certainty of evidence. The balance of effects was judged to does not favour either the intervention or the comparison. For cost-effectiveness the judgement does not favour either the intervention or the comparison. Additionally, the intervention is both probably acceptable to stakeholders and probably feasible to implement across settings. A conditional recommendation in favour of either neoadjuvant chemotherapy (with or without immunotherapy) followed by surgery, or upfront surgery followed by adjuvant chemotherapy (with or without immunotherapy). The use of shared decision-making was considered essential, enabling clinicians and patients to discuss the substantial uncertainty in the evidence and incorporate individual preferences such as comorbidities, timing

		considerations, and surgical logistics, when choosing between neoadjuvant and upfront surgery strategies.
In early-stage operable non-small cell lung cancer (NSCLC), what is the comparative effectiveness of stereotactic body radiation therapy (SBRT) versus lobectomy/ segmentectomy in improving survival?	Stereotactic body radiation therapy (SBRT) is ***not recommended*** as compared to obectomy/segmentectomy, for treatment of patients with early-stage operable non-small cell lung cancer except for selected patients who are unwilling or medically unfit for surgery. **Strength**: Conditional **Certainty of evidence** – Low	The evidence suggests that the overall balance of effects probably favours surgery for operable early-stage NSCLC. Variability in resource requirements, cost-effectiveness, and acceptability along with reduced equity and limited feasibility in many settings, supports a cautious approach to recommending SBRT as an alternative. Therefore, the recommendation is **conditional against SBRT**, recognizing that it may be considered in selected patients who are medically unfit or unwilling to undergo surgery.
In patients with operable non-small cell lung cancer (NSCLC), does systematic mediastinal lymph node dissection improve overall survival compared to mediastinal lymph nodal sampling?	Mediastinal lymph node dissection is ***recommended*** as compared to mediastinal lymph node sampling, in patients with operable non-small cell lung cancer. **Strength**: Strong **Certainty of evidence**: Very low	The evidence showed large desirable effects with trivial harms accompanied by negligible costs, cost-effectiveness favouring lymph node dissection, and acceptability and feasibility supporting a strong recommendation despite very low certainty of evidence
In patients diagnosed with early-stage non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation, does the addition of adjuvant tyrosine kinase inhibitor (TKI) therapy, either alone or in combination improve overall survival compared to chemotherapy alone?	Addition of adjuvant tyrosine kinase inhibitor (TKI) therapy is ***recommended*** rather than chemotherapy alone for patients diagnosed with early-stage non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation. **Strength**: Strong	Evidence demonstrates large desirable effects of adjuvant tyrosine kinase inhibitor (TKI) therapy compared with chemotherapy alone, supported by high-certainty evidence for improvement in survival outcomes. Undesirable effects are small, and adverse events are generally manageable, although the certainty of evidence for side effects is very low. Overall, the balance of benefits and harms

	Certainty of evidence – High for efficacy and very low for side effects	clearly favours adjuvant TKI therapy. While resource requirements are moderate and cost-effectiveness may vary across settings, the substantial clinical benefit, favourable safety profile, and strong patient-important outcomes justify a strong recommendation.
In completely resected NSCLC, does the addition of postoperative radiotherapy to standard therapy improve survival compared to standard therapy alone?	Postoperative radiotherapy is ***not recommended*** for patients with completely resected Non-Small Cell Lung Cancer (NSCLC). **Strength**: Conditional **Certainty of evidence** – Very low	The evidence shows trivial desirable effects and moderate undesirable effects, with very low certainty. Consequently, the overall balance of effects favours omission of postoperative radiotherapy (PORT). Resource requirements are moderate and the available cost effectiveness does not support PORT, and is likely to worsen equity and has limited acceptability. Hence, the recommendation remains conditional against routine PORT, while allowing consideration of PORT for selected patients judged to be at higher risk of locoregional recurrence.

In patients with oligometastatic non-small cell lung cancer (NSCLC), what is the comparative effectiveness of radical local treatment of the primary & metastatic sites compared to systemic therapy alone? (Radical treatment included radiotherapy alone or in combination with surgery)	Radical local treatment of primary and metastatic sites is ***recommended*** as compared to treatment with systemic therapy alone for patients with oligometastatic non-small cell lung cancer. **Strength**: Conditional **Certainty of evidence**: Very low	The evidence showed large desirable effects with small harms, alongside cost-effectiveness probably favouring radical local treatment. However, due to its large costs, reduced equity, and variable feasibility compared to systemic therapy alone, the recommendation is conditional
In patients with advanced NSCLC harbouring sensitizing EGFR mutations, how effective are 2nd and 3rd generation TKI in comparison to first generation TKI with or without chemotherapy/antiangiogenic agents?	The use of second and third generation Tyrosine Kinase Inhibitor (TKI) is ***recommended*** rather than first generation TKI for patients with advanced Non-Small Cell Lung Cancer (NSCLC) harbouring sensitizing Epidermal Growth Factor Receptor (EGFR) mutations **Strength:** Conditional **Certainty of evidence** – High for efficacy & Low for side effects	Evidence shows moderate desirable effects and small undesirable effects with overall balance of effects favors the use of second- and third-generation TKI therapy. However, resource requirements are large, and although current cost-effectiveness analyses probably favor the comparison, they are likely to reduce equity due to high costs and limited accessibility. Hence a conditional recommendation was made for patients in whom therapy is accessible through any available financing mechanism (self-payment, patient-assistance programs, insurance, health schemes etc)
In patients with advanced NSCLC and no oncogenic driver alteration, does immunotherapy (immune check point inhibitors) either alone or in combination improve overall survival as compared to chemotherapy alone?	Immunotherapy ((immune check point inhibitors) either alone or in combination is ***recommended*** rather than chemotherapy alone for patients with advanced non-small cell lung cancer (NSCLC) and no oncogenic driver alteration. **Strength**: Conditional	Evidence shows a large desirable effect and moderate undesirable due to increased immune-related toxicities that are generally manageable when recognised early. However, the cost of the immunotherapy is large thereby reducing the equity.

	Certainty of evidence – Low	Hence, a conditional recommendation was made in favour of immunotherapy, for patients who can afford treatment (self-payment, patient-assistance programs, insurance, CGHS etc) and access to centres capable of monitoring and managing immune-related adverse events.
In patients with NSCLC, how effective is immunotherapy (immune checkpoint inhibitors) delivered as individualized dosing regimen (low dose) compared to standard full dose immunotherapy?	In patients with advanced NSCLC without driver mutations, lower-dose pembrolizumab (100 mg) may be considered on an individual basis when the standard dose (200 mg) is unaffordable or unavailable. Such use should occur after documenting the rationale for dose modification, and obtaining informed consent outlining the uncertain efficacy and associated evidence limitations. **Strength:** Conditional **Certainty of evidence:** Very low	The desirable and undesirable effects of reduced dosage was comparable to the standard full-dose regimen, with very low-certainty evidence supporting comparable clinical outcomes rather than superiority. Given the moderate resource savings, probable cost-effectiveness, and potential to improve equity, alongside the intervention's acceptability and likely feasibility, the panel judged the balance of effects to probably favour individualized dosing. The available evidence for reduced-dose pembrolizumab is derived solely from non-randomized cohort studies, which carry a high risk of confounding and selection bias. In view of the methodological limitations and the uncertainty around comparative efficacy, any consideration of a lower dose should be undertaken cautiously and restricted to settings where the standard dose is not feasible.

In patients with Small Cell Lung Cancer (SCLC), what is the comparative effectiveness of Prophylactic Cranial Irradiation (PCI) as compared to patients who did not receive PCI?	Prophylactic Cranial Irradiation (PCI) is ***recommended*** as compared to no PCI, for treatment of patients with small cell lung cancer. **Strength**: Strong **Certainty of evidence:** very low	The evidence shows moderate desirable effects and moderate undesirable effects with balance of effects favouring prophylactic cranial irradiation. The intervention was feasible and acceptable with probably no impact on equity, and therefore the recommendation is strong in favour of prophylactic cranial irradiation despite very low certainty of evidence.
In limited stage small cell lung cancer (SCLC), what would be the most effective timing and fractionation of radiation with concurrent chemotherapy that could significantly impact patient outcome?	For patients with limited-stage small cell lung cancer, either early (with first or second cycle of chemotherapy) or late (with third cycle of chemotherapy or after) integration of thoracic radiotherapy with standard chemotherapy is ***recommended***. **Strength**: Conditional **Certainty of evidence** – Low	The evidence showed trivial desirable effects with small undesirable effects, particularly a higher risk of acute esophagitis with early integration of radiotherapy. Resource requirements are similar with negligible cost differences, equity is probably not affected, and both approaches are considered probably acceptable and feasible. The small differences in benefits and harms do not clearly favor one approach over the other, requiring individualized decision-making based on clinical judgment and patient preferences.

GUIDELINE DEVELOPMENT PROCESS

Introduction:

A new process has been established within the Ministry of Health and Family Welfare (MoHFW) whereby comprehensive evidence-based guidelines are jointly developed by the Department of Health and Family Welfare (DoHFW), Directorate General of Health Services (DGHS), and the Department of Health Research (DHR) through a rigorous and robust scientific methodology. This initiative aims to bring clarity and consistency for key stakeholders, including patients, clinicians, and society at large. Evidence generation involved systematic reviews and meta-analyses of existing literature based on well-defined review questions structured using the PICO framework. The synthesized evidence was subsequently appraised for certainty using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This assessment informed the formulation of recommendations through structured Evidence-to-Decision (EtD) frameworks. Such rigorously developed evidence-based guidelines have the potential to bridge the research-to-policy gap by translating the best available evidence on healthcare interventions into routine clinical practice. (Figure 1).

Steps of Guideline Development

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

Rationale/Scope:

Over the past decade, lung cancer care has advanced rapidly with breakthroughs in molecular diagnostics, precision-targeted agents, immunotherapy, and refinements in surgical and radiotherapeutic techniques. In India, practice variation, access barriers, and implementation gaps persist, underscoring the need for cohesive, context-specific guidance. These guidelines synthesize evidence on prehabilitation, surgery, radiotherapy, chemotherapy, and palliative care, with existing available literature. By offering an ethically grounded framework tailored to India's healthcare landscape, these evidence-based recommendations aim to standardize care, improve equity, and enhance outcomes for individuals with lung cancer.

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.

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IN PATIENTS PLANNED FOR LUNG CANCER SURGERY, DOES PREHABILITATION IMPROVE PERIOPERATIVE OUTCOMES OVER STANDARD OF CARE?

Table of Contents

1. **Background…….** **11**
2. **Recommendations……..** **11**
3. **Rationale/Justification……** **11**
4. **Summary of Evidence……** **11**
5. **Key question in PICO format……..** **12**
6. **Risk of Bias……..** **14**
7. **Forest Plot……** **15**
8. **Summary of Findings Table……** **20**
9. **Evidence Profile Table……..** **21**
10. **Summary of Judgements……..** **23**
11. **Caveats in Existing Evidence……** **23**

Background

Lung cancer is the leading cause of cancer-related mortality worldwide, with surgery being a primary treatment for patients with resectable lung neoplasms. Despite advances in surgical techniques, lung cancer surgery is associated with significant perioperative risks, including respiratory complications, reduced functional capacity, prolonged hospital stays, and decreased quality of life. As a result, preoperative optimization strategies have become increasingly important to improve surgical outcomes and recovery. Prehabilitation, a concept that focuses on enhancing a patient's physical and mental health before surgery, has emerged as a potential means to improve postoperative outcomes in lung cancer patients. Prehabilitation interventions can include physical exercise, nutritional support, breathing exercises, and psychological counselling, each aimed at preparing the patient for the physiological stress of surgery. These interventions have been shown to reduce complications, improve functional recovery, and shorten hospital stays in various surgical populations.

Recommendations

Prehabilitation is ***recommended*** for patients planned to undergo lung cancer surgery.

Strength: Strong
Certainty of Evidence: Very low

Rationale/Justification

The evidence showed moderate desirable effects with trivial harms, alongside cost-effectiveness favouring the prehabilitation, increased equity, acceptability, and feasibility supporting a strong recommendation despite very low certainty of evidence

Summary of Evidence

Key Question

In patients planned for lung cancer surgery, does prehabilitation improve perioperative outcomes over standard of care?

Included Studies

A total of 4229 records from electronic databases were identified till date. Of the 4229 articles, 971 duplicate articles were removed. Further 3141 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 117 articles. After application of inclusion and exclusion criteria, 22 articles were selected for systematic review.

Population and Study Characteristics

All the studies included patients planned for lung cancer surgery. The review includes patients undergoing surgical treatment for lung cancer. Eligible studies are those that evaluate the effect of prehabilitation compared with standard of care in patients planned for lung cancer surgery.

Subgroups:

1. Surgical approach (open vs minimally invasive)
2. Type of surgery (lobectomy vs pneumonectomy)
3. Pre-existing cardiopulmonary comorbidities / poor performance status

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

1. Perioperative outcomes: pulmonary complications (*19 studies*)
2. Mortality (*4 studies*)
3. Quality of life (*4 studies*)
4. Length of hospital stay (*20 studies*)
5. Surgical complications (*11 studies*)
6. Functional recovery (*2 studies*)

Key question in PICO format

In patients planned for lung cancer surgery, does prehabilitation improve perioperative outcomes over standard of care?

Frame work	Description
Population	Patients planned for lung cancer surgery *Subgroup*: 1. Surgical approach (Open vs minimally invasive) 2. Type of surgery (lobectomy vs pneumonectomy) 3. Pre-existing cardiopulmonary comorbidities / poor performance status
Intervention	Prehabilitation
Comparator	Standard of care
Outcome	• Perioperative outcomes (*Critical outcome*) • Mortality (*Critical outcome*) • Quality of life (*Critical outcome*) • Length of hospital stay (*Important outcome*) • Surgical complications (*Important outcome*) • Functional recovery (*Important outcome*)

Critical Outcome reviewed and their MCID provided by GDG

Sr. No	Critical outcome reviewed	What does it measure	MCID decided by GDG
1	Perioperative Outcomes	Absolute risk reduction of Surgery/surgical procedure related complications/outcomes	5% difference at 30 days and at 90 days
2	Mortality following lung cancer surgery	Absolute risk reduction in mortality rate	3% at 2 years 3% at 5 years
		Proportion increases in median survival time	10% at all time points
3	Quality of Life	VAS score (ranging from 0-10)	2-point change
		QLQ -C30 (ranging from 0-100)	0.5 SD change for QLQ-C30 or 2.5 absolute difference

Risk of Bias Assessment

Assessment for Prehabilitation for Lung Cancer

Pulmonary Complications

	D1	D2	D3	D4	D5	Overall
Benzo et al	-	+	-	+	+	-
Chen et al	+	-	+	+	+	-
Garcia et al	+	-	X	+	+	X
Han et al	+	-	-	-	+	-
Huang et al a	-	-	+	+	+	-
Huang et al b	-	-	+	+	+	-
Karenovics et al	+	-	-	+	+	-
Kaya et al	-	-	-	-	+	-
Lai et al a	-	-	+	+	+	-
Lai et al b	-	-	+	+	+	-
Lai et al c	+	-	+	+	+	-
Laurent et al	-	-	+	-	+	-
Liu et al	+	-	+	+	+	-
Morano et al	+	-	+	+	+	-
Pehlivan et al	X	-	+	-	+	X
Tenconi et al	+	-	-	-	+	-
Yao et al	-	-	+	-	+	-
Zhou et al	+	-	+	-	+	-
Zou et al	-	-	+	+	+	-

Hospital stay

	D1	D2	D3	D4	D5	Overall
Benzo et al	-	+	-	+	+	-
Chen et al	+	-	+	+	+	-
Garcia et al	+	-	X	+	+	X
Han et al	+	-	-	-	+	-
Huang et al a	-	-	+	+	+	-
Huang et al b	-	-	+	+	+	-
Lai et al a	-	-	+	+	+	-
Lai et al b	-	-	+	+	+	-
Lai et al c	+	-	+	+	+	-
Laurent et al	-	-	+	-	+	-
Liu et al a	+	-	+	+	+	-
Liu et al b	+	-	+	+	+	-
Machado et al	+	-	+	+	+	-
Morano et al	+	-	+	+	+	-
Pehlivan et al	X	-	+	-	+	X
Tenconi et al	+	-	-	-	+	-
Wang et al	+	-	+	+	+	-
Yao et al	-	-	+	-	+	-
Zhou et al	+	-	+	-	+	-
Zou et al	-	-	+	+	+	-

+	Low risk
-	Some concerns
X	High risk

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

Pulmonary Complications

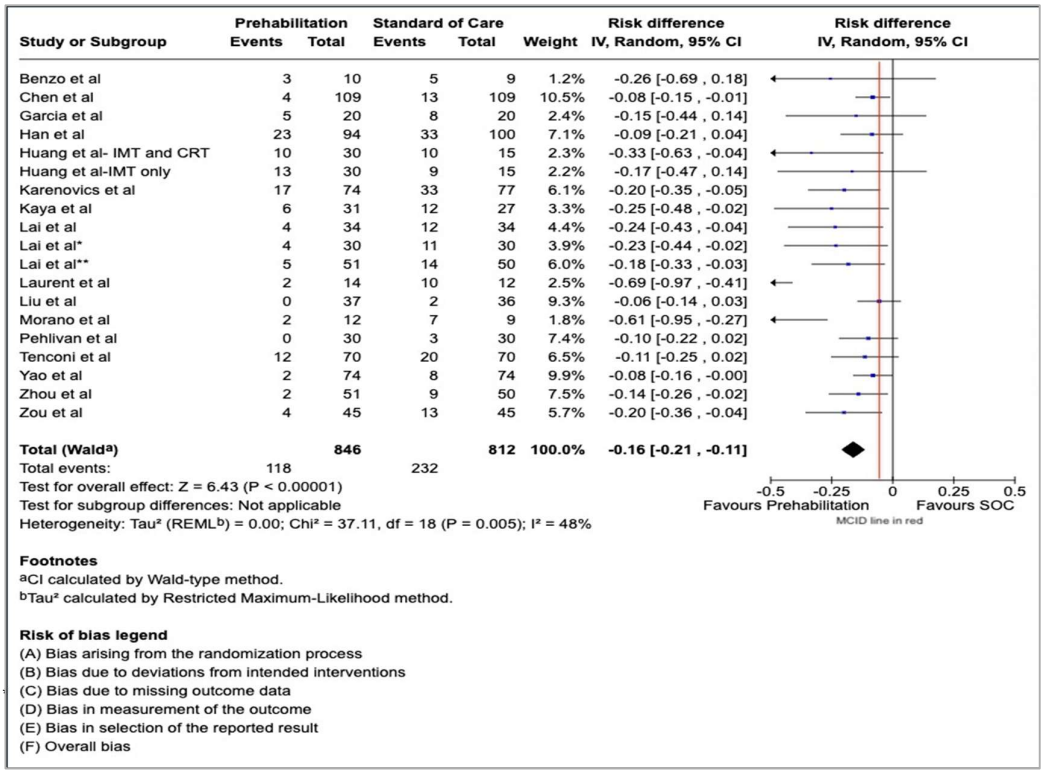
	D1	D2	D3	D4	D5	Overall
Huang et al	-	-	+	+	+	-
Karenovics et al	+	-	-	+	+	-
Lai et al	-	-	+	+	+	-
Laurent et al	-	-	+	-	+	-

Forest Plot: Desirable Effects

Perioperative outcomes: Pulmonary complications

Prehabilitation reduced the risk of pulmonary complications from 28.6% with standard care to 13.9%, with a risk difference of 0.16 lower (95% CI: 0.21 lower to 0.11 lower) based on data from 1,658 participants across 19 randomized controlled trials (Figure 3.1a), although the moderate heterogeneity and some risk of bias concerns indicate a need for cautious interpretation. The GDG defined a minimum clinically important difference (MCID) of 5% difference between the intervention and the standard of care, and the observed effect size substantially exceeded this threshold. Thus, the evidence showed a significant and clinically meaningful benefit of prehabilitation in reducing postoperative pulmonary complications in lung cancer patients.

Figure 3.1 (a): Forest plot - Pulmonary complications



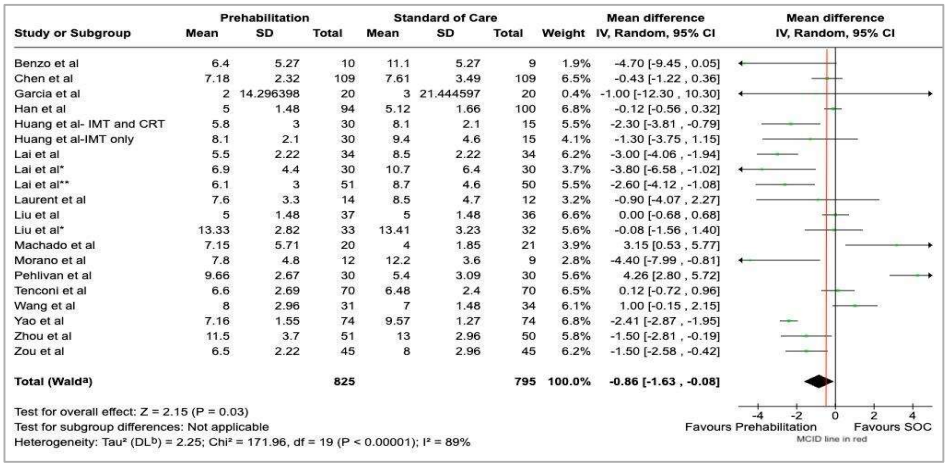
Hospital stays followed by lung cancer surgery is also a critical outcome decided by the GDG. Prehabilitation reduced the hospital stay by 14% (Mean difference 0.86 lower, 95% CI 1.63)

*- Orange line shows MCID given by GDG

Perioperative outcomes: Hospital stay following lung cancer surgery

Hospital stays followed by lung cancer surgery is also a critical outcome decided by the GDG. Prehabilitation reduced the hospital stay by 14% (Mean difference 0.86 lower, 95% CI 1.63 lower to 0,08 lower). (Figure 3.1b)

Figure 3.1 (b): Forest Plot - Hospital Stays

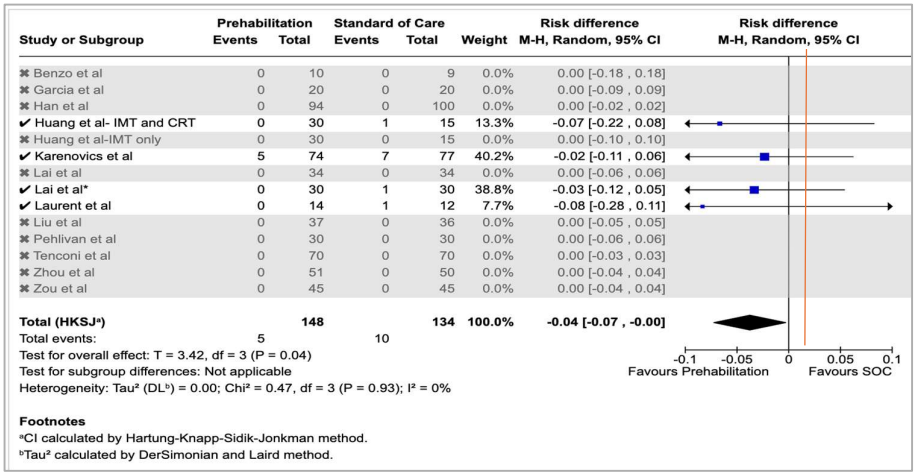


*- Orange line shows MCID given by GDG

Mortality following lung cancer surgery

Evidence from the studies show that prehabilitation was associated with a statistically significant 4% absolute reduction in postoperative mortality (risk difference: 0.04 lower; 95% CI: 0.07 lower to 0.00 lower; p = 0.04), with consistent findings across studies, suggesting a potential clinical benefit despite low event rates.

Figure 3.2: Forest plot – Mortality



*- Orange line shows MCID given by GDG

Quality of Life

Evidence indicates that prehabilitation significantly improves quality of life (QoL) outcomes in patients undergoing lung cancer surgery, with observed benefits across physical, mental, and functional domains, including reduced symptom burden and enhanced recovery of physical function postoperatively. Individual studies using tools like EQ-5D, SF-36, FACT-L, and EORTC QLQ-C30 consistently reported improvements in mobility, self-care, mental health, fatigue, and appetite loss. A formal meta-analysis of quality-of-life outcomes was not performed because the included studies employed diverse instruments (e.g., EQ-5D, SF-36, FACT-L, EORTC QLQ-C30) with non-equivalent constructs, scoring systems, assessment time-points, and inconsistent reporting of variances, rendering quantitative pooling unreliable. Future research should prioritize standardized assessment tools and uniform interventions to enable pooled analysis and stronger clinical guidance.

Figure 3.3: QoL outcomes of included studies

Study	QoL Tool Used	Key Findings	Conclusion
Chen et al.	EQ-5D	Better general health status in Prehab group; significant improvements in mobility ($p=0.002$), self-care ($p<0.001$), activity ($p=0.002$), pain ($p<0.001$), anxiety ($p=0.05$), and overall QoL ($p=0.01$).	Prehabilitation improved overall health across multiple domains, supporting its role in maintaining function post-surgery.
Ferreira et al.	SF-36 & FACT-L	Higher general health ($p=0.007$) and mental health ($p=0.044$) scores in Prehab group; FACT-L Total Score (105.6 vs. 101.3, $p=0.17$) and Lung Cancer Subscale (21 vs. 20.2, $p=0.35$) were also higher.	Prehabilitation improved general and mental health, though some differences were not statistically significant.
Garcia et al.	SF-36	Better physical function recovery in Prehab group; mean reduction in physical score was smaller (-2.8 vs. -7.4 post-surgery). At 3 months, physical function improved (+4.3 in Prehab) while it declined (-4.8) in SOC ($p<0.001$).	Prehabilitation enhanced physical function recovery and maintained improvements at 3 months post-surgery.
Machado et al.	EORTC QLQ-C30	Better QLQ-C30 scores at 4 weeks post-surgery (mean difference: 12.4 points, $p=0.029$). Lower deterioration rates in physical ($p=0.004$), role ($p=0.006$), and social function ($p=0.043$). Improved fatigue ($p=0.047$), pain ($p=0.041$), and appetite loss ($p=0.024$).	Prehabilitation led to lower deterioration in physical, role, and social function, with improved symptom burden.

Undesirable Effects

Adverse Events

Prehabilitation was generally safe and well tolerated across included studies. Out of 22 studies, adverse events were evaluated in 15 studies involving 840 participants: 11 studies reported no adverse effects, while four studies documented only minor, self-limiting effects attributable to the intervention. None of these studies reported serious or life-threatening intervention-related complications.

Machado et al. systematically reported Grade 1 adverse events in 30% of participants, primarily leg muscle soreness. Zhou et al. noted fatigue in 6 patients, dizziness in 2, and nausea in 1 during exercise sessions — all resolved with rest and without serious consequences. Han et al. reported dropouts due to acute exacerbation of COPD and knee pain, and Lai et al. (2016) noted withdrawals related to intensity intolerance and musculoskeletal discomfort. Lai et al. (2017) also reported dropouts due to perceived lack of benefit or inability to tolerate the program.

Summary of Findings Table

&

Evidence Profile Table

Summary of Findings Table

Prehabilitation compared to Standard of Care for patients planned to undergo lung cancer surgery

Patient or population: Patients with operable non-small cell lung cancer

Intervention: Prehabilitation

Comparison: Standard of Care

Outcomes	Anticipated absolute effects* (95% CI)		Risk Difference (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Standard of Care	Risk with Prehabilitation			
Pulmonary Complications	28.6% (232/812)	13.9% (118/846)	**RD -0.16** (0.21 lower to 0.11 lower)	1658 (19 RCTs)	⊕⊕◯◯ Low[a]
Hospital stays following lung cancer surgery	The mean hospital stays 8.2 days	The mean hospital stays 7.4 days	MD -**0.86** (1.63 lower to 0.08 lower)	1620 (20 RCTs)	⊕◯◯◯ Very low[a,b,c]
Mortality following lung cancer surgery	7.4% (10 per 134)	3.3% (5 per 148)	**RD -0.04** (0.07 lower to 0.00)	282 (4 RCTs)	⊕◯◯◯ Very low[a,c]

*__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

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. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 89%*
c. *Downgraded one level for imprecision as the 95% CI crossed the MCID.*

Evidence Profile Table

Prehabilitation compared to standard of care for patients planned to undergo lung cancer surgery

Patient or population: Patients with operable non-small cell lung cancer
Intervention: Prehabilitation
Comparison: Standard of Care

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prehabilitation	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality following lung cancer surgery												
4	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	5 per 148 (3.3%)	10 per 134 (7.4%)	-	-0.04 (-0.07 to 0.00)	⨁◯◯◯ Very low[a,c]	CRITICAL
Pulmonary Complications												

19	randomised trials	very serious[a]	not serious	not serious	not serious	none	116/1000 (11.6%)	232/812 (28.6%)	-	-0.16 (-0.21 to -0.11)	⊕⊕◯◯ Low[a]	CRITICAL
Hospital stays												
20	randomised trials	very serious[a]	Serious[b]	not serious	Serious[c]	None	Mean hospital stays 8.2 days	Mean hospital stays 7.4 days		-0.86 (-1.63 to -0.08)	⊕◯◯◯ Very low[a,b,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. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 89%*
c. *Downgraded one level for imprecision as the 95% CI crossed the MCID.*

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	Favors the intervention
Resources required	Varies
Certainty of evidence of required resources	Very Low
Cost effectiveness	Favors the intervention
Equity	Probably increased
Acceptability	Yes
Feasibility	Yes
Recommendations: Prehabilitation is ***recommended*** for patients planned to undergo lung cancer surgery. **Strength:** Strong **Certainty of Evidence**: Very low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

Health Economic Evaluations: There is a lack of formal cost-effectiveness and cost-utility analyses of prehabilitation versus standard care using Indian cost data, including personnel, delivery models, hospital resource use, and QALYs to inform policy and payer decisions.

Equity-Focused Research: There is limited evidence examining disparities in access and benefits across urban–rural settings, socioeconomic groups, and public versus private centres, restricting understanding of structural, financial, and geographic barriers.

Feasibility & Acceptability Studies: There is a paucity of mixed-methods and implementation research assessing institutional readiness, workforce capacity, infrastructure needs, and stakeholder perspectives to guide scalable implementation.

IN PATIENTS WITH OPERABLE NON-SMALL CELL LUNG CANCER, DOES NEOADJUVANT CHEMOTHERAPY WITH/WITHOUT IMMUNOTHERAPY FOLLOWED BY SURGERY AS COMPARED TO UPFRONT SURGERY FOLLOWED BY ADJUVANT CHEMOTHERAPY WITH/WITHOUT IMMUNOTHERAPY IMPROVE OVERALL SURVIVAL?

Table of Contents

12. Background…… 27

13. Recommendations…… 27

14. Rationale/Justification…… 27

15. Summary of Evidence…… 27

16. Key question in PICO format…… 28

17. Risk of Bias…… 30

18. Forest Plot…… 31

19. Summary of Findings Table…… 32

20. Evidence Profile Table…… 33

21. Summary of Judgements…… 34

22. Caveats in Existing Evidence…… 34

Background

Surgery is the primary treatment for early-stage NSCLC, but only about 25% of patients are eligible, and recurrence occurs in 30–55% of cases, often with metastasis. This underscores the need for perioperative therapies, either neoadjuvant or adjuvant to address micrometastases. While overall survival (OS) appears similar between these approaches, adjuvant therapy remains more commonly used, reflecting clinical preference. However, neoadjuvant therapy offers benefits such as tumor downstaging, increased resectability, and earlier micrometastatic control, potentially improving OS and disease-free survival (DFS). The introduction of immunotherapies, particularly immune checkpoint inhibitors, has further advanced outcomes in NSCLC. Despite these developments, the optimal timing, preoperative vs. postoperative remains unclear due to limited head-to-head evidence.

Recommendation

Recommendation: For patients with operable non-small cell lung cancer (NSCLC), either neoadjuvant chemotherapy with or without immunotherapy followed by surgery, or upfront surgery followed by adjuvant chemotherapy with or without immunotherapy, is ***recommended***.

Strength: Conditional

Certainty of evidence: Very low

Rationale/Justification

The evidence showed trivial desirable effects and trivial undesirable effects with low certainty of evidence. The balance of effects was judged to does not favour either the intervention or the comparison. For cost-effectiveness the judgement does not favour either the intervention or the comparison. Additionally, the intervention is both probably acceptable to stakeholders and probably feasible to implement across settings.

A conditional recommendation in favour of either neoadjuvant chemotherapy (with or without immunotherapy) followed by surgery, or upfront surgery followed by adjuvant chemotherapy (with or without immunotherapy).

The use of shared decision-making was considered essential, enabling clinicians and patients to discuss the substantial uncertainty in the evidence and incorporate individual preferences such as comorbidities, timing considerations, and surgical logistics, when choosing between neoadjuvant and upfront surgery strategies.

Summary of Evidence

Key Question

In patients with operable non-small cell lung cancer, does neoadjuvant chemotherapy with/without immunotherapy followed by surgery as compared to upfront surgery followed by adjuvant chemotherapy with/without immunotherapy improve overall survival?

Included Studies

A total of 25487 records from electronic databases were identified till 28th May 2024. Of the 25487 articles, 6503 duplicate articles were removed. Further 18,894 articles were excluded after title and abstract screening because they were not relevant. Full text examination was done for 90 articles. After application of inclusion and exclusion criteria, 1 article were included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with operable non-small cell Lung cancer. The review includes adults of all ages and genders. Eligible study was the one that evaluated the effect of preoperative chemotherapy plus surgery or surgery plus adjuvant chemotherapy as compared with surgery for treating operable non-small cell lung cancer in patients.

Subgroups:

1. T stage
2. Nodal involvement
3. Histology
4. PDL1
5. Smoking status

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

1. Overall survival (*1 study*)
2. Adverse effects (*No study*)
3. Quality of life (*No study*)
4. Disease-free survival (*1 study*)
5. Response rate (*No study*)
6. Surgical outcomes (intraoperative and postoperative complications) (*1 study*)

PICO

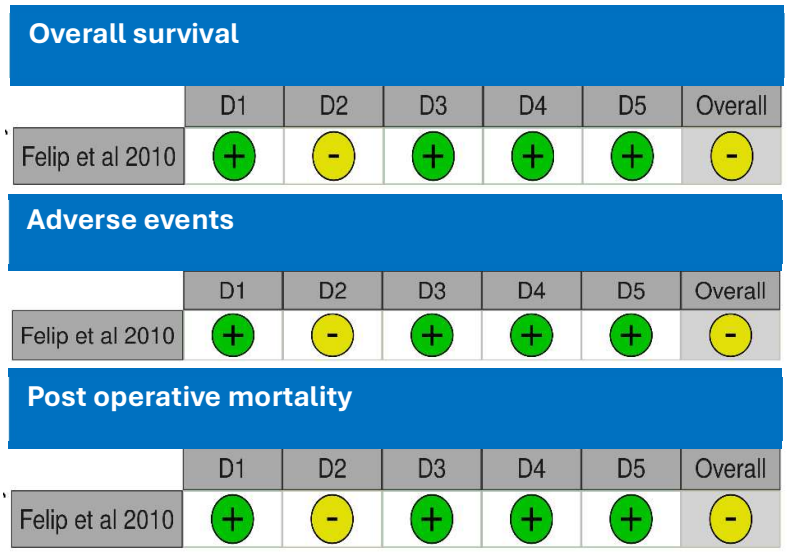
Framework	Description
Population	Patients with operable non-small cell lung cancer *Subgroups*: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status
Intervention	Neoadjuvant chemotherapy with/without immunotherapy followed by surgery *Subgroups*: Neoadjuvant chemotherapy only followed by surgery Neoadjuvant chemotherapy with immunotherapy followed by surgery
Comparator	Upfront surgery followed by adjuvant chemotherapy with/without immunotherapy

	Subgroups: 1. Upfront surgery followed by chemotherapy only 2. Upfront surgery followed by chemotherapy and immunotherapy 3. Upfront surgery followed by immunotherapy only
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Quality of life (*Critical Outcome*) • Disease-free survival (*Important Outcome*) • Response rate (*Important Outcome*) • Surgical outcomes (intraoperative and postoperative complications) (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

	Critical outcome	**MCID**
Overall survival	OS (Proportion of people who have survived at a particular time point)	5% at 2 years 5% at 5 years
	OS (Proportion increase in median survival)	20% at all time points
Adverse events		5% difference in grade 3 or higher AEs 10% difference in any grade AEs

Risk of Bias Assessment



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

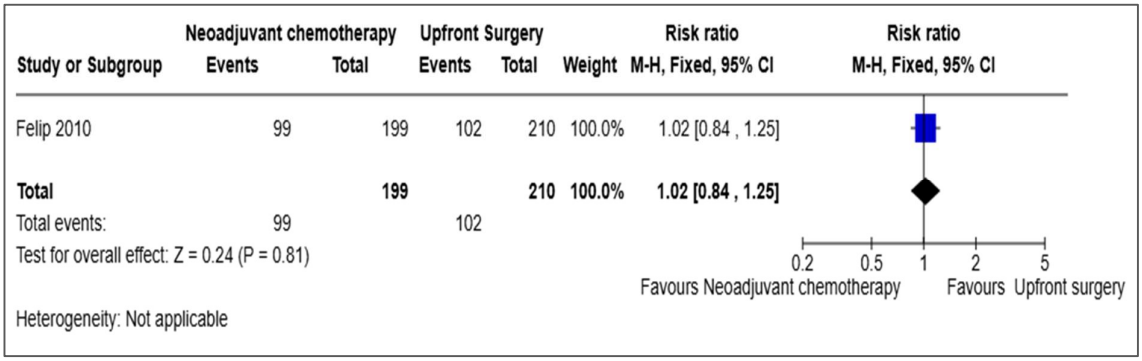
+	**Low risk**
-	**Some concerns**
-	**High risk**

Forest Plot: Desirable Effects

Overall Survival

The relative risk (RR) for mortality was 1.02 (95% CI: 0.84 to 1.25; P = 0.81), indicating no statistically significant difference in the risk of death between the two treatment groups. The results are based on only one study which did not had immunotherapy. The study dates back when the immunotherapy was not a prevalent practice.

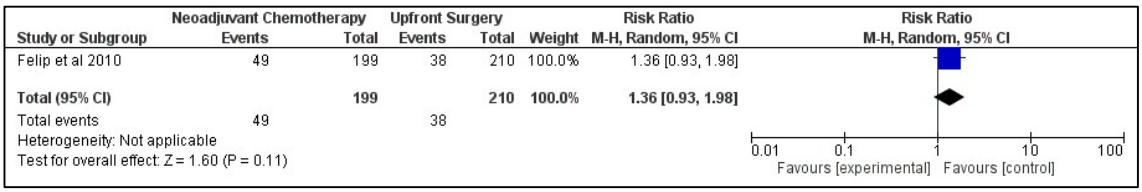
Figure1: Forest plot: Overall Survival



Undesirable Effects

The evidence indicates no statistically significant difference in serious adverse events between neoadjuvant chemotherapy and upfront surgery, with a reported risk ratio of 1.36 (95% CI 0.93–1.98). The review had only one study in which immunotherapy was also missing. The included study reported a total of 448 adverse events in the neoadjuvant chemotherapy group, including 49 (10.9%) serious adverse events (SAEs) of grade 3 or higher. In comparison, the upfront surgery group experienced 370 adverse events, with 38 (10.2%) SAEs.

Figure2: Forest Plot: Adverse events of grade 3 or higher



Summary of Findings Table

Neoadjuvant chemotherapy versus upfront surgery followed by adjuvant chemotherapy with/without immunotherapy.

Patient or population: Operable Non-Small Cell Lung Cancer
Intervention: Neoadjuvant chemotherapy
Comparison: Upfront surgery followed by adjuvant chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Upfront Surgery	Risk with Neoadjuvant chemotherapy			
Overall Survival	486 per 1000	496 per 1000 (408 to 607)	RR 1.02 (0.84 to 1.25)	409 (1 RCT)	⊕◯◯◯ very low[a,b,c]
Adverse events grade ≥3	181 per 1,000	246 per 1,000	RR 1.36 (0.84 to 1.25)	409 (1 RCT)	⊕◯◯◯ very low

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

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

Explanation:

a. *Some concerns were identified in the study included for this outcome*
b. *Single study was downgraded one level for inconsistency as it was in evaluable*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

Evidence Profile Table

Neoadjuvant chemotherapy versus upfront surgery followed by adjuvant chemotherapy with/without immunotherapy.

Patient or population: Operable Non-Small Cell Lung Cancer

Intervention: Neoadjuvant chemotherapy

Comparison: Upfront surgery followed by adjuvant chemotherapy

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemotherapy	Upfront Surgery	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	randomised trial	serious[a]	serious[b]	not serious	serious[c]	none	99/199 (49.7%)	102/210 (48.6%)	**RR 1.02** (0.84 to 1.25)	**10 more per 1000** (from 78 fewer to 121 more)	⊕◯◯◯ very low[a,b,c]	CRITICAL
Adverse events Grade ≥ 3												
1	randomised trial	serious[a]	serious[b]	not serious	serious[c]	none	49/199 (10.9%)	38/210 (10.2%)	**RR 1.36** (0.84 to 1.25)	**65 more per 1,000** (from 13 fewer to 177 more)	⊕◯◯◯ very low[a,b,c]	CRITICAL

CI: Confidence Interval

Explanations:

a. *Some concerns were identified in the study included for this outcome*

b. *Single study was downgraded one level for inconsistency as it was in evaluable*

c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

Summary of Judgements

Problem	Yes
Desirable Effects	Trivial
Undesirable Effects	Trivial
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Negligible costs and savings
Certainty of evidence of required resources	Low
Cost effectiveness	Does not favor either the intervention or the comparison
Equity	Probably no impact
Acceptability	Probably yes
Feasibility	Probably yes
Recommendation: For patients with operable non-small cell lung cancer (NSCLC), either neoadjuvant chemotherapy with or without immunotherapy followed by surgery, or upfront surgery followed by adjuvant chemotherapy with or without immunotherapy, is ***recommended***. **Strength:** Conditional **Certainty of evidence:** Very low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

There is an absence of high-quality RCTs directly comparing neoadjuvant versus adjuvant chemo-immunotherapy in operable NSCLC using current standard regimens, limiting applicability to present-day practice.

IN EARLY-STAGE OPERABLE NON-SMALL CELL LUNG CANCER (NSCLC), WHAT IS THE COMPARATIVE EFFECTIVENESS OF STEREOTACTIC BODY RADIATION THERAPY (SBRT) VERSUS LOBECTOMY/ SEGMENTECTOMY IN IMPROVING SURVIVAL?

Table of Contents

23. Background…….. 37

24. Recommendations…….. 37

25. Rationale/Justification…… 37

26. Summary of Evidence…… 38

27. Key question in PICO format…….. 39

28. Risk of Bias…….. 40

29. Forest Plot…… 41

30. Summary of Findings Table…… 49

31. Evidence Profile Table…… 52

32. Summary of Judgements…….. 55

33. Caveats in Existing Evidence…… 55

Background

Lung cancer is the most commonly diagnosed cancer worldwide, with approximately 2.2 million new cases. Broadly, lung cancer comprises of two major categories: non-small cell lung cancer (NSCLC) which includes around 85% of all lung cancer patients and small cell lung cancer (SCLC) that includes the remaining 15% of the patients. NSCLC has been reported to be responsible for 1.8 million deaths in 2020. Management of the NSCLC poses a significant challenge considering the fact that most of the patients reach the healthcare system at a late-stage of the disease. This makes the early stage of the NSCLC more suitable for interventions with a significant impact on the outcomes and prognosis of the disease. Since the 1995 publication by the Lung Cancer Study Group (LCSG) of their randomized trial comparing lobectomy with limited resection for stage I NSCLC, lobectomy has been considered the gold standard treatment for all early-stage tumors. Over the period, sub-lobar resection, which includes segmentectomy, was also found to be equally effective in the management of early-stage NSCLC. Radiation therapy for the early-stage operable NSCLC has been under study since long time. Albeit surgery being the current gold standard, stereotactic body radiation therapy (SBRT), is being recommended and practiced for patients who are not medically fit for undergoing the operative procedure. SBRT is highly tolerated, performed on an outpatient basis, and has demonstrated local tumor control rates exceeding 90%. It presents an appealing alternative to invasive surgical procedures. Yet, SBRT' role in the patients who are fit for surgeries and its comparative efficacy with the lobectomy or segmentectomy in such patients is still under study.

In this background, it is paramount to undertake a systematic review and meta-analysis on the comparative effectiveness of stereotactic body radiation therapy (SBRT) versus lobectomy/segmentectomy in improving survival of early-stage operable non-small cell lung cancer (NSCLC).

Recommendations

Stereotactic body radiation therapy (SBRT) is ***not recommended*** as compared to lobectomy/segmentectomy, for treatment of patients with early-stage operable non-small cell lung cancer except for selected patients who are unwilling or medically unfit for surgery.

Strength: Conditional

Certainty of evidence – Low

Rationale/Justification

Based on the available evidence, the panel concluded that surgery remains the preferred treatment; however, SBRT may be considered for selected patients who are unwilling or medically unfit for surgery. The rationale for this recommendation is as follows:

- Quality and maturity of evidence: The available RCT evidence for SBRT is of very low quality and lacks long-term follow-up. In contrast, observational studies provide mature survival data supporting the effectiveness and durability of surgical outcomes.

- Time-tested nature of surgery: Multiple experts emphasized that surgery remains the established and time-tested standard for operable early-stage lung cancer, with predictable long-term outcomes.
- Appropriate use of SBRT: SBRT should be reserved for patients who are medically inoperable or unwilling to undergo surgery.
- Patient autonomy: Given the limited high-quality RCT data, treatment choice should ultimately be guided by patient preference after informed discussion.
- Tumour size limitation: Any consideration of SBRT should be restricted to tumours smaller than 4 cm (T1–IIA stage), in line with evidence from existing studies.

Final Judgement:

The GDG concluded that lobectomy (surgery) remains the preferred option for operable early-stage lung cancer, given its established evidence base and long-term survival advantage. SBRT may be offered as an alternative only to patients who are unfit for or decline surgery, with full disclosure of the limitations in existing evidence.

Summary of Evidence

Key Question

In early-stage operable non-small cell lung cancer (NSCLC), what is the comparative effectiveness of stereotactic body radiation therapy (SBRT) versus lobectomy/ segmentectomy in improving survival?

Included Studies

A total of 2123 records from electronic databases were identified June 2024. Of the 2123 articles, 708 duplicate articles were removed. Further 1247 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 62 articles after removing 109 studies during full text screening with reasons. After application of inclusion and exclusion criteria, 3 articles were selected for systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with non-small cell lung carcinoma. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effectiveness of stereotactic body radiation therapy versus lobectomy/segmentectomy in improving survival for patients with non-small cell lung cancer.

Subgroups:

1. T stage
2. Nodal involvement
3. Histology
4. PDL1
5. Smoking status

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

1. Overall survival (*Two studies*)
2. Quality of life (*Two studies*)
3. Adverse Effects (*One Study*)
4. Disease free survival (*One Study*)
5. Cost (*No studies*)
6. Surgical outcomes (*No studies*)
7. Post operative Pulmonary function (*No studies*)

Key Question in PICO Format

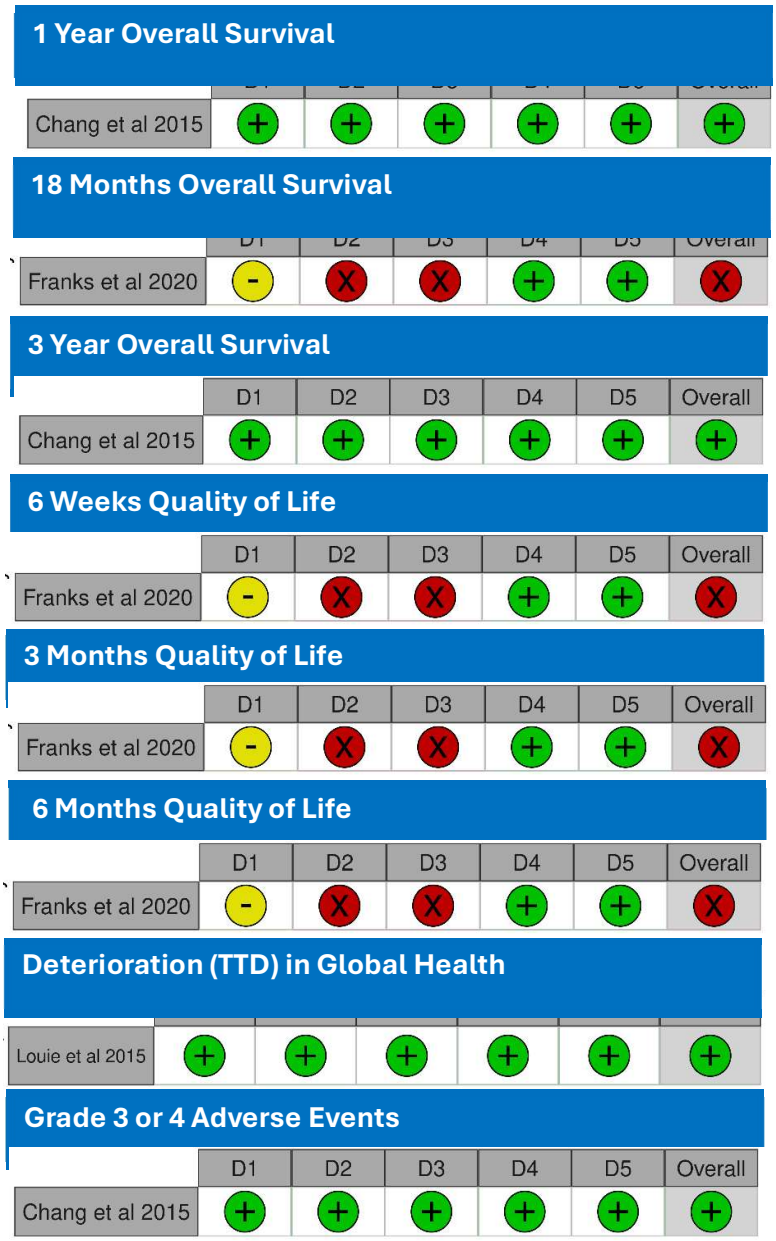
In early-stage operable non-small cell lung cancer (NSCLC), what is the comparative effectiveness of stereotactic body radiation therapy (SBRT) versus lobectomy/ segmentectomy in improving survival?

Framework	Description
Population	People with early-stage operable non-small cell lung cancer (NSCLC) *Subgroups*: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status
Intervention	Stereotactic Body Radiation Therapy (SBRT)
Comparator	Lobectomy or segmentectomy
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Quality of life (*Critical Outcome*) • Disease free survival (*Important Outcome*) • Cost (*Important Outcome*) • Surgical outcomes (*Important Outcome*) • Post operative pulmonary function (*Important Outcome*)

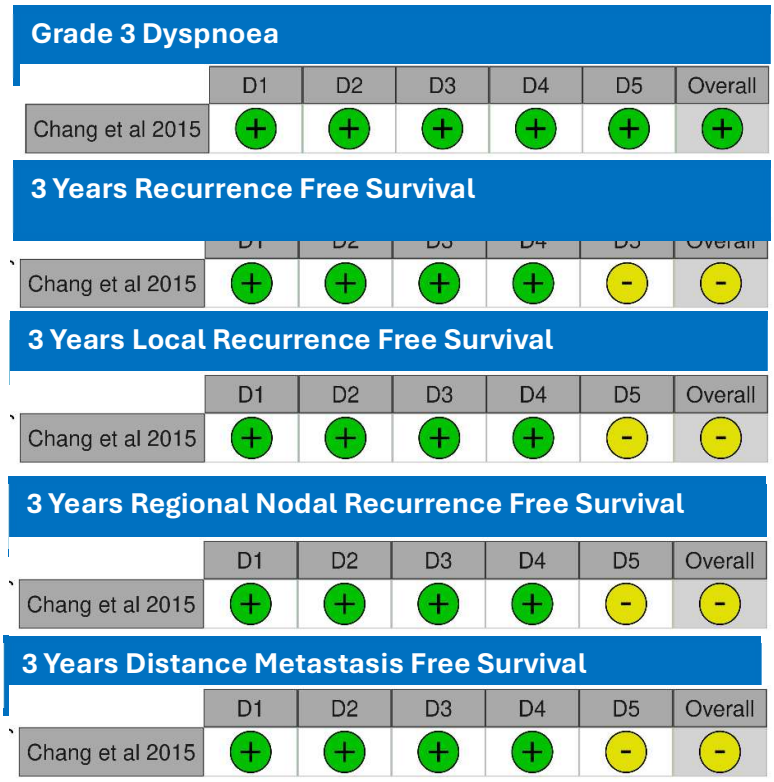
Critical Outcome reviewed and their MCID

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) (At all time points)	-2.5% non-inferiority
2	Adverse Events	Proportion difference in grade 3 or higher AEs	10%
3	Quality of Life	Point of change on the 0-100 scale	10 Points

Risk of Bias Assessment



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



Forest Plot: Desirable Effects

Overall Survival

Evidence showed no statistically significant difference between SBRT and surgery for 1 year of overall survival. The analysis of studies comparing overall survival for SBRT vs surgery yielded a risk ratio of 1.13 (95% CI: 0.97 to 1.30). Evidence showed no statistically significant difference between SBRT and surgery for 1-year overall survival. The analysis of studies comparing overall survival for SBRT versus surgery yielded a risk ratio of 1.13 (95% CI: 0.97 to 1.30). Although this result is not statistically significant, the lower bound of the confidence interval (0.97) remains above the prespecified non-inferiority margin (RR = 0.975), indicating that SBRT is likely clinically non-inferior to surgery.

Figure 3.1 – Forest plot: 1 Year Overall survival

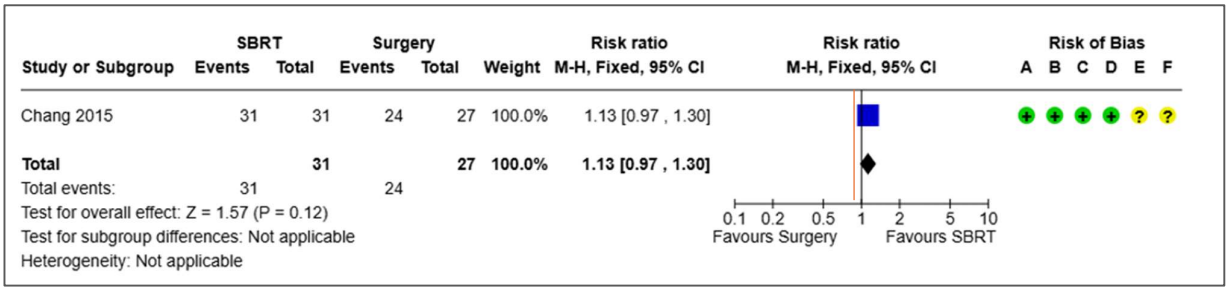


Figure 3.2 – Forest plot: 18 Months Overall survival

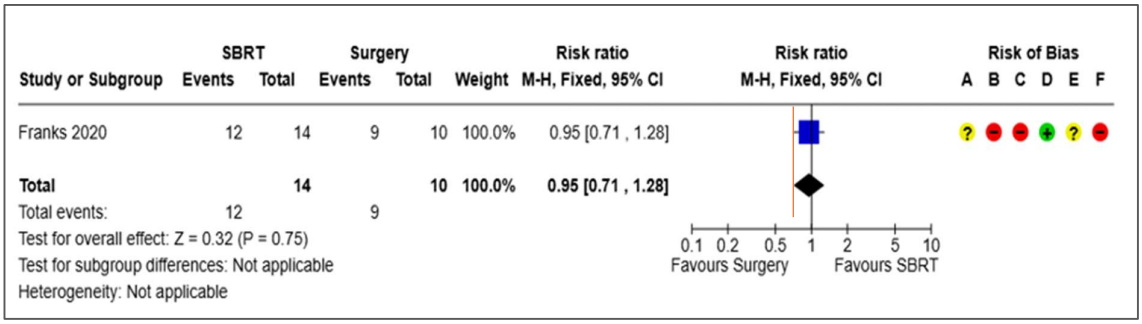


Figure 3.3 – Forest plot: 3 Years Overall survival

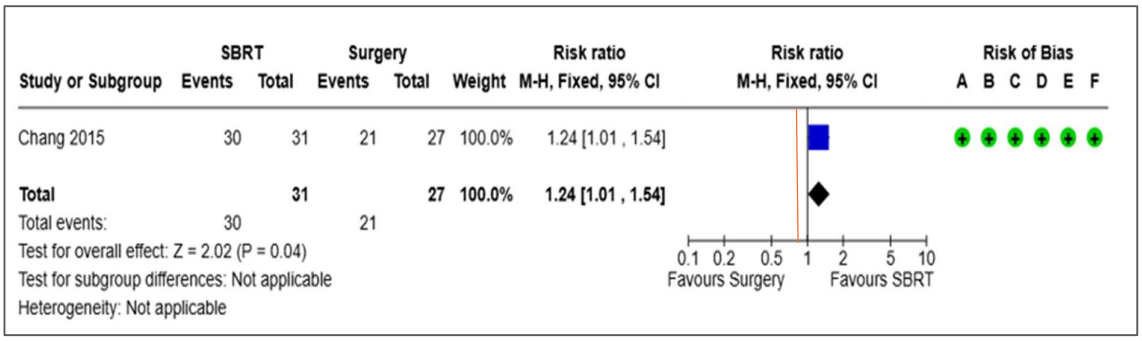
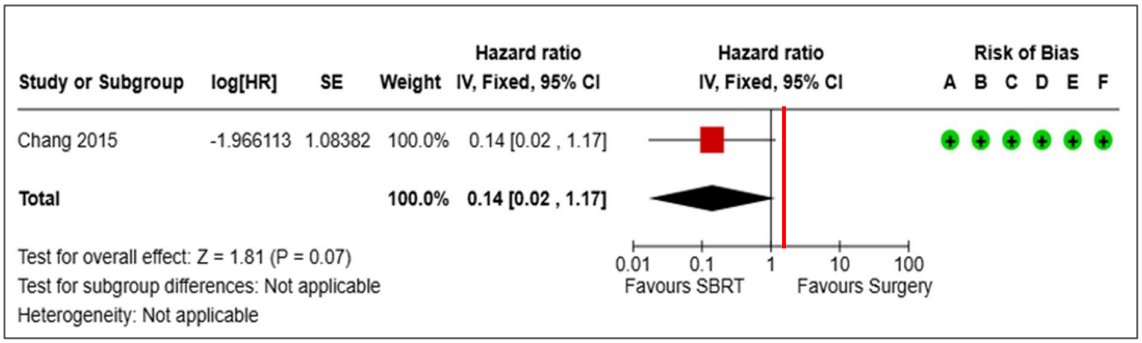
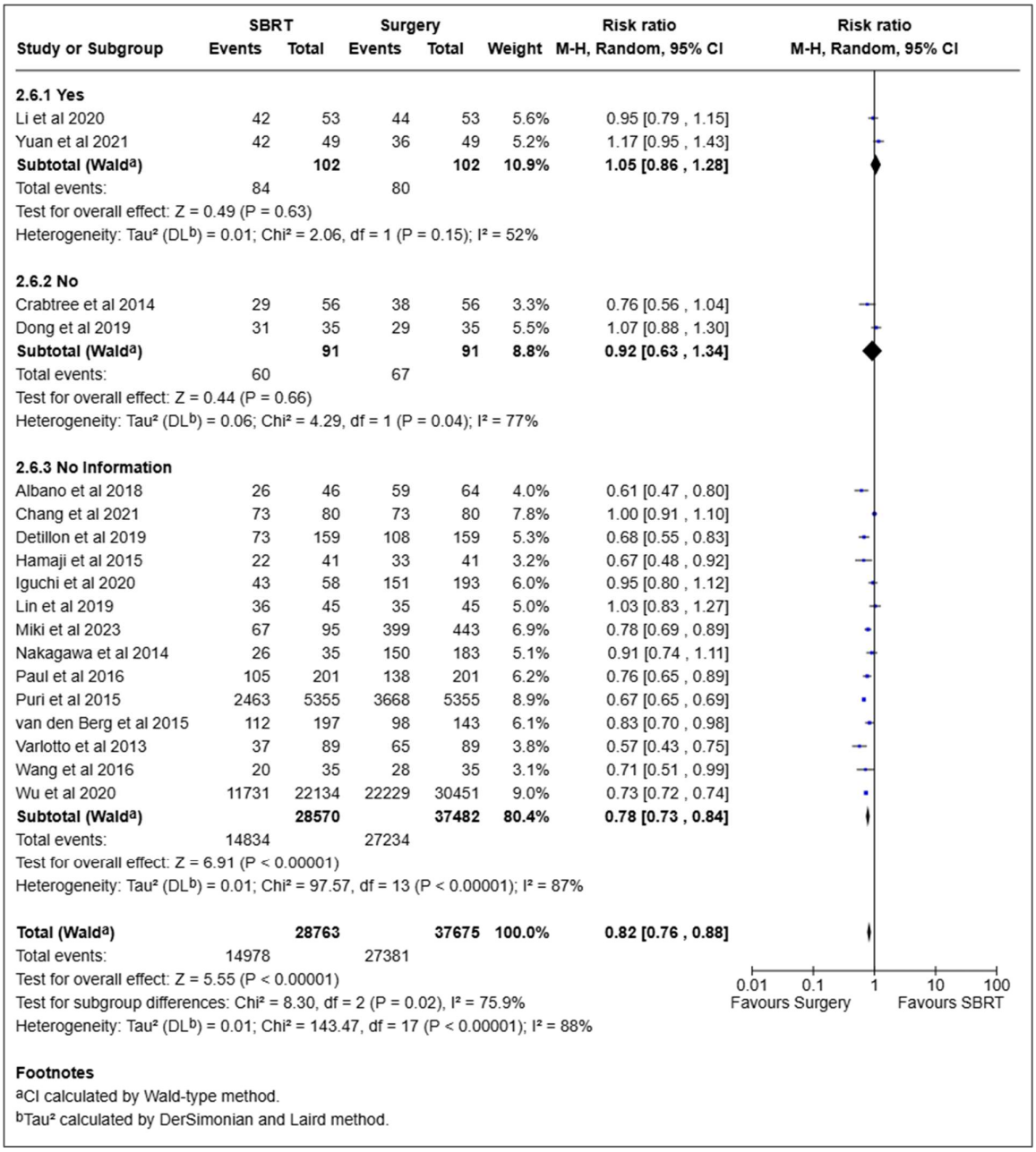


Figure 3.4 – Forest plot: 3 Years Overall survival (HR)



Forest plots from observational studies

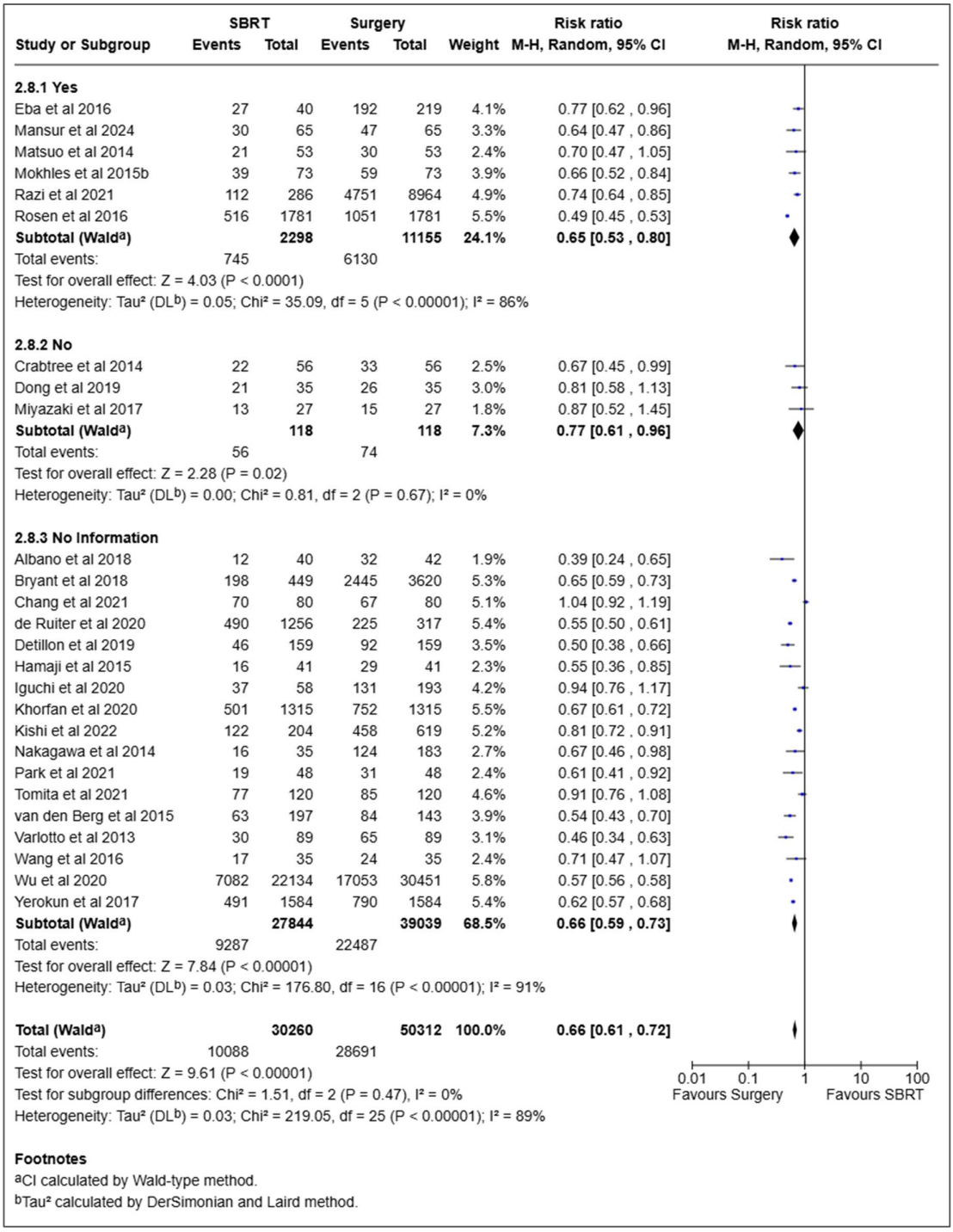
Figure 3.5: ***3-year overall survival***



Sub-groups:

1. Yes- Studies that included patients who could have been fit for both surgery and SBRT
2. No- Studies that included surgery ineligible patients in the SBRT group
3. No information- Not mentioned anything on this explicitly

Figure 3.6: ***5-year overall survival***



Quality of Life

Evidence for Quality of life showed no statistically significant or clinically meaningful difference between SBRT and surgery for 6 weeks, 3 months and 6 months. The analysis of studies comparing QoL for SBRT vs surgery yielded a risk ratio of 0.10 (95% CI: 0.17 lower to 0.37) for 6 weeks and the risk ratio for 3-month and 6-month are 0.00 (95% CI: 0.29 lower to 0.29) and 0.00 (95% CI: 0.45 lower to 0.45) respectively. Additionally, studies comparing QoL as deterioration of Global Health reported a risk ratio of 0.28 (95% CI: 0.08 to 0.98) suggesting large reduction in deterioration in global health/QoL.

Figure 3.7 – Forest plot: 6 weeks Quality of Life

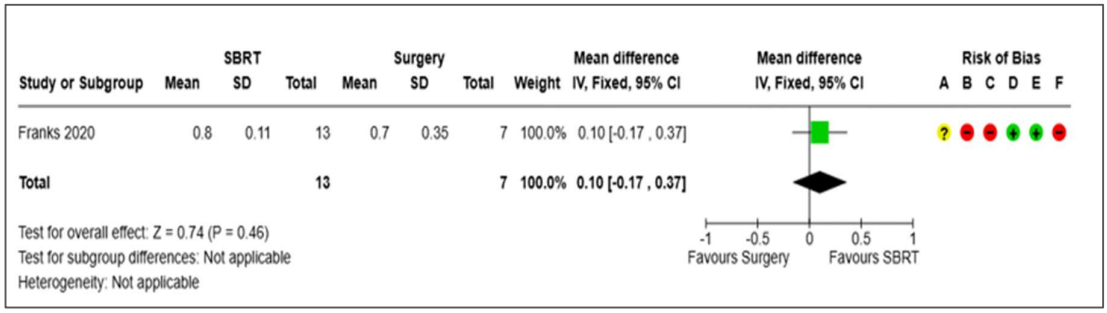


Figure 3.8 – Forest plot: 3 months Quality of Life

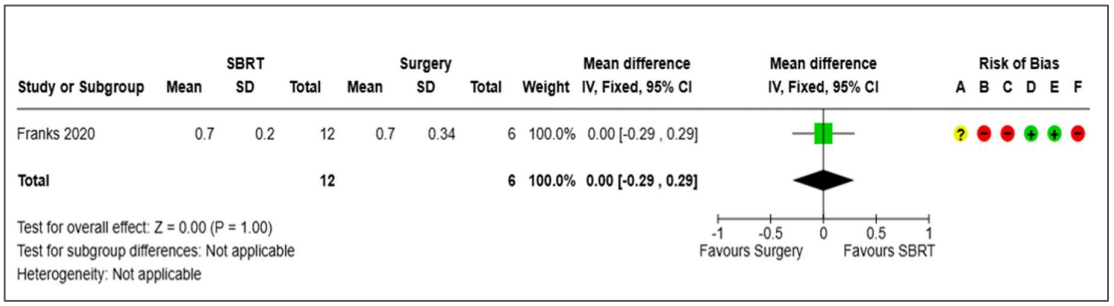


Figure 3.9 – Forest plot: 6 months Quality of Life

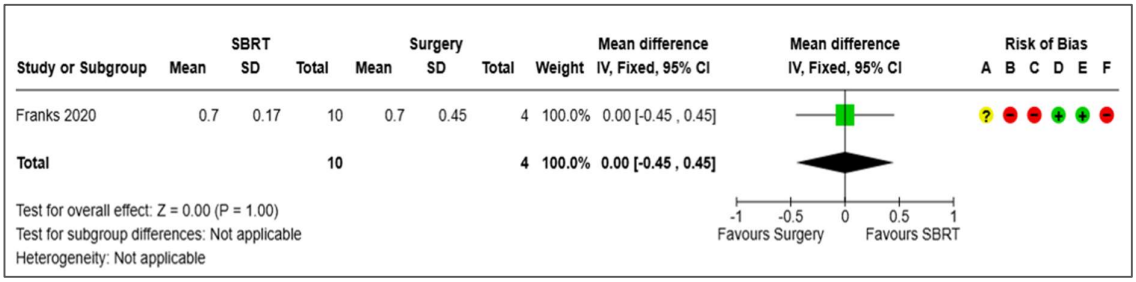
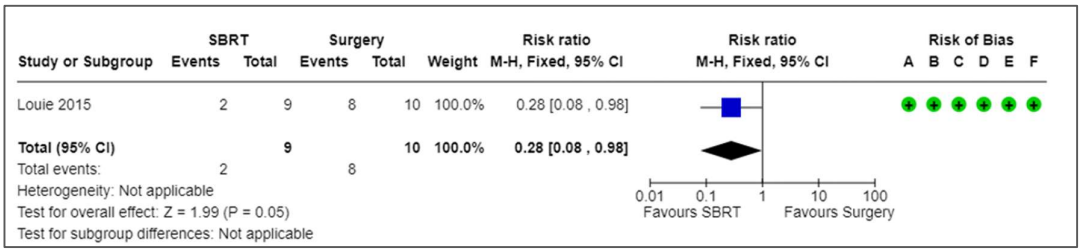


Figure 3.10 – Forest plot: Deterioration of Global Health/QoL



Undesirable Effects

Adverse Effects

Evidence for adverse events showed statistically significant and clinically meaningful difference between SBRT and surgery for Grade 3 or Grade 4 events. The analysis of studies comparing adverse effects for SBRT vs surgery yielded a risk ratio of 0.22 (95% CI: 0.07 to 0.69) suggesting in large reduction in grade 3 or 4 adverse events. Additionally, studies comparing Grade 3 dyspnoea showed no statistical significance and yielded a risk ratio of 0.44 (95% CI: 0.09 to 2.19).

Figure 4- Forest Plot: Grade 3 or 4 adverse events

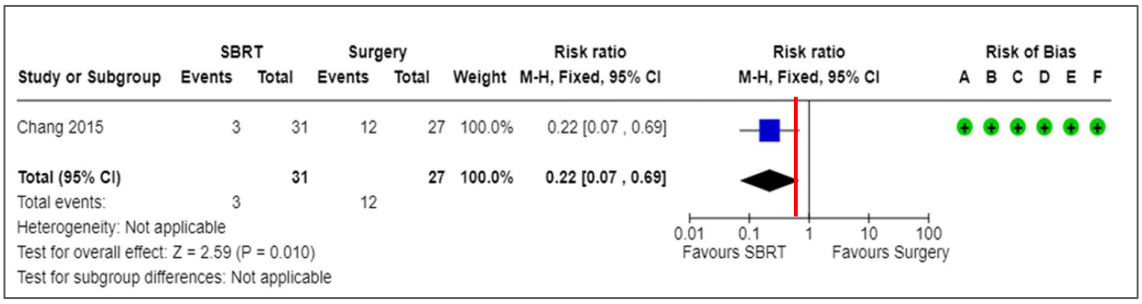
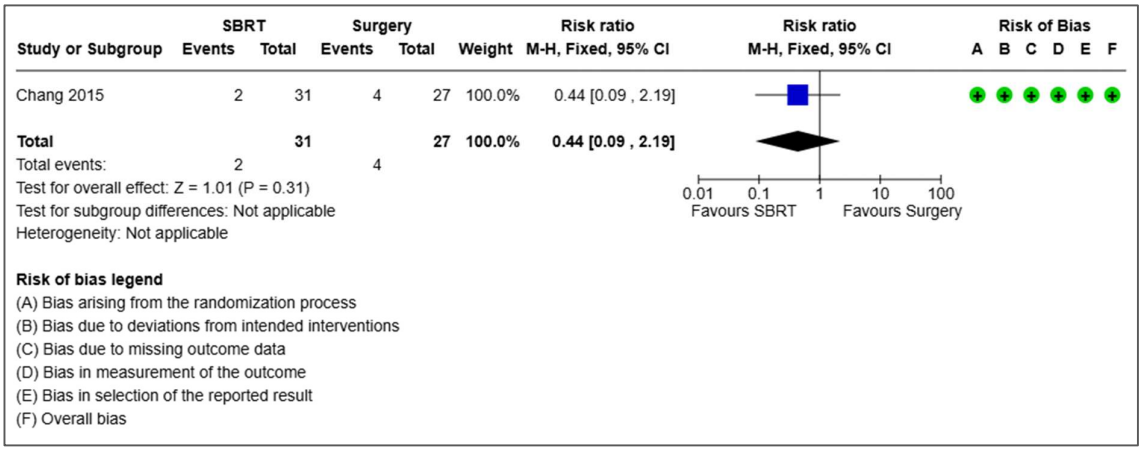
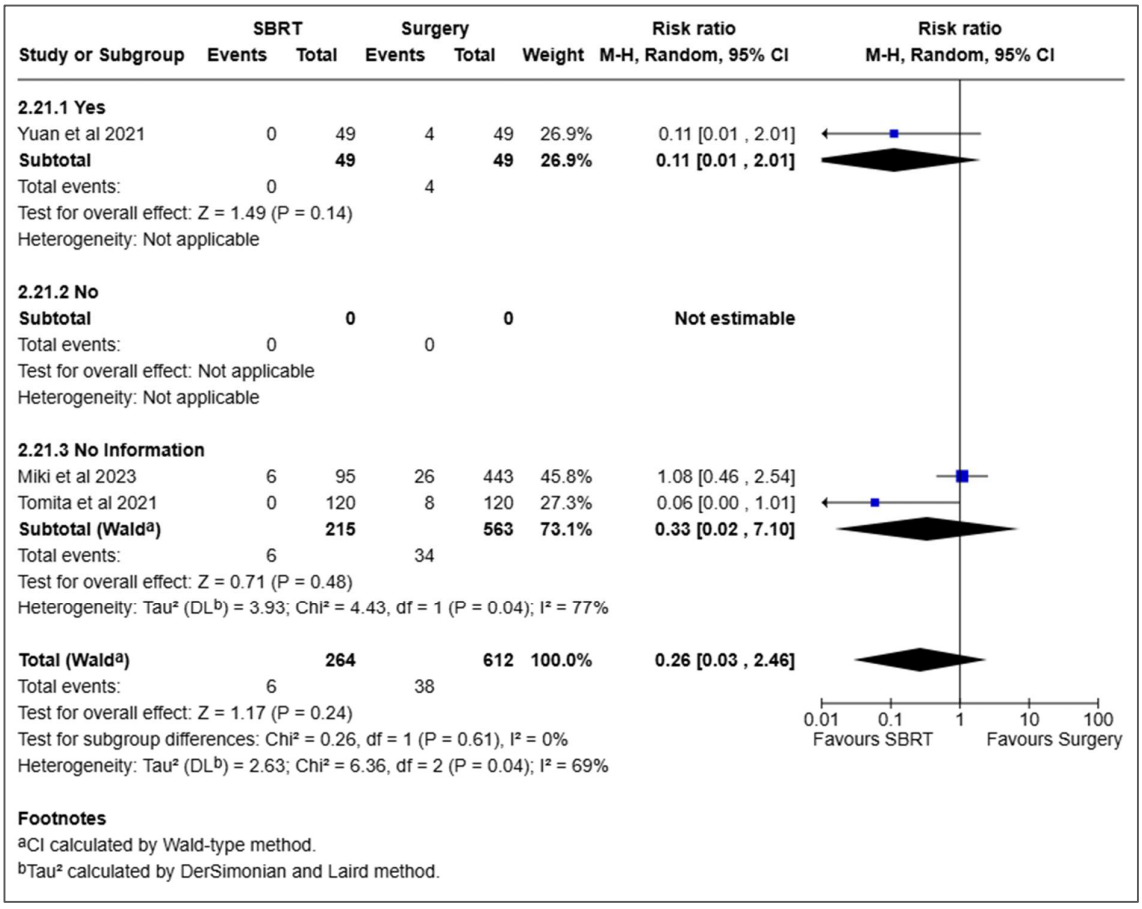


Figure 5: Forest Plot: Grade 3 dyspnoea



Undesirable effects from observational studies

Figure 6: Grade 3 or 4 adverse events



Summary of Findings Table

SBRT compared to Surgery (Limited Resection) for early-stage operable non-small cell lung cancer (NSCLC)

Patient or population: Early-stage operable non-small cell lung cancer (NSCLC)
Intervention: SBRT
Comparison: Surgery (Limited Resection)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Surgery (Limited Resection)	Risk with SBRT				
1-year overall survival (1Y OS)	889 per 1,000	**1000 per 1,000** (862 to 1,000)	**RR 1.13** (0.97 to 1.30)	58 (1 RCT)	⊕⊕◯◯ Low[a,b]	The evidence suggests that SBRT does not increase 1-year overall survival.
18-months overall survival (18m OS)	900 per 1,000	**855 per 1,000** (639 to 1,000)	**RR 0.95** (0.71 to 1.28)	24 (1 RCT)	⊕◯◯◯ Very low[c,a,b]	The evidence is very uncertain about the effect of SBRT on 18-months overall survival.

3-Year Overall survival	77.8% survival (FU 18 to 49 months)	-	**HR 0.14** (0.02 to 1.17)	58 (1 RCT)	⊕⊕◯◯ Low[a,b]	The evidence suggests that SBRT does not increase 3-year overall survival.
Grade 3 or 4 adverse events (AE)	444 per 1,000	**98 per 1,000** (31 to 307)	**RR 0.22** (0.07 to 0.69)	58 (1 RCT)	⊕⊕◯◯ Low[a,d]	Grade 3 or 4 adverse events were significantly more in surgery group
Grade 3 dyspnoea	148 per 1,000	**65 per 1,000** (13 to 324)	**RR 0.44** (0.09 to 2.19)	58 (1 RCT)	⊕⊕◯◯ Low[a,b]	Grade 3 dyspnoea was more in surgery group compared to SBRT but not statistically significant
6 weeks quality of life (6W QoL)	The mean 6 weeks quality of life was **0**	MD **0.1 higher** (0.17 lower to 0.37 higher)	-	20 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of SBRT on 6 weeks quality of life.
3 months quality of life (3M QoL)	The mean 3 months quality of life was **0**	MD **0** (0.29 lower to 0.29 higher)	-	18 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of SBRT on 3 months quality of life.

6 months quality of life (6M QoL)	The mean 6 months quality of life was **0**	MD **0** (0.45 lower to 0.45 higher)	-	14 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of SBRT on 6 months quality of life.
Deterioration in global health/QoL (Deter Global QoL)	800 per 1,000	**263 per 1,000** (62 to 769)	**HR 0.19** (0.04 to 0.91)	19 (1 RCT)	⊕⊕◯◯ Low[a,d]	SBRT results in large reduction in deterioration in global health/QoL.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
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. *Single study was downgraded one level for inconsistency as it was in evaluable*
b. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
c. *Some concerns were identified in the study included for this outcome*
d. *Optimal information size (OIS) not met*

Evidence Profile Table

SBRT compared to Surgery (Limited Resection) for early-stage operable non-small cell lung cancer (NSCLC)

Patient or population: Early-stage operable non-small cell lung cancer (NSCLC)

Intervention: SBRT

Comparison: Surgery (Limited Resection)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Surgery (Limited Resection)	With SBRT		Risk with Surgery (Limited Resection)	Risk difference with SBRT
1-year overall survival											
58 (1 RCT)	not serious	serious[a]	not serious	serious[b]	none	⨁⨁◯◯ Low[a,b]	24/27 (88.9%)	31/31 (100.0%)	**RR 1.13** (0.97 to 1.30)	24/27 (88.9%)	**116 more per 1,000** (from 27 fewer to 267 more)
18-months overall survival											
24 (1 RCT)	Serious[c]	Serious[a]	not serious	Serious[b]	none	⨁◯◯◯ Very low[c,a,b]	9/10 (90.0%)	12/14 (85.7%)	**RR 0.95** (0.71 to 1.28)	9/10 (90.0%)	**45 fewer per 1,000** (from 261 fewer to 252 more)

3-Year Overall survival											
58 (1 RCT)	not serious	Serious[a]	not serious	serious[b]	none	⊕⊕◯◯ Low[a,b]	21/27 (77.8%)	30/31 (96.8%)	**HR 0.14** (0.02 to 1.17)	21/27 (77.8%)	**588 fewer per 1,000** (from 748 fewer to 50 more)
Grade 3 or 4 adverse events											
58 (1 RCT)	not serious	Serious[a]	not serious	Serious[d]	none	⊕⊕◯◯ Low[a,d]	12/27 (44.4%)	3/31 (9.7%)	**RR 0.22** (0.07 to 0.69)	12/27 (44.4%)	**347 fewer per 1,000** (from 413 fewer to 138 fewer)
6 weeks quality of life											
20 (1 RCT)	Serious[c]	Serious[a]	not serious	Serious[b]	none	⊕◯◯◯ Very low[a,b,c]	7	13	-	7	MD **0.1 higher** (0.17 lower to 0.37 higher)
3 months quality of life											
18 (1 RCT)	Serious[c]	Serious[a]	not serious	Serious[b]	none	⊕◯◯◯ Very low[a,b,c]	6	12	-	6	MD **0** (0.29 lower to

											0.29 higher)
6 months quality of life											
14 (1 RCT)	Serious[c]	Serious[a]	not serious	Serious[b]	none	⊕◯◯◯ Very low[a,b,c]	4	10	-	4	MD **0** (0.45 lower to 0.45 higher)
Deterioration in global health/QoL											
19 (1 RCT)	not serious	Serious[a]	not serious	Serious[d]	none	⊕⊕◯◯ Low[a,d]	8/10 (80.0%)	2/9 (22.2%)	**HR 0.19** (0.04 to 0.91)	8/10 (80.0%)	**537 fewer per 1,000** (from 738 fewer to 31 fewer)
Grade 3 dyspnoea											
58 (1 RCT)	not serious	Serious[a]	not serious	Serious[b]	none	⊕⊕◯◯ Low[a,b]	4/27 (14.8%)	2/31 (6.5%)	**RR 0.44** (0.09 to 2.19)	4/27 (14.8%)	**83 fewer per 1,000** (from 135 fewer to 176 more)

CI: Confidence Interval

Explanations:

a. *Single study was downgraded one level for inconsistency as it was in evaluable*
b. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
c. *Some concerns were identified in the study included for this outcome*
d. *Optimal information size (OIS) not met*

Summary of Judgements

Problem	Yes
Desirable Effects	Varies
Undesirable Effects	Varies
Certainty of evidence	Low
Values	Probably No important uncertainty or variability
Balance of effects	Probably favours the comparison
Resources required	Varies
Certainty of evidence of required resources	Very Low
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Varies
Feasibility	Probably Yes
Recommendation: Stereotactic body radiation therapy (SBRT) is ***not recommended*** as compared to lobectomy/segmentectomy, for treatment of patients with early-stage operable non-small cell lung cancer except for selected patients who are unwilling or medically unfit for surgery. **Strength**: Conditional **Certainty of evidence** – Low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

- There is a lack of high-quality randomized evidence comparing surgery with SBRT, and the feasibility of conducting a large RCT is limited due to the small pool of eligible patients who could be randomized.

- There is also a paucity of implementation research examining the feasibility of widespread SBRT availability and the acceptability of SBRT among patients with early-stage disease.

IN PATIENTS WITH OPERABLE NON-SMALL CELL LUNG CANCER (NSCLC), DOES SYSTEMATIC MEDIASTINAL LYMPH NODE DISSECTION IMPROVE OVERALL SURVIVAL COMPARED TO MEDIASTINAL LYMPH NODAL SAMPLING?

Table of Contents

1. **Background**..... **60**
2. **Recommendations**..... **60**
3. **Rationale/Justification**..... **60**
4. **Summary of Evidence**..... **60**
5. **Key question in PICO format**..... **61**
6. **Risk of Bias**..... **63**
7. **Forest Plot**..... **64**
8. **Summary of Findings Table**..... **69**
9. **Evidence Profile Table**..... **72**
10. **Summary of Judgements**..... **78**
11. **Caveats in Existing Evidence**..... **78**

Background

Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer, representing approximately 85% of all cases, and continues to be the leading cause of cancer-related mortality globally. For patients with operable NSCLC, surgical resection remains the cornerstone of curative treatment, particularly in early-stage disease (Stage I-IIIA). Accurate staging of mediastinal lymph nodes is pivotal for determining prognosis, guiding adjuvant therapy, and ultimately influencing long-term outcomes. Two primary techniques for mediastinal lymph node assessment during surgery are mediastinal lymph node sampling (MLNS) and systematic mediastinal lymph node dissection (MLND).

The clinical implications of selecting the optimal lymph node management strategy are profound. Inadequate staging may lead to under-treatment and poorer outcomes, while more aggressive approaches like MLND could increase postoperative complications, prolong hospital stays, and escalate healthcare costs. The trade-offs between surgical morbidity, cost, and potential survival benefit necessitate a careful evaluation of the evidence.

Recommendations

Mediastinal lymph node dissection is **recommended** as compared to mediastinal lymph node sampling, in patients with operable non-small cell lung cancer.

Strength: Strong
Certainty of evidence: Very low

Rationale/Justification

The evidence showed large desirable effects with trivial harms accompanied by negligible costs, cost-effectiveness favouring lymph node dissection, and acceptability and feasibility supporting a strong recommendation despite very low certainty of evidence.

Summary of Evidence

Key Question

In patients with operable non-small cell lung cancer (NSCLC), does systematic mediastinal lymph node dissection improve overall survival compared to mediastinal lymph nodal sampling?

Included Studies

A total of 1840 records from electronic databases were identified till date. Of the 1840 articles, 503 duplicate articles were removed. Further 1287 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 50 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 operable non-small cell lung cancer. The review includes adults of all ages and genders. Eligible studies are those that used two primary techniques for mediastinal lymph node assessment during surgery i.e., mediastinal lymph node sampling (MLNS) or systematic mediastinal lymph node dissection (MLND).

Subgroups:

1. T stage
2. Nodal involvement
3. Histology
4. PDL1
5. Smoking status

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

1. Overall survival (*Six studies*)
2. Surgery/surgical procedure related complications (*Four studies*)
3. Disease free survival (*Two studies*)
4. Length of hospital stay (T*hree studies*)
5. Cost (*No studies*)

Key question in PICO format

In patients with operable non-small cell lung cancer (NSCLC), does systematic mediastinal lymph node dissection improve overall survival compared to mediastinal lymph nodal sampling?

Frame work	Description
Population	Patients with resectable/operable non-small cell lung cancer (NSCLC) *Subgroups:* 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status
Intervention	Mediastinal lymph nodal dissection
Comparator	Systematic mediastinal lymph node sampling
Outcome	• Overall survival (*Critical Outcome*) • Surgery/surgical procedure related complications (*Critical Outcome*) • Disease free survival (*Important Outcome*) • Length of hospital stay (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

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)	3% at 2 years 3% at 5 years
		OS (Proportion increase in median survival)	10% at all time points
2	Pulmonary Complications	Surgery/surgical procedure related complications	5% difference at 30 days and at 90 days

Risk of Bias Assessment

Overall survival

	D1	D2	D3	D4	D5	Overall
Izbicki et al 1994	-	+	X	+	+	X
Sugi et al 1998	-	+	+	+	+	-
Izbicki et al 1998	-	+	-	+	+	-
Darling et al 2011	-	+	-	+	+	-
Zhang et al 2013	-	+	-	+	+	-
Wu et al 2002	-	+	+	+	+	-

Surgical Procedure related Complications

	D1	D2	D3	D4	D5	Overall
Izbicki et al 1994	-	+	X	+	+	X
Sugi et al 1998	-	+	+	+	+	-
Allen at al 2006	-	+	+	+	+	-
Zhang et al 2013	-	+	+	+	+	-

Disease free survival

	D1	D2	D3	D4	D5	Overall
Izbicki et al 1998	-	+	-	+	+	-
Darling et al 2011	-	+	-	+	+	-

Hospital stay

	D1	D2	D3	D4	D5	Overall
Izbicki et al 1994	-	+	X	+	+	X
Sugi et al 1998	-	+	+	+	+	-
Allen at al 2006	-	+	+	+	+	-

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

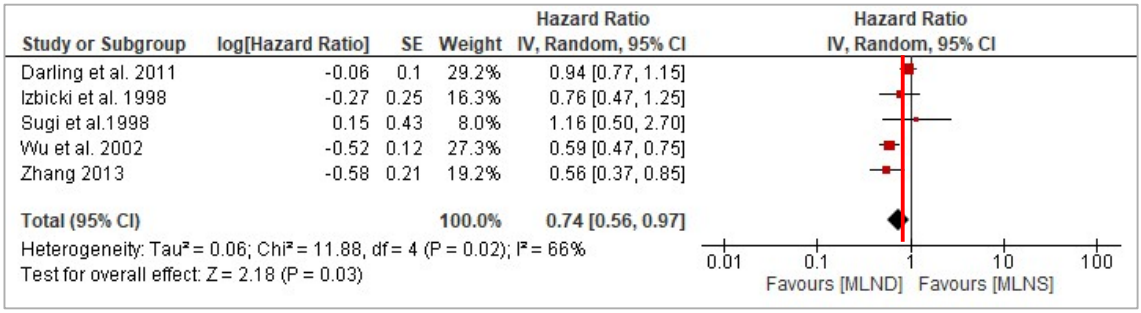
+	**Low risk**
-	**Some concerns**
X	**High risk**

Forest Plot: Desirable Effects

Overall Survival

Evidence shows a significant and clinically meaningful benefit of mediastinal lymph node dissection in improving overall survival of patients with non-small cell lung cancer. The pooled analysis of five studies comparing mediastinal lymph node dissection (MLND) to mediastinal lymph node sampling (MLNS) showed a hazard ratio of 0.74 (95% CI: 0.56 to 0.97), indicating a 26% relative reduction in the risk of death with MLND. This effect was statistically significant (p = 0.03), with the confidence interval not crossing the null value of 1. Moderate heterogeneity was observed across studies (I^2 = 66%, p = 0.02). Among the included studies, three demonstrated a significant benefit of MLND, while two showed no significant difference. Overall, the findings suggest that MLND may be associated with improved survival outcomes compared to MLNS.

Figure 3.1 – Forest plot: Overall Survival



*- Red line shows MCID given by GDG

Undesirable Effects

A statistically significant reduction in the risk of myocardial infarction was observed with mediastinal lymph node dissection (OR 0.12; moderate-certainty), while the incidence of other complications—such as acute respiratory distress syndrome (ARDS), pneumonia, respiratory failure, haemorrhage, and air leaks—did not differ significantly between groups. Some adverse events, including atrial fibrillation, chylothorax, and seropneumothorax, showed numerically higher risks with MLND; however, the wide confidence intervals and imprecision limit interpretability. Overall, the evidence suggests comparable perioperative safety between MLND and LNS, though certainty in most estimates remains low.

Surgery/surgical procedure-related complications

Figure 4.1: Forest Plot: Acute respiratory distress syndrome

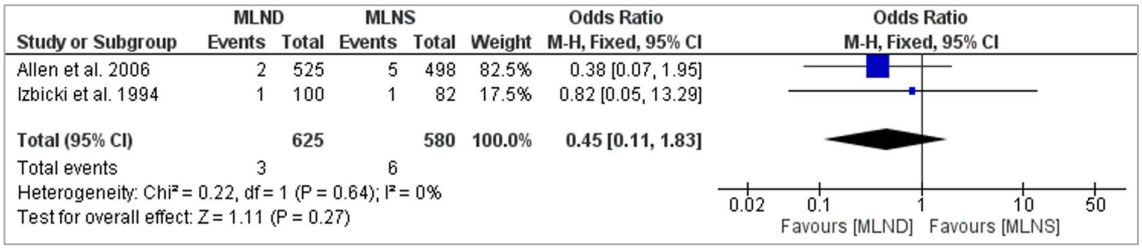


Figure 4.2: Forest Plot: Atelectasis

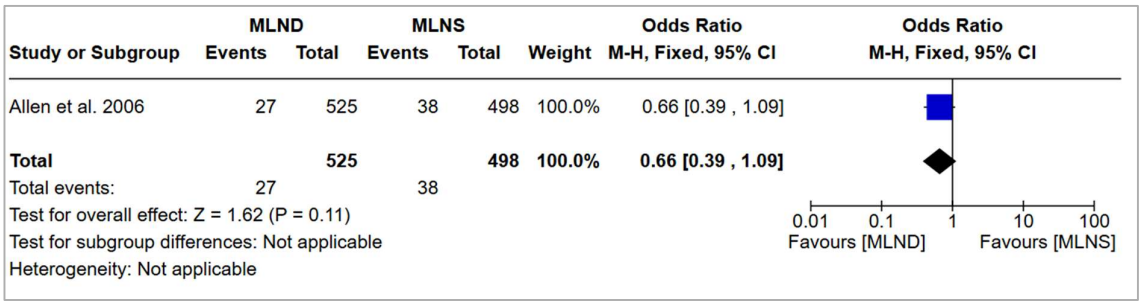


Figure 4.3: Forest Plot: Atrial fibrillation

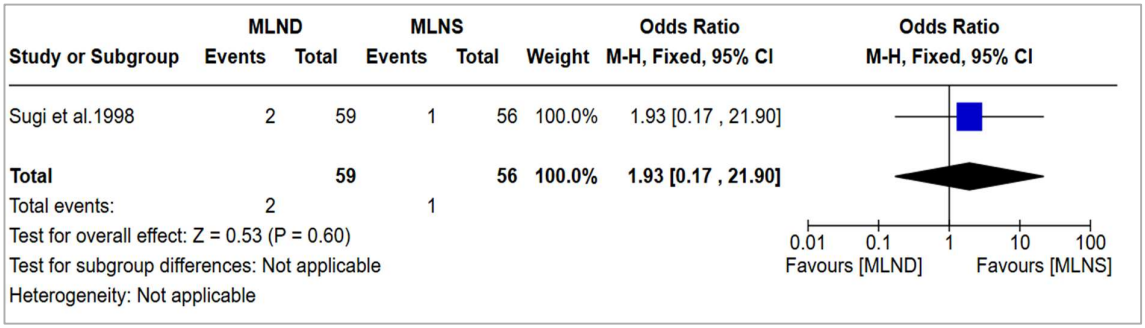


Figure 4.4: Forest Plot: Air leaks

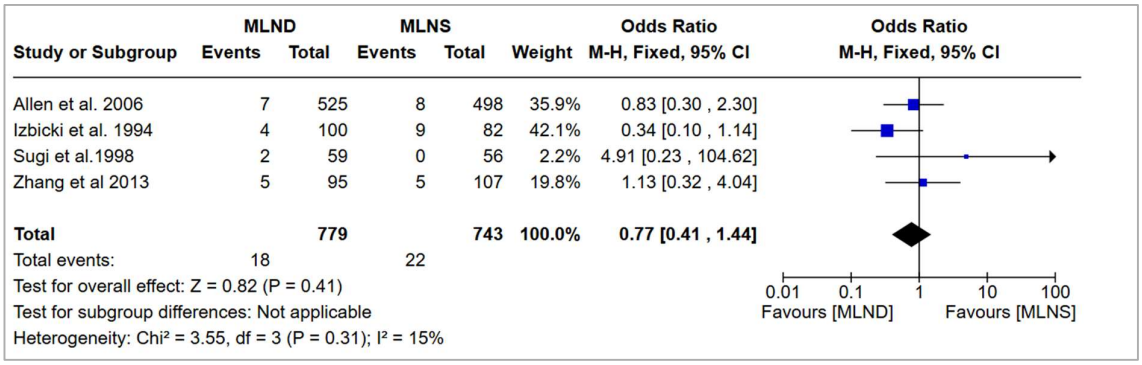


Figure 4.5 - Forest Plot: Broncho pleural fistula

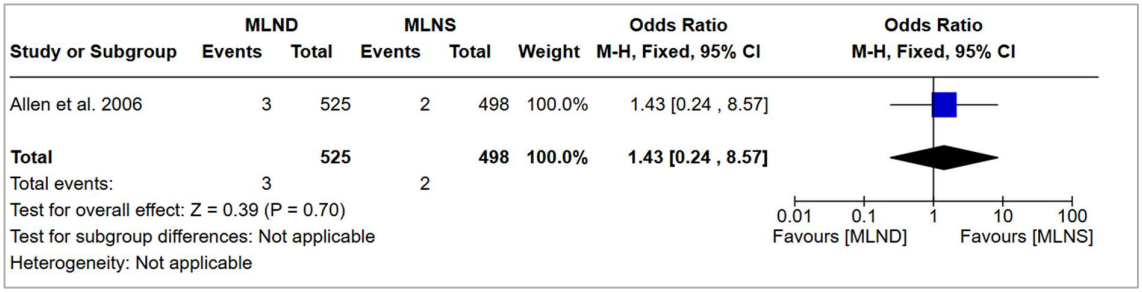


Figure 4.6 – Forest Plot: Chylothorax

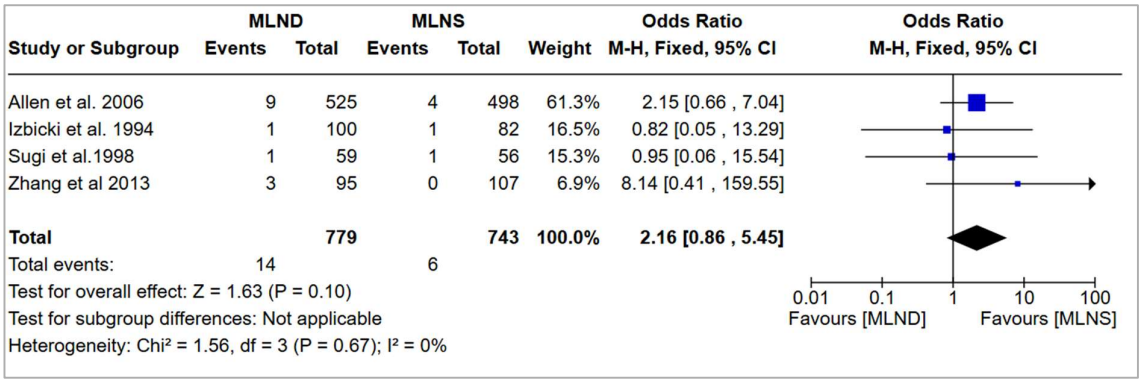


Figure 4.7: Forest Plot: Haemorrhage

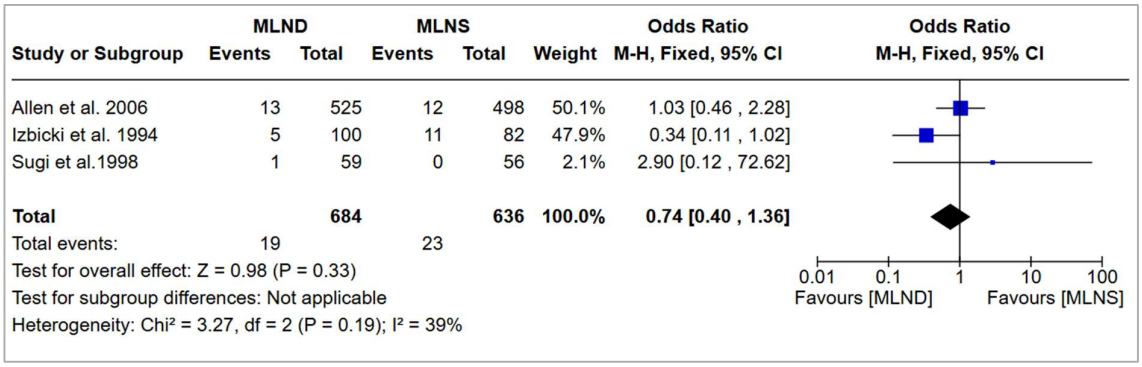
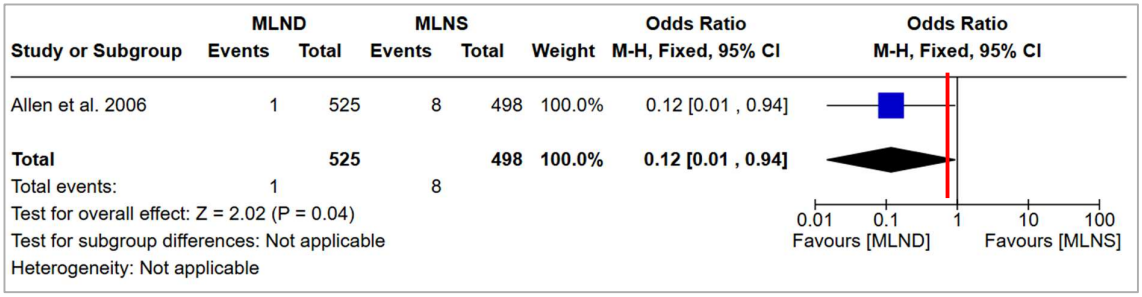


Figure 4.8 – Forest Plot: Myocardial Infarction



*- Red line shows MCID given by GDG

Figure 4.9 – Forest Plot: Pneumonia

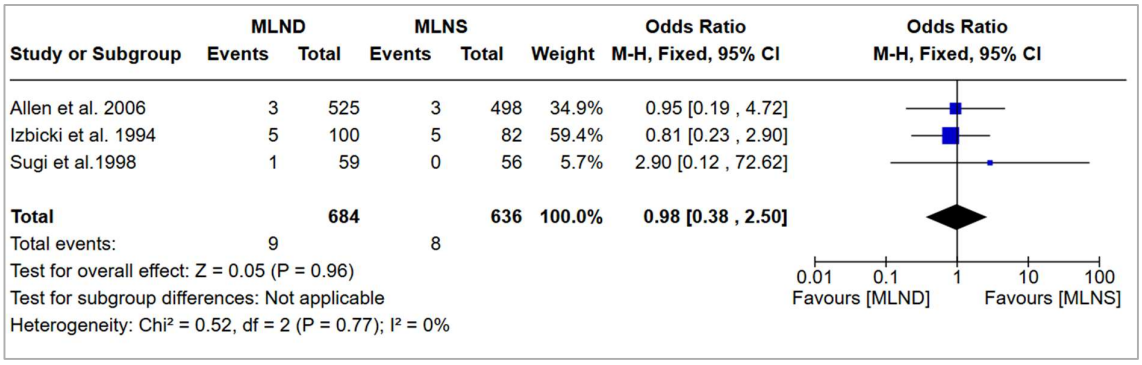


Figure 4.10 – Forest Plot: Recurrent nerve injury

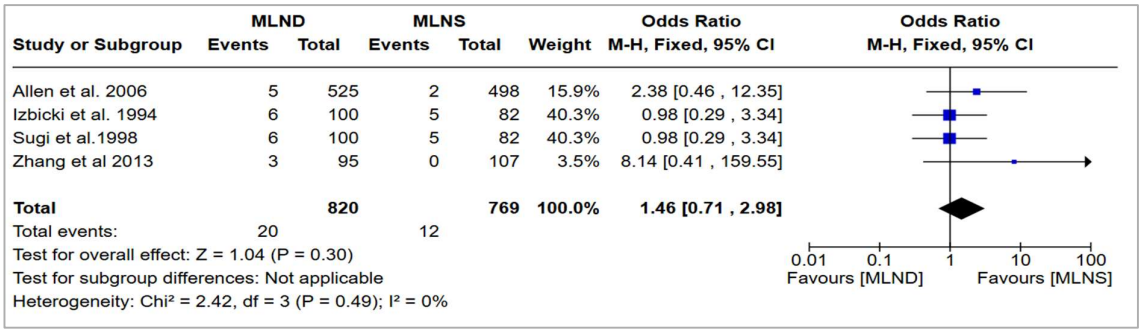


Figure 4.11 – Forest Plot: Respiratory failure

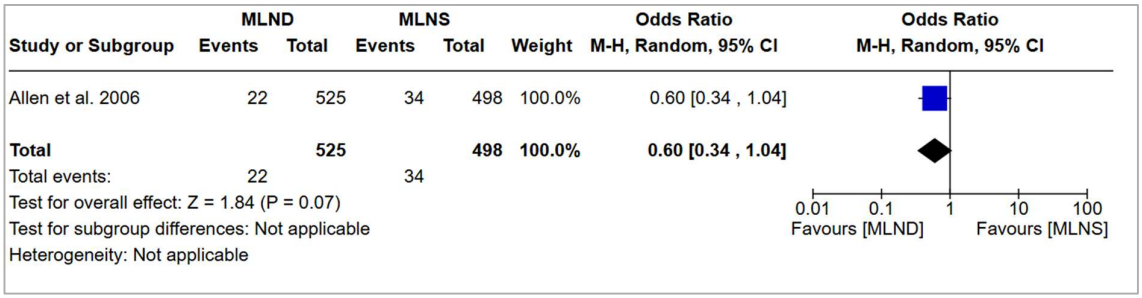


Figure 4.12 – Forest Plot: Retained bronchial secretion

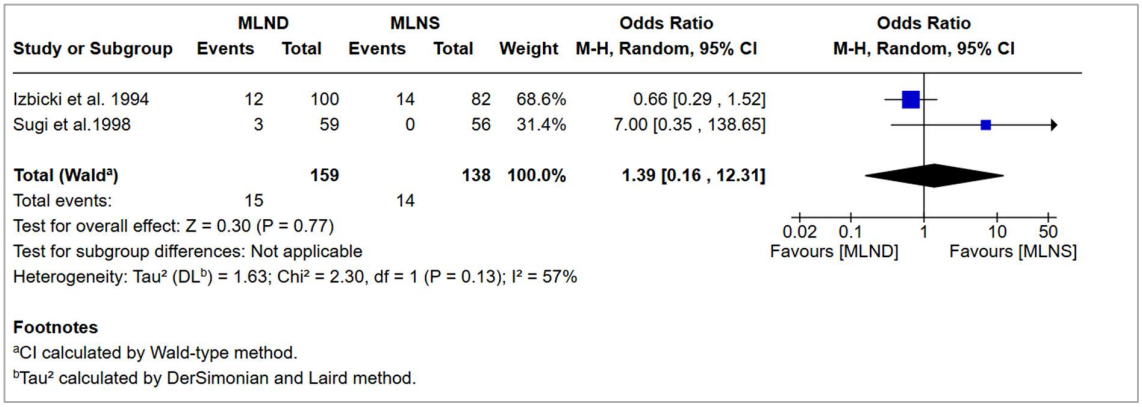
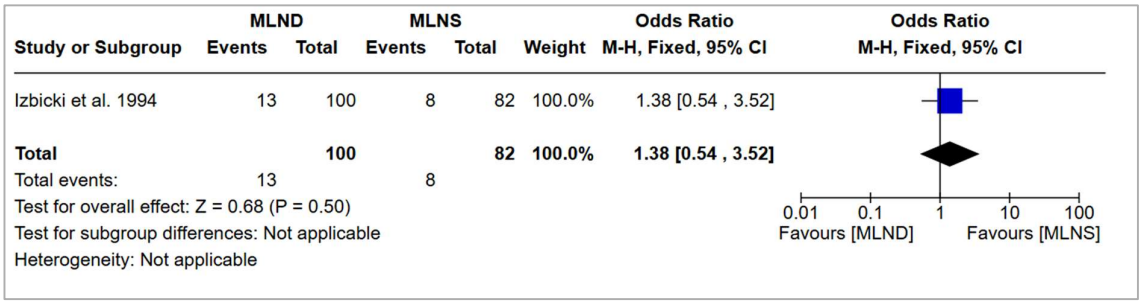


Figure 4.13 – Forest Plot: Sero pneumothorax



Summary of Findings

Mediastinal lymph node dissection compared to lymph node sampling in operable NSCLC

Patient or population: Operable Non-Small Cell Lung Cancer
Intervention: Mediastinal lymph node dissection
Comparison: Lymph node sampling

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with lymph node sampling	Risk with Mediastinal lymph node dissection			
Overall survival	48.46* % (range 16.1 to 62) Fu (3.9 to 6.5 yrs)	-	**HR 0.74** (0.56 to 0.97)	1980 (5 RCTs)	⊕◯◯◯ Very low[a,b,c]
ARDS	10 per 1,000	**5 per 1,000** (1 to 19)	**OR 0.45** (0.11 to 1.83)	1205 (2 RCTs)	⊕⊕◯◯ Low[a,d]
Atelectasis	76 per 1,000	**52 per 1,000** (31 to 83)	**OR 0.66** (0.39 to 1.09)	1023 (1 RCT)	⊕⊕◯◯ Low[a,d]
Atrial fibrillation	18 per 1,000	**34 per 1,000** (3 to 285)	**OR 1.93** (0.17 to 21.90)	115 (1 RCT)	⊕⊕◯◯ Low[a,d]

Air leaks	30 per 1,000	**23 per 1,000** (12 to 42)	**OR 0.77** (0.41 to 1.44)	1522 (4 RCTs)	⊕⊕◯◯ Low[a,d]
Bronchopleural fistula	4 per 1,000	**6 per 1,000** (1 to 33)	**OR 1.43** (0.24 to 8.57)	1023 (1 RCT)	⊕⊕◯◯ Low[a,d]
Chylothorax	8 per 1,000	**17 per 1,000** (7 to 42)	**OR 2.16** (0.86 to 5.45)	1522 (4 RCTs)	⊕⊕◯◯ Low[a,d]
Haemorrhage	36 per 1,000	**27 per 1,000** (15 to 49)	**OR 0.74** (0.40 to 1.36)	1320 (3 RCTs)	⊕⊕◯◯ Low[a,d]
MI	16 per 1,000	**2 per 1,000** (0 to 15)	**OR 0.12** (0.01 to 0.94)	1023 (1 RCT)	⊕⊕⊕◯ Moderate[a]
Pneumonia	13 per 1,000	**12 per 1,000** (5 to 31)	**OR 0.98** (0.38 to 2.50)	1320 (3 RCTs)	⊕⊕◯◯ Low[a,d]
Recurrent nerve injury	16 per 1,000	**23 per 1,000** (11 to 45)	**OR 1.46** (0.71 to 2.98)	1589 (4 RCTs)	⊕⊕◯◯ Low[a,d]
Retained bronchial secretion	101 per 1,000	**136 per 1,000** (18 to 582)	**OR 1.39** (0.16 to 12.31)	297 (2 RCTs)	⊕⊕◯◯ Low[a,d]
Respiratory failure	68 per 1,000	**42 per 1,000** (24 to 71)	**OR 0.60** (0.34 to 1.04)	1023 (1 RCT)	⊕⊕◯◯ Low[a,d]

Seropneumothorax	98 per 1,000	**130 per 1,000** (55 to 276)	**OR 1.38** (0.54 to 3.52)	182 (1 RCT)	⊕⊕◯◯ Low[a,d]
Disease free survival	0 per 1,000	**NaN per 1,000** (-- to --)	**HR 0.95** (0.79 to 1.16)	(2 RCTs)	⊕⊕◯◯ Low[a,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

Explanation:

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 in evaluable*
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*

Evidence Profile

Mediastinal lymph node dissection compared to lymph node sampling in operable NSCLC

Patient or population: Operable Non-Small Cell Lung Cancer

Intervention: Mediastinal lymph node dissection

Comparison: Lymph node sampling

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk with Mediastinal lymph node sampling	lymph node dissection	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
5	randomised trials	serious[a]	Serious[b]	not serious	Serious[c]	none	48.46* % (range 16.1 to 62) Fu (3.9 to 6.5 yrs)	-	**HR 0.74** (0.56 to 0.97)		⊕◯◯◯ Very low[a,b,c]	CRITICAL
ARDS												

2	randomised trials	Very seriou[d]	not serious	not serious	Serious[c,f]	none	3/625 (0.5%)	6/580 (1.0%)	**OR 0.45** (0.11 to 1.83)	**6 fewer per 1,000** (from 9 fewer to 8 more)	⊕◯◯◯ Very Low[d,c,f]	CRITICAL

Atelactasis

1	randomised trials	serious[a]	serious[e]	not serious	Serious[f]	none	27/525 (5.1%)	38/498 (7.6%)	**OR 0.66** (0.39 to 1.09)	**25 fewer per 1,000** (from 45 fewer to 6 more)	⊕⊕◯◯ Low[a,d]	CRITICAL

Atrial fibrillation

1	randomised trials	serious[a]	serious[e]	not serious	Serious[f]	none	2/59 (3.4%)	1/56 (1.8%)	**OR 1.93** (0.17 to 21.90)	**16 more per 1,000** (from 15 fewer to 267 more)	⊕◯◯◯ very Low[a,e,f]	CRITICAL

Air leaks

4	randomised trials	Very serious[d]	not serious	not serious	Serious[f]	none	18/779 (2.3%)	22/743 (3.0%)	**OR 0.77** (0.41	**7 fewer per 1,000** (from 17	⊕◯◯◯ very Low[d,f]	CRITICAL

									to 1.44)	fewer to 12 more)		
Bronchopleural fistula												
1	randomised trials	serious[a]	serious[e]	not serious	Serious[f]	none	3/525 (0.6%)	2/498 (0.4%)	**OR 1.43** (0.24 to 8.57)	**2 more per 1,000** (from 3 fewer to 29 more)	⊕◯◯◯ Low[a,e,d]	CRITICAL
Chylothorax												
4	randomised trials	Serious[d]	not serious	not serious	serious[d]	none	14/779 (1.8%)	6/743 (0.8%)	**OR 2.16** (0.86 to 5.45)	**9 more per 1,000** (from 1 fewer to 34 more)	⊕⊕◯◯ Low[a,d]	CRITICAL
Haemorrhage												
3	randomised trials	Very serious[d]	not serious	not serious	Serious[f]	none	19/684 (2.8%)	23/636 (3.6%)	**OR 0.74** (0.40 to 1.36)	**9 fewer per 1,000** (from 21 fewer to 12 more)	⊕◯◯◯ Low[d,f]	CRITICAL
MI												

1	randomised trials	serious[a]	serious[e]	not serious	serious[b]	none	1/525 (0.2%)	8/498 (1.6%)	**OR 0.12** (0.01 to 0.94)	**14 fewer per 1,000** (from 16 fewer to 1 fewer)	⊕◯◯◯ Very low[a,b]	CRITICAL
Pneumonia												
3	randomised trials	Very serious[d]	not serious	not serious	Serious[f]	none	9/684 (1.3%)	8/636 (1.3%)	**OR 0.98** (0.38 to 2.50)	**0 fewer per 1,000** (from 8 fewer to 18 more)	⊕◯◯◯ Low[d,f]	CRITICAL
Recurrent nerve injury												
4	randomised trials	Very serious[d]	not serious	not serious	Serious[f]	none	20/820 (2.4%)	12/769 (1.6%)	**OR 1.46** (0.71 to 2.98)	**7 more per 1,000** (from 4 fewer to 30 more)	⊕◯◯◯ Low[d,f]	CRITICAL
Retained bronchial secretion												
2	randomised trials	Very serious[d]	not serious	not serious	Serious[f]	none	15/159 (9.4%)	14/138 (10.1%)	**OR 1.39** (0.16	**34 more per 1,000** (from 84	⊕◯◯◯ Low[d,f]	CRITICAL

									to 12.31)	fewer to 480 more)		
Respiratory failure												
1	randomised trials	serious[a]	serious[e]	not serious	Serious[f]	none	22/525 (4.2%)	34/498 (6.8%)	**OR 0.60** (0.34 to 1.04)	**26 fewer per 1,000** (from 44 fewer to 3 more)	⊕◯◯◯ very Low[a,e,f]	CRITICAL
Seropneumothorax												
1	randomised trials	Very serious[a]	serious[e]	not serious	Serious[f]	none	13/100 (13.0%)	8/82 (9.8%)	**OR 1.38** (0.54 to 3.52)	**32 more per 1,000** (from 42 fewer to 178 more)	⊕◯◯◯ very Low[a,e,f]	CRITICAL

CI: Confidence Interval

Explanations:

a. *Some concerns were identified in the study included for this outcome*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 66%*
c. *Downgraded one level for imprecision as the 95% CI crossed the MCID*
d. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
e. *Single study was downgraded one level for inconsistency as it was in evaluable*
f. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Summary of Judgements

Problem	Yes
Desirable Effects	Large
Undesirable Effects	Trivial
Certainty of evidence	Very Low
Values	No important uncertainty or variability
Balance of effects	Favors the intervention
Resources required	Negligible costs and savings
Certainty of evidence of required resources	Low
Cost effectiveness	Favors the intervention
Equity	Probably no impact
Acceptability	Yes
Feasibility	Yes
Recommendations: Mediastinal lymph node dissection is ***recommended*** as compared to mediastinal lymph node sampling, in patients with operable non-small cell lung cancer. **Strength**: Strong **Certainty of evidence**: Very low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

- There is a lack of comprehensive health economic evaluations comparing MLND versus MLNS using Indian cost data (operative time, hospital stay, complication management, and training costs), along with limited evidence on equity-related disparities in access across geographic, institutional, and socioeconomic settings.
- The GDG identified an important implementation and training consideration related to the competency requirements for performing mediastinal lymph node dissection.

IN PATIENTS DIAGNOSED WITH EARLY-STAGE NON-SMALL CELL LUNG CANCER (NSCLC) HARBOURING AN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION, DOES THE ADDITION OF ADJUVANT TYROSINE KINASE INHIBITOR (TKI) THERAPY, EITHER ALONE OR IN COMBINATION IMPROVE OVERALL SURVIVAL COMPARED TO CHEMOTHERAPY ALONE?

Table of Contents

1. **Background**..... **82**
2. **Recommendations**..... **82**
3. **Rationale/Justification**..... **82**
4. **Summary of Evidence**..... **83**
5. **Key question in PICO format**..... **84**
6. **Risk of Bias**..... **85**
7. **Forest Plot**..... **86**
8. **Summary of Findings Table**..... **93**
9. **Evidence Profile Table**..... **95**
10. **Summary of Judgements**..... **98**
11. **Caveats in Existing Evidence**..... **98**

Background

Worldwide, lung cancer is the primary cause of cancer-related death. Non-small-cell lung cancer (NSCLC), is the most prevalent pathological form. 50% patients are diagnosed in advanced stage and only 25-30% are diagnosed early and are fit for curative surgery. With high rates of recurrence (>50%) and distant metastases, long-term clinical outcomes for early-stage NSCLC remain dismal even after full resection**.** Treatment options for early-stage NSCLC consist of surgery, radiation, and chemotherapy but molecular characterization and identification of certain mutation can be crucial for management. EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy is advised as the first-line treatment for individuals with EGFR mutations with significant survival-benefit. Individuals with EGFR-mutant-NSCLC have been compared to adjuvant EGFR-TKIs with or without chemotherapy in many clinical trials. Therefore, the present review focuses on comprehensive analysis of the overall survival, disease free survival, adverse events and HRQoL of EGFR-TKIs with or without chemotherapy in the treatment of early-stage non-small cell lung cancer harboring an EGFR mutation.

Recommendation

Addition of adjuvant tyrosine kinase inhibitor (TKI) therapy, either alone or in combination is ***recommended*** rather than chemotherapy alone for patients diagnosed with early-stage non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation.

Strength: Strong
Certainty of evidence – High for efficacy and low for side effects

Rationale/Justification

Evidence demonstrates large desirable effects of adjuvant tyrosine kinase inhibitor (TKI) therapy compared with chemotherapy alone, supported by high-certainty evidence for improvement in survival outcomes. Undesirable effects are small, and adverse events are generally manageable, although the certainty of evidence for side effects is very low. Overall, the balance of benefits and harms clearly favours adjuvant TKI therapy.

While resource requirements are moderate and cost-effectiveness may vary across settings, the substantial clinical benefit, favourable safety profile, and strong patient-important outcomes justify a strong recommendation.

Summary of Evidence

Key Question

In patients diagnosed with early-stage non-small cell lung cancer (NSCLC) harbouring an EGFR mutation, does the addition of adjuvant tyrosine kinase inhibitor (TKI) therapy, either alone or in combination improve overall survival compared to chemotherapy alone?

Included Studies

A total of 4405 records from electronic databases were identified till 03 Aug 2024. Of the 4405 articles, 376 duplicate articles were removed. Further 3977 articles were excluded after title and abstract screening. The remaining 52 articles were examined for full text and after full text examination a total of 36 articles were excluded resulting in 16 articles with full text. A set of 16 articles were finally included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with early-stage NSCLC harbouring an EGFR mutation and on adjuvant TKI therapy either alone or in combination. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effect adjuvant TKI therapy, either alone or in combination when compared to chemotherapy alone in patients early-stage NSCLC.

Subgroups:

1. T stage
2. Nodal involvement
3. Histology
4. PDL1
5. Smoking status
6. Type of EGFR mutation

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

1. Overall survival (*6 studies*)
2. Adverse effects (*7 studies*)
3. Quality of life (*3 studies*)
4. Disease free survival (*9 studies*)
5. Response Rate (*No studies*)
6. Cost (*No studies*)

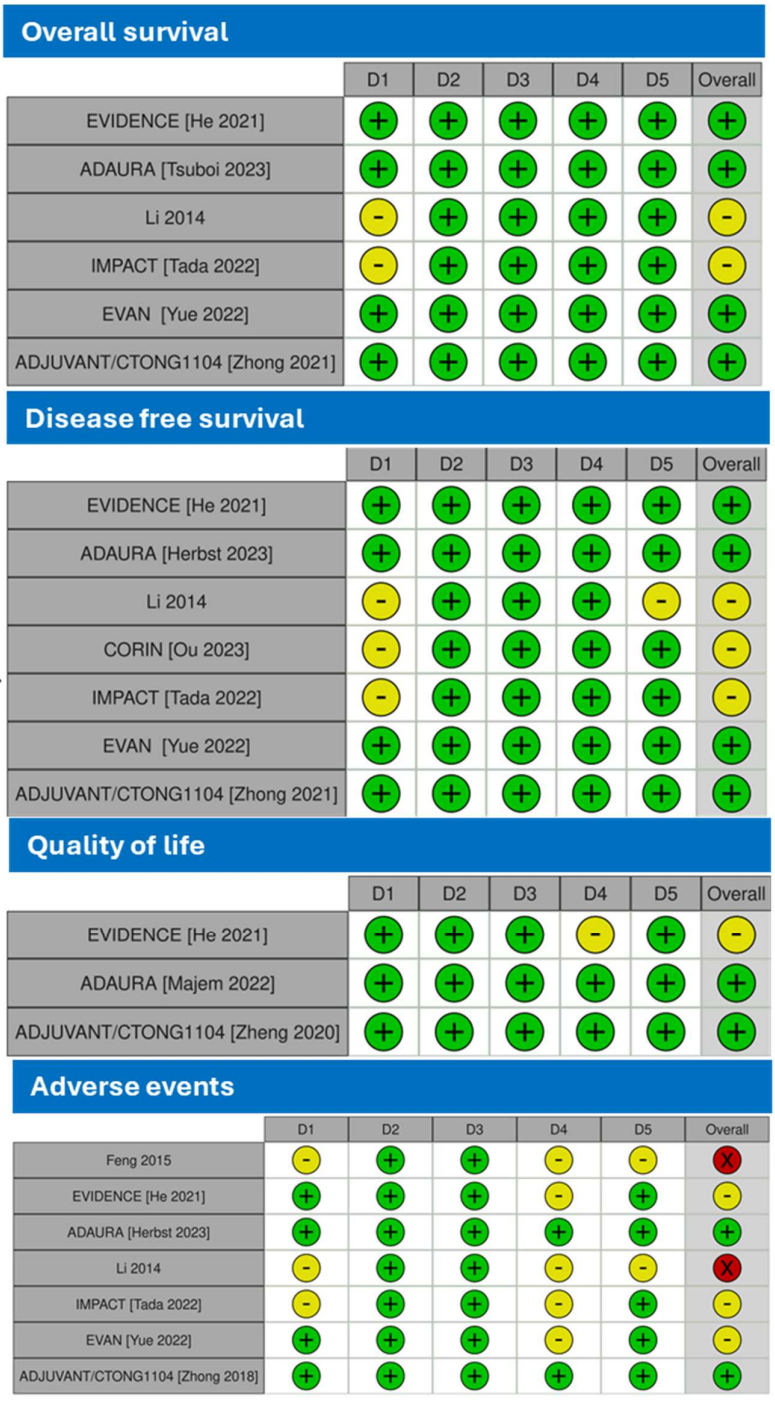
Key Question in PICO Format

Framework	Inclusion criteria
Population	Patients diagnosed with early-stage non-small cell lung cancer (NSCLC) with an EGFR mutation Subgroups: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status 6. Type of EGFR mutation
Intervention	Adjuvant TKI therapy with or without chemotherapy *Subgroups*: Adjuvant TKI therapy e.g. Gefitinib/Erlotinib/Afatinib/Osimertinib
Comparator	Chemotherapy alone or observation *Subgroups*: 1. chemotherapy vs observation
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Quality of life (*Critical Outcome*) • Disease free survival (*Important Outcome*) • Response rate (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

Sr. No	Critical outcome reviewed	What does it measure	MCID decided by GDG
1	Overall Survival	Absolute survival gain	5%
		OS (Proportion increase in median survival)	6 months
2	Adverse events	Proportion difference in grade 3 or higher AEs	10%
3	Quality of life	Improvement in the scores	5 units in 0-100 scale

Risk of Bias Assessment



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

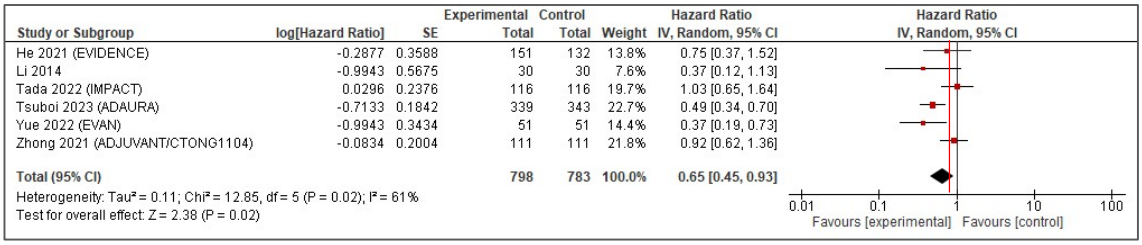
+	**Low risk**
-	**Some concerns**
X	**High risk**

Forest Plot: Desirable Effects

Overall Survival

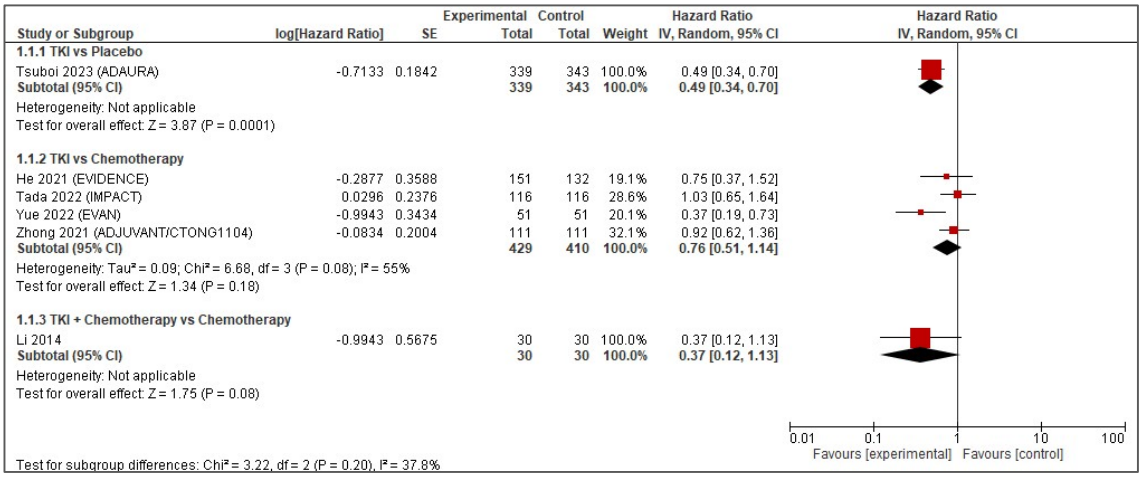
The evidence from six trials (total ≈1,581 patients; 798 experimental vs 783 control) shows that TKI ± chemotherapy reduced the hazard of death by about 35% versus chemotherapy/observation (HR 0.65, 95% CI 0.45–0.93; Z=2.38, p=0.02) in patients with early-stage non-small cell lung cancer (NSCLC) indicating a statistically significant benefit. The absolute survival gain exceeds the minimally important clinical difference (MCID) of 5%, confirming clinically meaningful improvement in outcomes.

Figure 1: Outcome: Overall survival (TKI ± Chemotherapy vs. Chemotherapy or Observation)



Red line denoted MCID of 5% (absolute survival gain)

Figure 2: Subgroup analysis of overall survival outcome based on type of comparators



The test for subgroup differences is non-significant (p=0.20), meaning there is no reliable evidence that the effect truly differs across subgroups

Figure 3: Subgroup analysis of overall survival outcome based on TKIs and comparators

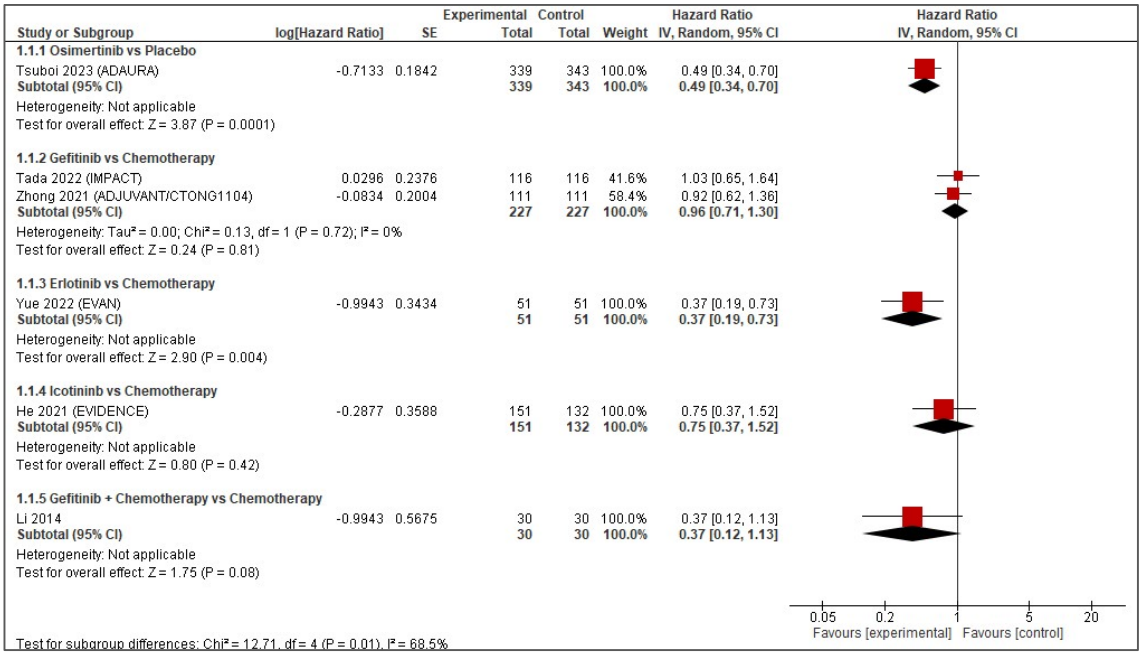


Figure 4: Subgroup analysis of overall survival outcome based on staging of NSCLC (TKI vs Chemotherapy)

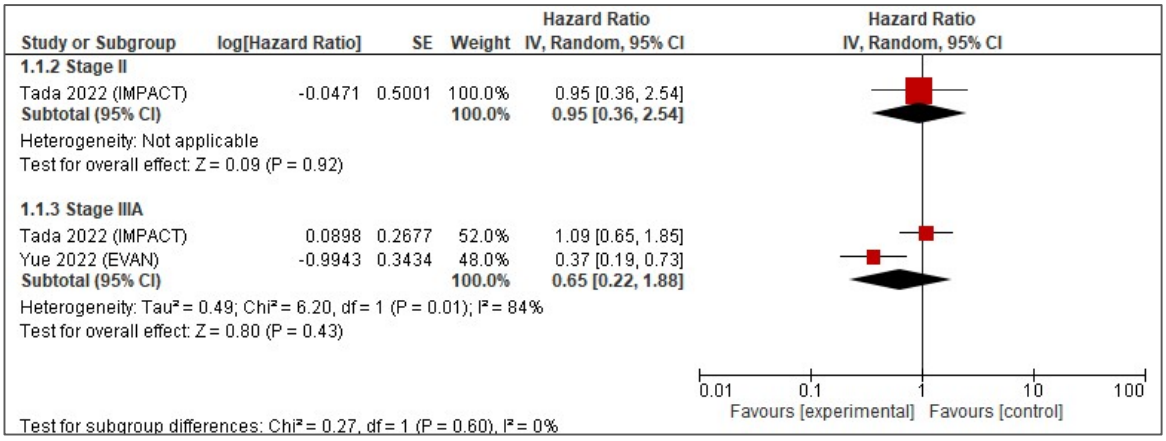
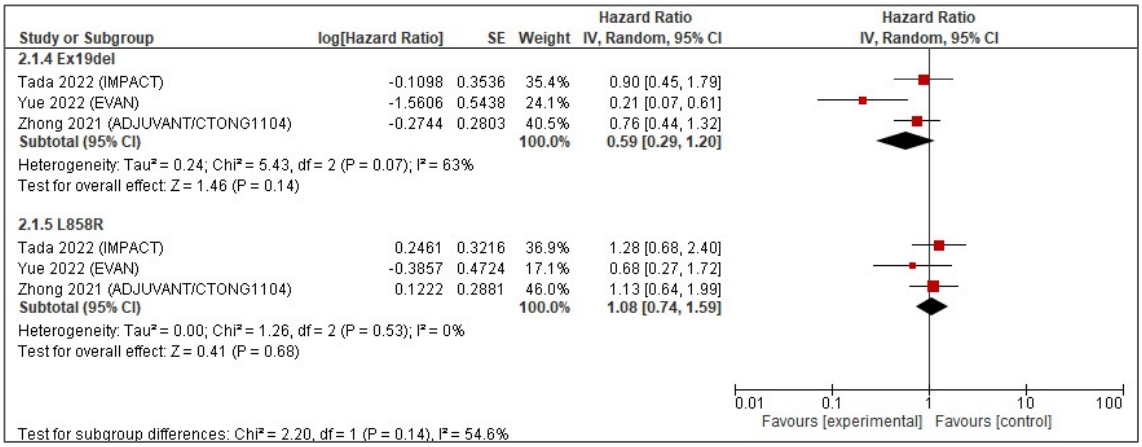
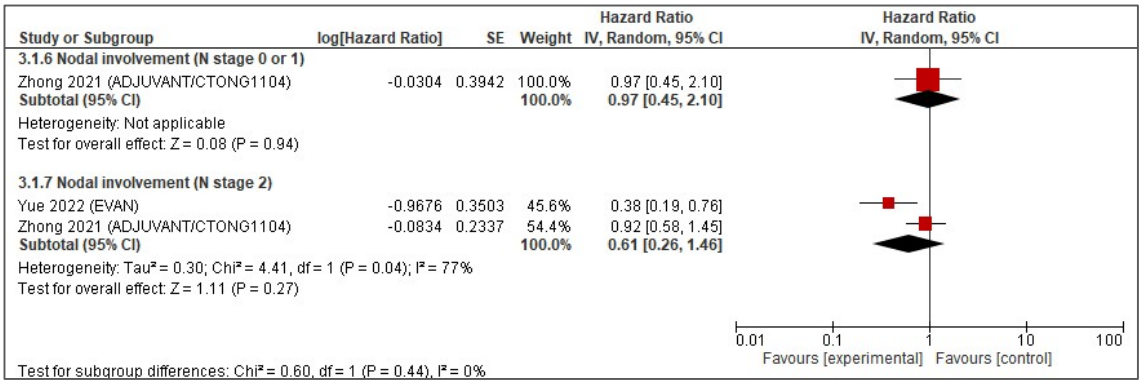


Figure 5: Subgroup analysis of overall survival outcome based on type of EGFR mutation (TKI vs Chemotherapy)



The test for subgroup differences is non-significant (p=0.14), meaning there is no reliable evidence that the effect truly differs across subgroups

Figure 6: Subgroup analysis of overall survival outcome based on nodal involvement (TKI vs Chemotherapy)



The test for subgroup differences is non-significant (p=0.44), meaning there is no reliable evidence that the effect truly differs across subgroups

Figure 6: Outcome: Quality of Life (QoL)

QoL (FACT-L) score at the end of the 36-week follow-up period based on type of TKI and comparator

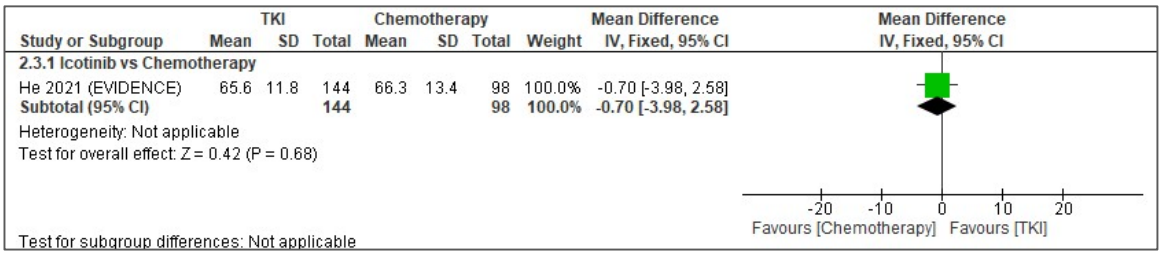
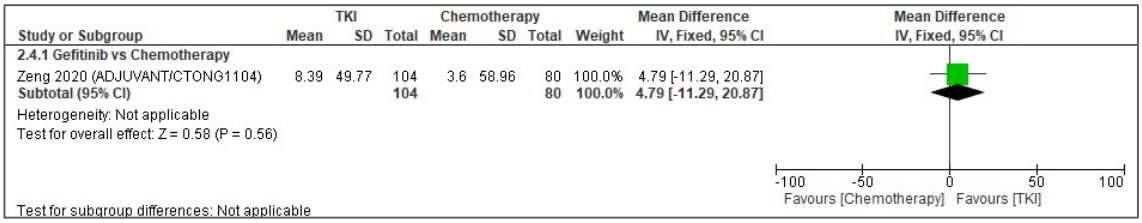


Figure 7: QoL (FACT-L) changes in QoL score at 141 weeks from baseline based on type of TKI and comparator



He et al presented the mean QoL score at the end of the 36-week follow-up period, while Zeng et al presented mean changes in QoL score at 141 weeks from baseline.

Figure 8: QoL (LCSS) score at the end of the 36-week follow-up period based on type of TKI and comparator

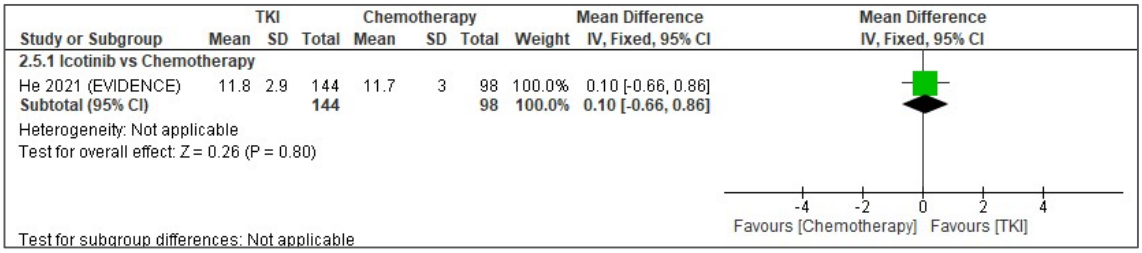
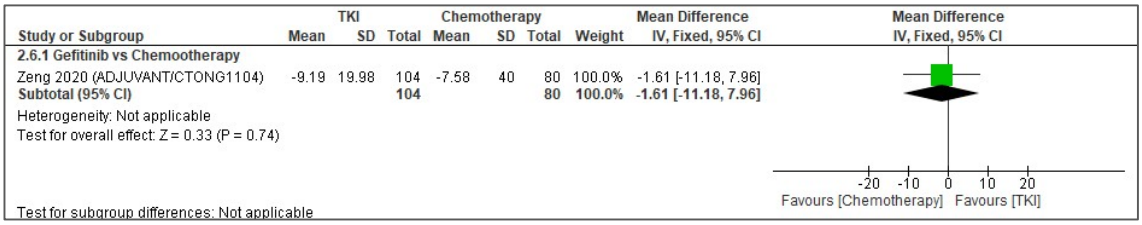


Figure 9: Subgroup analysis of QoL (LCSS) changes in QoL score at 141 weeks from baseline based on type of TKI and comparator



He et al presented the mean QoL score at the end of the 36-week follow-up period, while Zeng et al presented mean changes in QoL score at 141 weeks from baseline.

Undesirable Effects

The pooled analysis shows no statistically significant difference in Grade ≥3 adverse events between TKI ± chemotherapy and chemotherapy/observation (RR 0.60, 95% CI 0.27–1.33; p=0.21). The most commonly reported grade ≥3 events were hepatic enzyme elevations (ALT/AST), hematologic toxicities (neutropenia/leukopenia, mostly in chemotherapy arms), severe dermatologic events/rash and paronychia, diarrhoea, and occasional cardiac (QTc) prolongation or pneumonitis/ILD. The pattern varies by drug; Osimertinib trials reported relatively few grade-3 events, gefitinib trials mainly reported raised ALT/AST (whereas the chemotherapy arms had much more neutropenia/leukopenia).

Figure 1: Outcome: Adverse events Grade 3 or more (TKI ± Chemotherapy vs. Chemotherapy or Observation)

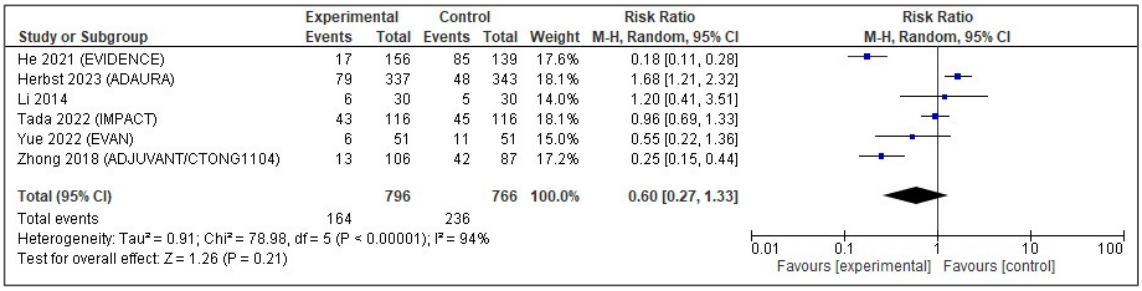


Figure 2: Subgroup analysis of adverse events of Grade 3 or more outcome based on for the type of comparators

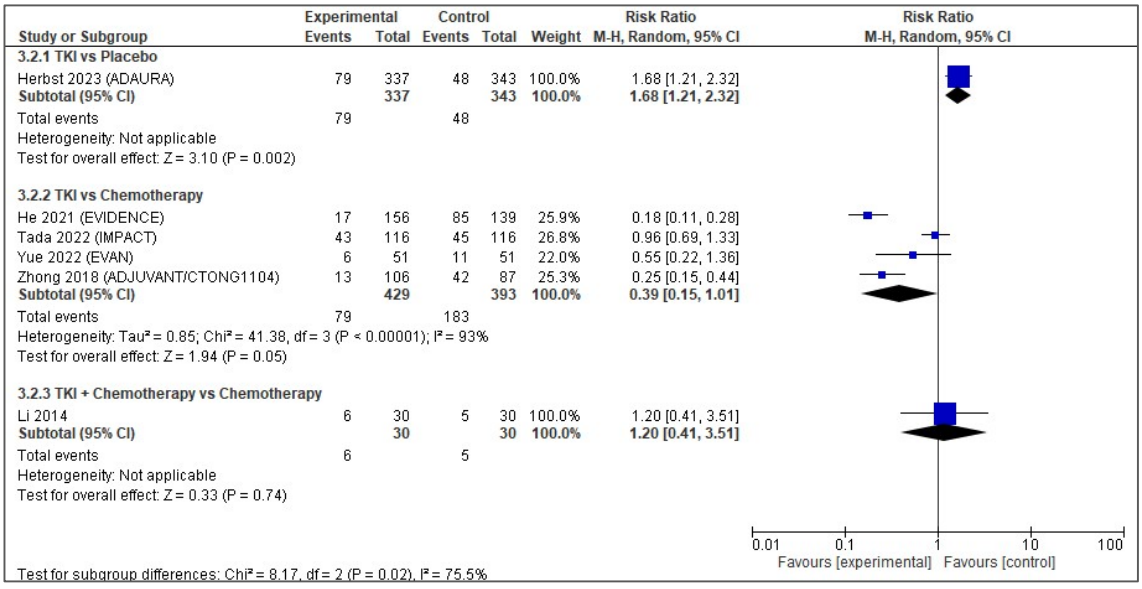
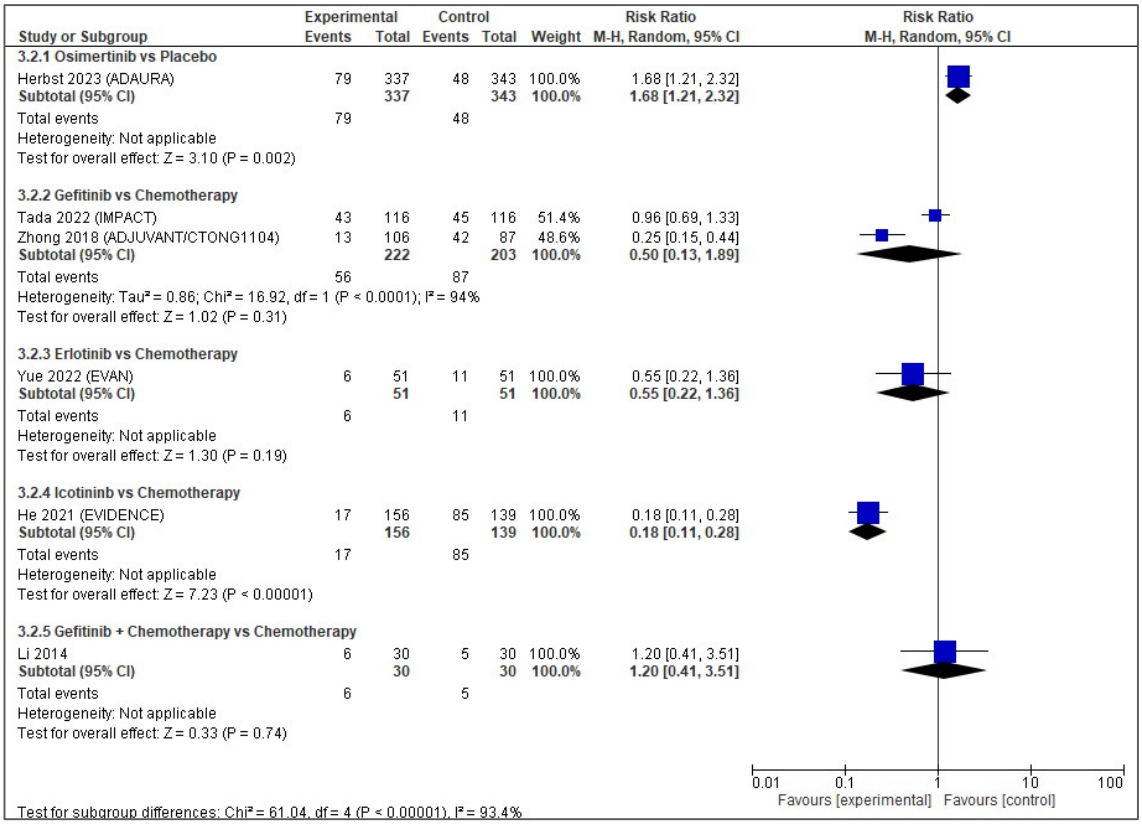


Figure 3: Subgroup analysis of adverse events of Grade 3 or more outcome based on for the type of TKI and comparators



Summary of Findings Table Overall survival outcome

Population: Patients diagnosed with early-stage non-small cell lung cancer (NSCLC) with an EGFR mutation

Intervention: TKI ± Chemotherapy

Comparison: Chemotherapy or Observation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy or Observation	Risk with TKI ± Chemotherapy				
Overall Survival (OS) follow-up: range 0.1 years to 82 months	30.11%* (range 11-48.9%) Follow-up (2 to 5.1 yr)	--	**HR 0.65** (0.45 to 0.93)	1581 (6 RCTs)	⊕⊕⊕⊕ High	TKI ± Chemotherapy probably increases overall Survival.
QoL (FACT-L) at the end of the 36-week follow-up period (FACT-L) Scale from: 0 to 136 follow-up: range 36 weeks to 36 weeks	66.3 mean score at the end of the 36-week follow-up period	65.6 mean score at the end of the 36-week follow-up period	MD 0.7 lower (3.98 lower to 2.58 higher)	242 (1 RCT)	⊕◯◯◯ very low[a,b,c]	The evidence suggests that TKI ± Chemotherapy results in little to no difference in hRQoL (FACT-L) at the end of the 36-week follow-up period.
QoL (FACT-L) changes in score at 141 weeks from baseline. (FACT-L) Scale from: 0 to 136 follow-up: range 141 weeks	58.96 mean score at 141 weeks	49.77 mean score at 141 weeks	MD 4.79 higher (11.29 lower to 20.87 higher)	184 (1 RCT)	⊕⊕◯◯ Low[b,c]	TKI ± Chemotherapy may result in little to no difference in hRQoL (FACT-L) changes in score at 141 weeks from baseline.

QoL (LCSS) at the end of the 36-week follow-up period (LCSS) Scale from: 0 to 190 follow-up: range 36 weeks to 36 weeks	11.7 mean score at the end of the 36-week follow-up period	11.8 mean score at the end of the 36-week follow-up period	MD 0.1 higher (0.66 lower to 0.86 higher)	242 (1 RCT)	⊕⊕◯◯ Low[b,c]	TKI ± Chemotherapy may result in little to no difference in hRQoL (LCSS) at the end of the 36-week follow-up period.
QoL (LCSS) changes in score at 141 weeks from baseline (LCSS) Scale from: 0 to 90 follow-up: range 141 weeks to 141 weeks	-7.58 mean changes in score at 141 weeks from baseline	-9.19 mean changes in score at 141 weeks from baseline	MD 1.61 lower (11.18 lower to 7.96 higher)	184 (1 RCT)	⊕⊕◯◯ Low[b,c]	TKI ± Chemotherapy may result in little to no difference in hRQoL (LCSS) changes in score at 141 weeks from baseline.
Adverse events of Grade 3 or more	308 per 1,000	185 per 1,000 (83 to 410)	RR 0.60 (0.27 to 1.33)	1562 (6 RCTs)	⊕◯◯◯ very low[c,d,e]	The evidence is very uncertain about the effect of TKI ± Chemotherapy on adverse events of Grade 3 or more.

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

CI: Confidence Interval; **HR**: Hazard Ratio

Explanation:

a. *Some concerns were identified in the study included for this outcome*
b. *Single study was downgraded one level for inconsistency as it was in evaluable*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
d. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 62%*
e. *Possibility of publication bias based on Egger's regression test (calculation provided below)*

Evidence Profile Table

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TKI ± Chemotherapy	Chemotherapy or Observation	Relative (95% CI)	Absolute (95% CI)	
Overall Survival (follow-up: range 24 months to 74 months)											
6	randomised trials	not serious	not serious	not serious	not serious	none	--	30.11%* (range 11-48.9%) Follow-up (2 to 5.1 yr)	HR 0.65 (0.45 to 0.93)	93 fewer per 1000 (152 fewer per 1000 to 18 fewer per 1000)	⊕⊕⊕⊕ High
QoL (FACT-L) at the end of the 36-week follow-up period - TKI vs Chemotherapy **(follow-up: range 36 weeks to 36 weeks; Scale from: 0 to 136)**											
1	randomised trial	serious[a]	Serious[b]	not serious	Serious[c]	none	144	98	-	MD 0.7 lower (3.98 lower to 2.58 higher)	⊕◯◯◯ very low[a,b,c]
QoL (FACT-L) changes in score at 141 weeks from baseline - TKI vs Chemotherapy (follow-up: range 141 weeks to 141 weeks; Scale from: 0 to 136)											
1	randomised trials	not serious	Serious[b]	not serious	Serious[c]	none	104	80	-	MD 4.79 higher (11.29 lower to 20.87 higher)	⊕⊕◯◯ Low[b,c]

QoL (LCSS) at the end of the 36-week follow-up period - TKI vs Chemotherapy (follow-up: range 36 weeks to 36 weeks; Scale from: 0 to 190)											
1	randomised trials	not serious	Serious[b]	not serious	Serious[c]	none	144	98	-	MD 0.1 higher (0.66 lower to 0.86 higher)	⊕⊕◯◯ Low[b,c]
QoL (LCSS) changes in score at 141 weeks from baseline - TKI vs Chemotherapy (follow-up: range 141 weeks to 141 weeks; Scale from: 0 to 90)											
1	randomised trials	not serious	Serious[b]	not serious	Serious[c]	none	104	80	-	MD 1.61 lower (11.18 lower to 7.96 higher)	⊕⊕◯◯ Low[b,c]
Adverse events of Grade 3 or more											
6	randomised trials	not serious	Serious[d]	not serious	Serious[c]	publication bias strongly suspected[e]	164/796 (20.6%)	236/766 (30.8%)	RR 0.60 (0.27 to 1.33)	123 fewer per 1,000 (from 225 fewer to 102 more)	⊕◯◯◯ very low[c,d,e]

Explanations:

a. *Some concerns were identified in the study included for this outcome*
b. *Single study was downgraded one level for inconsistency as it was in evaluable*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
d. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 62%*
e. *Possibility of publication bias based on Egger's regression test (calculation provided below)*

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Publication bias for the outcome, Adverse events of Grade 3 or more (n=6 studies)

Regression test ("Egger's test")

	z	P
sei	2.871	0.004

Interpretation: Possibility of publication bias for grade 3 or more adverse event outcome.

Summary of Judgements

Problem	Yes
Desirable Effects	Large
Undesirable Effects	Small
Certainty of evidence	High for efficacy and very low for side effects
Values	Probably no important uncertainty or variability
Balance of effects	Favors the intervention
Resources required	Moderate cost
Certainty of evidence of required resources	Low
Cost effectiveness	Varies
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendation: Addition of adjuvant tyrosine kinase inhibitor (TKI) therapy is ***recommended*** rather than chemotherapy alone for patients diagnosed with early-stage non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation. **Strength**: Strong **Certainty of evidence** – High for efficacy and very low for side effects	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

There is a lack of cost-effectiveness evidence evaluating adjuvant TKI therapy, alone or in combination with chemotherapy, compared to chemotherapy alone in patients with early-stage EGFR-mutated NSCLC.

IN COMPLETELY RESECTED NSCLC, DOES THE ADDITION OF POSTOPERATIVE RADIOTHERAPY TO STANDARD THERAPY IMPROVE SURVIVAL COMPARED TO STANDARD THERAPY ALONE?

Table of Contents

1. **Background**..... **102**
2. **Recommendations**..... **102**
3. **Rationale/Justification**..... **102**
4. **Summary of Evidence**..... **103**
5. **Key question in PICO format**..... **103**
6. **Risk of Bias**..... **105**
7. **Forest Plot**..... **106**
8. **Summary of Findings Table**..... **108**
9. **Evidence Profile Table**..... **111**
10. **Summary of Judgements**..... **113**
11. **Caveats in Existing Evidence**..... **113**

Background

Non-small cell lung cancer (NSCLC) makes up around 85% of all cases of lung cancer across the various histological categories. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the three main subtypes of non-small cell lung cancer. It has been observed that a total of 30% of patients have already reached the advanced stage at the time of detection. The subgroup with completely resected stage N2 NSCLC, is a comparatively heterogeneous group with poor prognosis. The only possible cure is the surgical resection which however, faces a very high risk of local recurrence. Based on the literature this local recurrence, post-surgery, has been found to be as high as 20–40% with low overall survival (OS) rate (15–25%) when observed at 5 years. The constant challenge which remains is to find out the approach to improve the OS and prognosis in such patients through comprehensive postoperative treatment. In this subgroup the postoperative radiation therapy (PORT) remains controversial and therefore we aim to study the role of PORT in better treatment and prognosis of lung cancer patients.

Recommendations

Postoperative radiotherapy is ***not recommended*** for patients with completely resected Non-Small Cell Lung Cancer (NSCLC).

Strength: Conditional

Certainty of evidence – Very low

Rationale/Justification

The evidence shows trivial desirable effects and moderate undesirable effects, with very low certainty. Consequently, the overall balance of effects favours omission of postoperative radiotherapy (PORT). Resource requirements are moderate and the available cost effectiveness does not support PORT, and is likely to worsen equity and has limited acceptability. Hence, the recommendation remains conditional against routine PORT, while allowing consideration of PORT for selected patients judged to be at higher risk of locoregional recurrence.

Rationale for the Conditional Recommendation:

Given the absence of subgroup analyses, any consideration of postoperative radiotherapy (PORT) for patients judged to be at higher risk of locoregional recurrence; for example, those with positive or very close surgical margins or bulky/multiple mediastinal nodes should be individualized and, where possible, undertaken within a clinical trial or following multidisciplinary team (MDT) review (no subgroup analyses were conducted in this review). Because the available randomized trials did not show an overall survival benefit and reported increased cardiopulmonary toxicity, the panel therefore issued a conditional recommendation against routine PORT; use of PORT should be based on indirect evidence and expert judgment, documented by the MDT, and limited to centres with modern radiotherapy techniques and appropriate expertise or to clinical-trial settings.

Summary of Evidence

Key Question

In completely resected NSCLC, does the addition of postoperative radiotherapy to standard therapy improve survival compared to standard therapy alone?

Included Studies

A total of 2943 records from electronic databases were identified till 17th May 2025. Of the 2943 articles, 808 duplicate articles were removed. Further 2013 articles were excluded after title and abstract screening because they were not relevant. Full text examination was done for 122 articles. After application of inclusion and exclusion criteria, 4 articles were included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with completely resected stage IIIA-N2 NSCLC. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effect of using post-operative radiotherapy (PORT) in conjunction with adjuvant chemotherapy (ACT + PORT) in patients with completely resected stage IIIA-N2 NSCLC.

Subgroups:

1. T stage
2. Nodal involvement
3. Histology
4. PDL1
5. Smoking status

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

1. Overall survival (*4 studies*)
2. Adverse effects (*4 studies*)
3. Quality of life (*No studies*)
4. Disease free survival (*3 studies*)
5. Cost (*No studies*)

Key question in PICO format

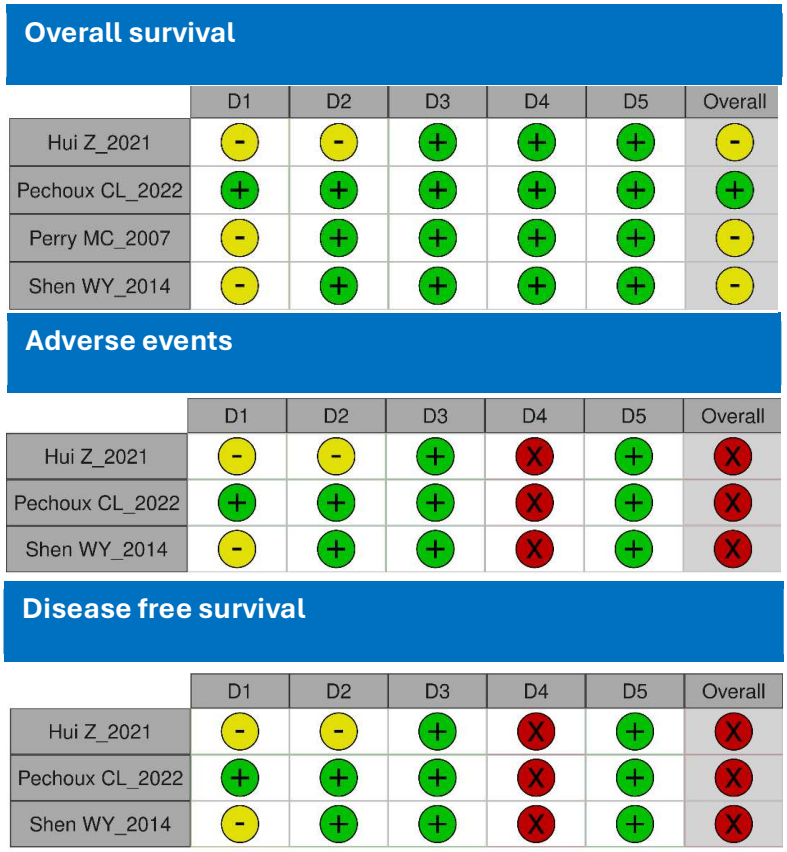
Framework	Inclusion criteria
Population	Patients with NSCLC with complete resection *Subgroups*: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status
Intervention	Post op radiotherapy with adjuvant chemotherapy *Subgroups*: i) 2D conformal ii) 3D conformal

Comparator	Adjuvant chemotherapy alone
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical outcome*) • Quality of life (*Critical outcome*) • Disease free survival (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

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)	5%
		OS (Proportion increase in median survival)	6 months
2	Adverse events	Adverse events	10%
3	Quality of life (QoL)	Quality of life (difference in the mean scores of QoL)	10-point change

Risk of Bias Assessment



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

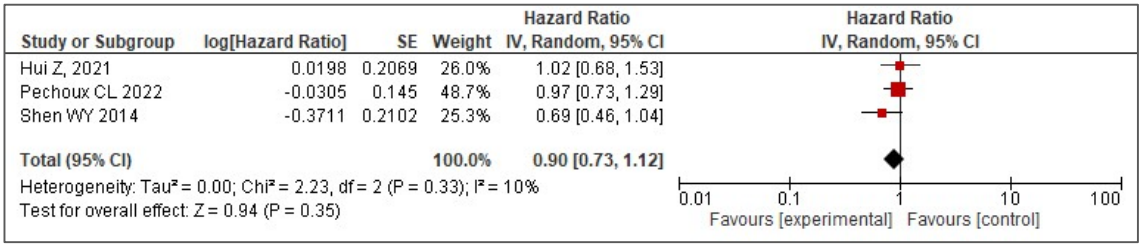
Forest Plot: Desirable Effects

Overall Survival

The evidence does not demonstrate a significant or clinically meaningful improvement in overall survival with the addition of postoperative radiotherapy to adjuvant chemotherapy in patients with completely resected non-small cell lung cancer (NSCLC). A pooled analysis of three randomized controlled trials (RCTs) showed only a trivial 10% relative reduction in the hazard of death with postoperative chemoradiotherapy compared to chemotherapy alone [HR 0.90; 95% CI 0.73–1.12; p = 0.33], with the confidence interval crossing the line of no effect.

Overall survival at 3- and 5-year follow-ups also showed no statistically significant difference between the groups.

Figure 1: Overall survival (OS) using HR



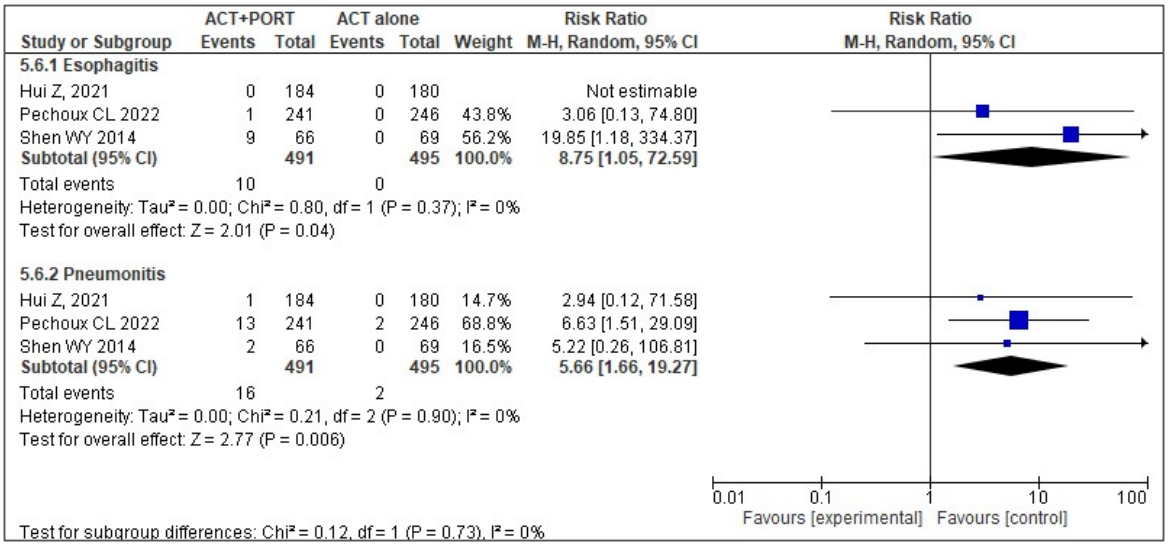
However, certain high-risk pathological features, notably positive (R1) or very close surgical margins and bulky or multi-station mediastinal (N2) nodal disease are consistently associated with higher locoregional recurrence and worse prognosis and therefore warrant individualised consideration of PORT.

(Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. J Clin Oncol. 2015 Mar 10;33(8):870-6. doi: 10.1200/JCO.2014.58.5380)

Undesirable Effects

Pooled results from randomized controlled trials indicate a moderate risk of adverse effects associated with the intervention. Non-hematologic adverse effects such as esophagitis (RR 8.75; 95% CI 1.05–72.59; p = 0.04) and pneumonitis (RR 5.35; 95% CI 1.56–18.31; p = 0.008) were significantly more common among patients receiving postoperative radiotherapy. However, in some individual studies, the confidence intervals crossed the line of no effect, indicating variability and uncertainty in the magnitude of these risks.

Figure 2: Non hematologic adverse events of grade 3 or more is showed in **figure 2**



Summary of Findings

Postoperative radiotherapy Vs standard therapy in completely resected NSCLC

Patient or population: [completely resected NSCLC]

Intervention: ACT+PORT

Comparison: ACT alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ACT	Risk with ACT+PORT				
OS Using HR	40.23% *(range 17-72 %) Follow-up 3 to 5yrs	-	**HR 0.90** (0.73 to 1.12)	(3 RCTs)	⊕⊕◯◯ Low[a,b]	PORT + ACT did not show a clear improvement in overall survival compared to ACT alone (very low certainty).
Esophagitis (AE Non-Hematologic Grade 3 or more)	0 per 1,000	**21 per 1,000**	**RR 8.75** (1.05 to 72.59)	986 (3 RCTs)	⊕◯◯◯ Very low[c,d]	Higher risk of esophagitis was seen with ACT+POCT (low certainty)
Pneumonitis (AE Non-Hematologic Grade 3 or more)	4 per 1,000	**23 per 1,000** (7 to 78)	**RR 5.66** (1.66 to 19.27)	986 (3 RCTs)	⊕◯◯◯ Very low[c,d]	Higher pneumonitis was seen in between ACT + POCT group compared to ACT alone (moderate certainty)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk 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. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
c. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
d. *Optimal information size (OIS) not met*

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Evidence Profile

GRADE all data ACT+PORT compared to ACT alone for [completely resected NSCLC]

Patient or population: Patients with NSCLC with complete resection

Intervention: Postoperative radiotherapy with adjuvant chemotherapy

Comparison: Adjuvant chemotherapy alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	POCRT	POCT	Relative (95% CI)	Absolute (95% CI)		
OS Using HR												
3	randomised trials	serious[a]	not serious	not serious	serious[b]	none	47.55 %	40.23 %	**HR 0.90** (0.73 to 1.12)	**32 fewer per 1,000** (from 89 fewer to 36 more)	⊕⊕◯◯ Low[a,b]	CRITICAL
Adverse Effects												
Esophagitis (AE Non-Hematologic Grade 3 or more)												
3	randomised trials	Very serious[c]	not serious	not serious	serious[d]	none	10/491 (2.0%)	0/495 (0.0%)	**RR 8.75** (1.05 to 72.59)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low[c,d]	CRITICAL
Pneumonitis (AE Non-Hematologic Grade 3 or more)												
3	randomised trials	Very serious[c]	not serious	not serious	serious[d]	none	16/491 (3.1%)	2/495 (0.4%)	**RR 5.66** (1.66 to 19.27)	**18 more per 1,000** (from 2 more to 70 more)	⊕◯◯◯ Very low[c,d]	CRITICAL

CI: Confidence Interval; **HR:** Hazard Ratio; **MD:** Mean Difference; **RR:** Risk Ratio

Explanations*:*

a) *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b) *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
c) *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
d) *Optimal information size (OIS) not met*

Summary of Judgements

Problem	Yes
Desirable Effects	Trivial
Undesirable Effects	Moderate
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Favors the comparison
Resources required	Moderate cost
Certainty of evidence of required resources	No included studies
Cost effectiveness	Probably favors the comparison
Equity	Reduced
Acceptability	Probably no
Feasibility	Probably yes
Recommendation: Postoperative radiotherapy is ***not recommended*** for patients with completely resected Non-Small Cell Lung Cancer (NSCLC). **Strength**: Conditional **Certainty of evidence** – Very low	

Rationale for the Conditional Recommendation:

Given the absence of subgroup analyses, any consideration of postoperative radiotherapy (PORT) for patients judged to be at higher risk of locoregional recurrence; for example, those with positive or very close surgical margins or bulky/multiple mediastinal nodes should be individualized and, where possible, undertaken within a clinical trial or following multidisciplinary team (MDT) review (no subgroup analyses were conducted in this review). Because the available randomized trials did not show an overall survival benefit and reported increased cardiopulmonary toxicity, the panel therefore issued a conditional recommendation against routine PORT; use of PORT should be based on indirect evidence and expert judgment, documented by the MDT, and limited to centres with modern radiotherapy techniques and appropriate expertise or to clinical-trial settings.

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

- Only four studies are available, with a lack of robust randomized controlled trial data specifically focused on patients with completely resected stage N2 NSCLC, limiting the certainty of conclusions.
- None of the included studies reported patient-reported outcomes or quality-of-life measures, restricting assessment of the broader impact of postoperative radiotherapy (PORT).
- Adverse event data were inconsistently reported, precluding a reliable evaluation of treatment-related toxicity.

IN PATIENTS WITH OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC), WHAT IS THE COMPARATIVE EFFECTIVENESS OF RADICAL LOCAL TREATMENT OF THE PRIMARY & METASTATIC SITES COMPARED TO SYSTEMIC THERAPY ALONE?

Table of Contents

1. **Background…….** **117**
2. **Recommendations……** **117**
3. **Rationale/Justification……** **117**
4. **Summary of Evidence……** **117**
5. **Key question in PICO format……** **118**
6. **Risk of Bias……** **120**
7. **Forest Plot……** **121**
8. **Summary of Findings Table……** **124**
9. **Evidence Profile Table……** **126**
10. **Summary of Judgements……** **127**
11. **Caveats in Existing Evidence……** **127**

Background

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all incidences of lung cancer. In two-thirds of these patients, the disease is advanced at presentation. The prognosis for metastatic non-small cell lung cancer is quite bad, and local therapy is only used for palliation. The oligometastatic disease entity has a specific place on an apparent continuum that extends from localized, well-controlled disease to poly-metastatic, widespread disease. The tumor lacks fully developed metastatic pathogenicity. This reduces the tumour growth and distant seeding, and also makes it more recommended to disease control by radical local treatment.

Using definitive local therapy in addition to systemic treatment has been shown to improve survival results in patients with oligometastatic non-small cell lung cancer. Radical treatment used to be mostly surgery, but it now includes radiation therapy as well. Radiotherapy is a non-invasive treatment that complements immunotherapy. For the treatment of individuals with oligometastatic non-small cell lung cancer, stereotactic radiosurgery (SRS) is fast taking the place of other approaches.

Recommendations

Radical local treatment of primary and metastatic sites is ***recommended*** in comparison to treatment with systemic therapy alone for patients with oligometastatic non-small cell lung cancer.

Strength: Conditional
Certainty of evidence: Very low

Rationale/Justification

The evidence showed large desirable effects with small harms, alongside cost-effectiveness probably favouring radical local treatment. However, due to its large costs, reduced equity, and variable feasibility compared to systemic therapy alone, the recommendation is conditional.

Summary of Evidence

Key Question

In patients with oligometastatic non-small cell lung cancer (NSCLC), what is the comparative effectiveness of radical local treatment of the primary & metastatic sites compared to systemic therapy alone?

Included Studies

A total of 936 records from electronic databases were identified till date. Of the 936 articles, 378 duplicate articles were removed. Further 480 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 44 articles. After application of inclusion and exclusion criteria, 9 articles were selected for systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with oligometastatic non-small cell lung cancer. The review includes adults of all ages and genders. Eligible studies are those that evaluate the comparative effectiveness of radical local treatment of the primary & metastatic sites compared to systemic therapy alone.

Subgroups:

1. Surgery
2. Radiation
3. Upfront/delayed

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

1. Overall survival (*Five studies*)
2. Adverse effects (*Nine studies*)
3. Quality of life (*No studies)*
4. Progression free survival (*Seven studies*)
5. Response rate (*Five studies*)
6. Cost (*No studies*)

Key question in PICO format

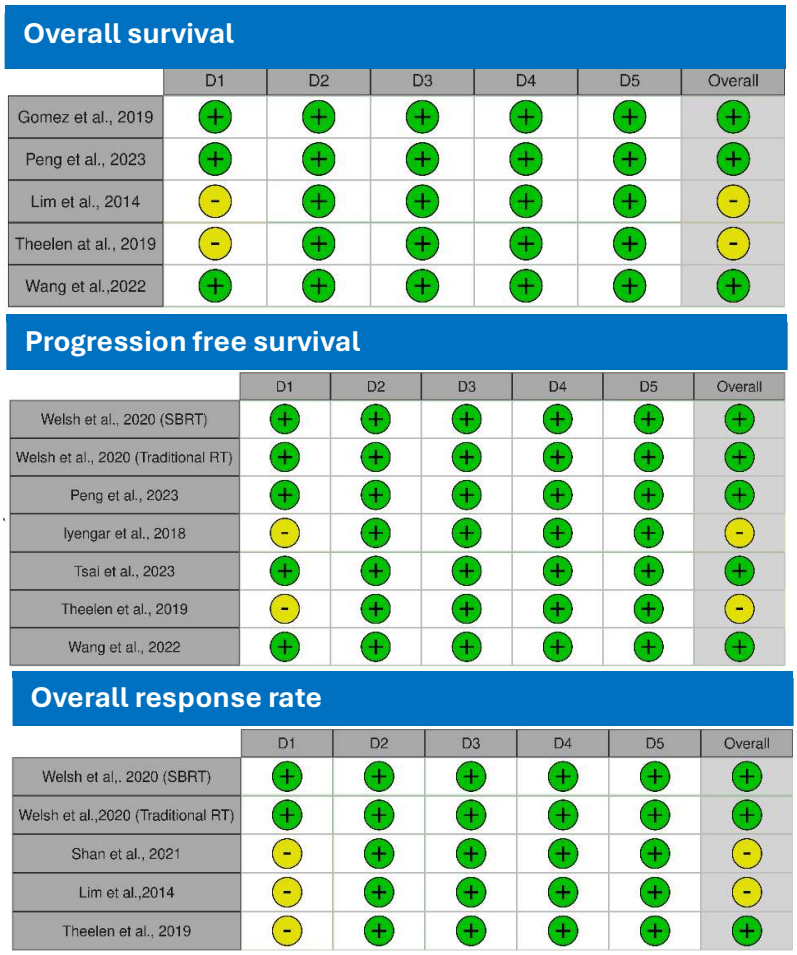
In patients with oligometastatic non-small cell lung cancer (NSCLC), what is the comparative effectiveness of radical local treatment of the primary & metastatic sites compared to systemic therapy alone?

Frame work	Description
Population	Oligometastatic non-small cell Lung cancer *Subgroups*: • Single metastatic sites vs more than one metastatic site • Site(s) of metastasis(es)
Intervention	Radical local treatment in addition to systemic therapy (chemo/immune /targeted) *Subgroups*: • Surgery • Radiation • Upfront/delayed
Comparator	Systemic therapy (chemo/immune/targeted) alone
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Quality of life (*Critical Outcome)* • Progression free survival (*Important Outcome*) • Response rate (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

Sr. No	Critical outcome reviewed	What does it measure	MCID decided by GDG
1	Overall Survival	Proportion of people who have survived at a particular time point	3% at 2 years 3% at 5 years
		Proportion increases in median survival	10% at all time points
2	Serious Adverse effects	Surgery/surgical procedure related complications	5% difference at 30 days and at 90 days
3	Quality of Life	VAS score (ranging from 0-10)	2-point change VAS score
		QLQ -C30 (ranging from 0-100)	0.5 SD change for QLQ-C30 or 2.5 absolute difference

Risk of Bias Assessment



+	Low risk
!	Some concerns
-	High risk

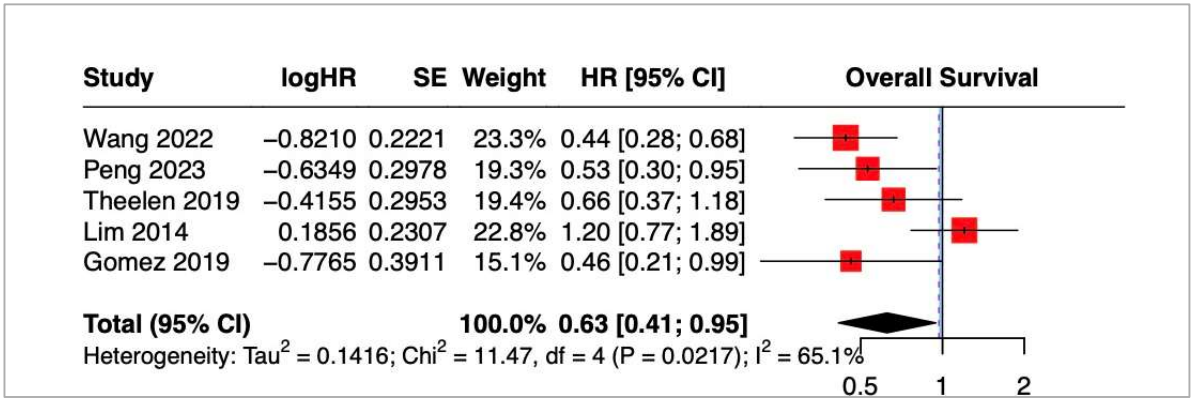
D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Forest Plot: Desirable Effects

Overall Survival

In this analysis, the evidence shows that radical local therapy using radiotherapy alone was associated with a non-significant reduction in risk (HR: 0.66; 95% CI: 0.41 to 1.06), with substantial heterogeneity observed across studies (I^2 = 72%). In contrast, a single study evaluating radiotherapy or surgery (or both) demonstrated a significant benefit (HR: 0.32; 95% CI: 0.13 to 0.77). These findings suggest a potential advantage of combined or surgical approaches, though the evidence for radiotherapy alone remains inconclusive due to variability and imprecision

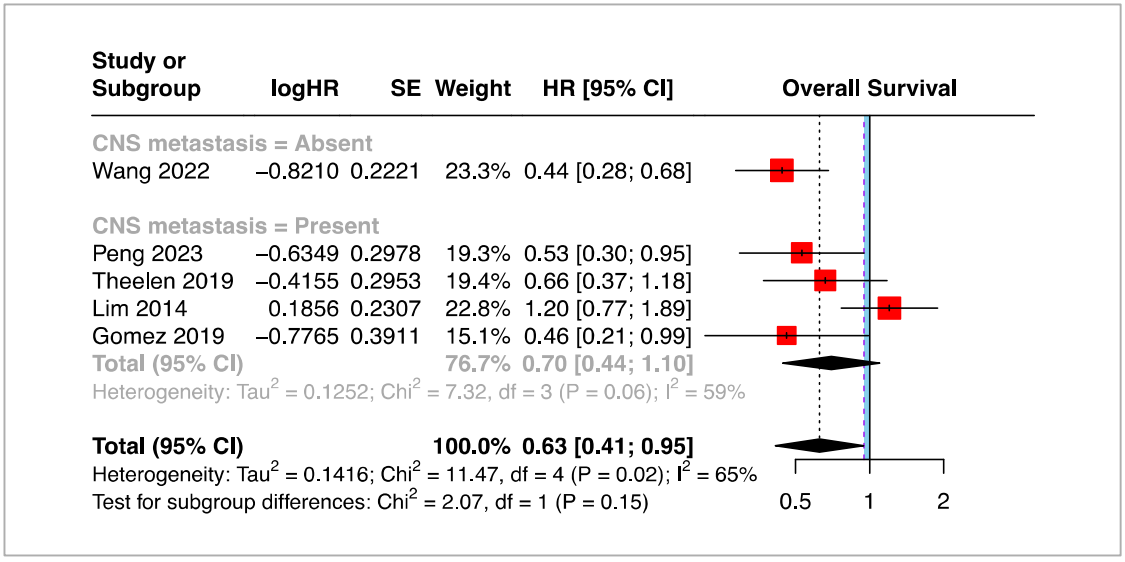
Figure 3.1 – Forest Plot – Overall Survival



*- Blue line represents MCID decided by GDG

In patients with non-small cell lung cancer (NSCLC), the addition of radical local therapy to systemic treatment was associated with a statistically significant improvement in health-related quality of life, as indicated by a pooled standardized mean difference (SMD) of 0.37 (95% CI: 0.13 to 0.60; p = 0.002). The effect size reflects a moderate and clinically meaningful benefit. Heterogeneity across studies was negligible (I^2 = 0%), suggesting consistency in the observed effect. These findings support the integration of local consolidative interventions with systemic therapy to enhance patient-reported outcomes in the management of NSCLC.

Figure 3.2 Forest Plot – with subgroup - metastasis

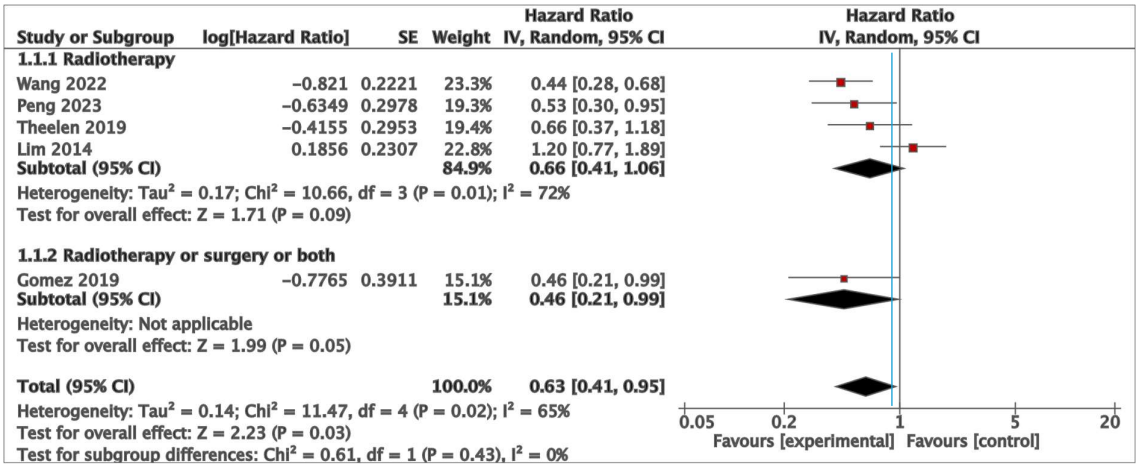


*- Blue line represents MCID decided by GDG

This meta-analysis evaluated the effect of radical local therapy (radiotherapy alone or in combination with surgery) in patients with non-small cell lung cancer. The overall pooled hazard ratio was 0.63 (95% CI: 0.41 to 0.95; p = 0.03), indicating a statistically significant 37% relative reduction in risk of the outcome in the experimental group compared to control. In the radiotherapy-only subgroup (4 studies), the pooled hazard ratio was 0.66 (95% CI: 0.41 to 1.06), suggesting a potential benefit, although this did not reach statistical significance (p = 0.09). The subgroup showed substantial heterogeneity (I^2 = 72%), indicating variation in effect estimates

across studies. The combined modality subgroup (radiotherapy or surgery or both, based on a single study) demonstrated a significant benefit with a hazard ratio of 0.46 (95% CI: 0.21 to 0.99; p = 0.05). No significant difference was detected between subgroups (χ^2 = 0.61, p = 0.43), and overall heterogeneity was moderate (I^2 = 65%). These results suggest that radical local therapy is associated with improved outcomes in NSCLC, with stronger evidence in favor of multimodal approaches compared to radiotherapy alone.

Figure 3.3 Forest Plot – Subgroup – type of therapy



*- Blue line represents MCID decided by GDG

Undesirable Effects

Serious Adverse Effects

Across the included studies, reporting of adverse events was inconsistent and largely incomplete. While a few studies, such as Iyengar et al. (2018) and Welsh et al. (2020), reported Grade 3 events (n=6 and n=6, respectively), others such as Lim et al. (2014), Gomez et al. (2019), and Peng et al. (2023) reported no ≥Grade 3 events in either arm. Notably, Theelen et al. (2019) and Tsai et al. (2023) reported total counts of ≥Grade 3 and ≥Grade 2 events, respectively, without disaggregating data by intervention or control arms. Wang et al. (2022) documented no Grade 5 events, and Shan et al. (2021) did not provide any information on adverse events. Overall, most studies did not systematically report or segregate adverse events by grade or type, limiting the interpretability and comparative analysis of toxicity profiles across treatment arms.

Study Grade events	Total	Intervention	Control
Iyengar et al., 2018 Grade 3 events	6	4	2
Lim et al., 2014 >=Grade 3 events	0	0	0
Theelen et al., 2019 >=Grade 3 events	12*	-	-
Tsai et al., 2023 >=Grade 2 events	55*	-	-
Wang et al., 2022 Grade 5 events	0	0	0
Welsh et al., 2020 Grade 3 events	6*	-	-
Gomez et al., 2019 >=Grade 3	0	0	0
Shan et al., 2021	No information about any grade events		
Peng et al., 2023 >=Grade 3 events	0	0	0

*- No distinction made between intervention and control group

Summary of Findings Table

Radical local therapy compared to control for NSCLC

Patient or population: Patients with Oligometastatic Non-small cell Lung cancer
Intervention: Radical local treatment in addition to systemic therapy (chemo /immune /targeted)
Comparison: Systemic therapy (chemo/immune/targeted) alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control (survived)	**Risk with Radical local therapy (survived)**			
OS follow-up: 1 years	**Control risk (pooled using eligible studies)**		**HR 0.63** (0.41 to 0.95)	432 (5 RCTs)	⊕◯◯◯ very Low[a,b,c]
	640 per 1,000	**755 per 1,000** (654 to 833)			

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

CI: Confidence Interval; **HR:** Hazard Ratio; **RR:** Risk 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. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 65.1%*
c. *Downgraded one level for imprecision as the 95% CI crossed the MCID*

Evidence Profile Table

Radical local treatment of the primary & metastatic sites vs. systemic therapy alone for patients with oligometastatic non-small cell lung cancer

Patient or population: Patients with Oligometastatic Non-small cell Lung cancer
Intervention: Radical local treatment in addition to systemic therapy (chemo /immune /targeted)
Comparison: Systemic therapy (chemo/immune/targeted) alone

Certainty assessment							№ of patients (survived)		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radical local therapy**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**		
OS (follow-up: 1 years)												
5	randomised trials	serious[a]	serious[b]	not serious	Serious[c]	none	165/208 (79.3%)	64.0%	**HR 0.63** (0.41 to 0.95)	**115 more per 1,000** (from 14 more to 193 more)	⊕◯◯◯ very Low[a,b,c]	CRITICAL

CI: Confidence Interval; **HR**: Hazard Ratio; **RR**: Risk Ratio

Explanations:

a. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 65.1%*
c. *Downgraded one level for imprecision as the 95% CI crossed the MCID*

Summary of Judgement

Problem	Yes
Desirable Effects	Large
Undesirable Effects	Small
Certainty of evidence	Very Low
Values	No important uncertainty or variability
Balance of effects	Probably favors the intervention
Resources required	Large costs
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the intervention
Equity	Probably reduced
Acceptability	Probably Yes
Feasibility	Varies
Recommendation: Radical local treatment of primary and metastatic sites is ***recommended*** as compared to treatment with systemic therapy alone for patients with oligometastatic non-small cell lung cancer. **Strength**: Conditional **Certainty of evidence**: Very low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

- There is a lack of comprehensive cost-effectiveness analyses comparing radical local treatment plus systemic therapy versus systemic therapy alone, limited evidence on equity-related disparities in access across geographic and socioeconomic settings, and insufficient implementation and acceptability research assessing real-world feasibility, infrastructure readiness, workforce capacity, and patient and clinician perspectives on radical local treatments.

- The GDG recognized the potential value of targeted investigations in specific patient subgroups (for example, those with driver mutations) where local treatment may plausibly confer additional survival benefit.

-

IN PATIENTS WITH ADVANCED NSCLC HARBOURING SENSITIZING EGFR MUTATIONS, HOW EFFECTIVE ARE 2ND AND 3RD GENERATION TKI IN COMPARISON TO FIRST GENERATION TKI WITH OR WITHOUT CHEMOTHERAPY/ANTIANGIOGENIC AGENTS?

-

Table of Contents

1. **Background**..... **131**
2. **Recommendations**..... **131**
3. **Rationale/Justification**..... **132**
4. **Summary of Evidence**..... **132**
5. **Key question in PICO format**..... **133**
6. **Risk of Bias**..... **134**
7. **Forest Plot**..... **135**
8. **Summary of Findings Table**..... **138**
9. **Evidence Profile Table**..... **140**
10. **Summary of Judgements**..... **141**
11. **Caveats in Existing Evidence**..... **141**

Background

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for approximately 85% of all cases. Among patients with NSCLC, the presence of epidermal growth factor receptor (EGFR) mutations, particularly sensitizing mutations such as exon 19 deletions and exon 21 L858R substitutions, represents an important biomarker for treatment selection. These mutations drive oncogenesis by promoting cell proliferation and survival through continuous activation of the EGFR signaling pathway. Targeted therapies, particularly tyrosine kinase inhibitors (TKIs), have transformed the treatment landscape for NSCLC patients harboring sensitizing EGFR mutations. First-generation TKIs, such as gefitinib and erlotinib, were initially developed to target mutated EGFR, demonstrated significant improvement in progression-free survival (PFS) compared to standard chemotherapy. However, resistance mechanisms, particularly the emergence of the T790M mutation, have limited the long-term efficacy of these agents.

Second- and third-generation TKIs, including afatinib, dacomitinib, and Osimertinib, were developed to overcome these resistance mechanisms and improve outcomes in patients. These newer agents offer distinct pharmacologic advantages, such as irreversible binding to EGFR and broader activity against various mutations, including the T790M mutation. Osimertinib, a third-generation TKI, has also demonstrated central nervous system (CNS) penetration, providing a potential benefit in patients with brain metastases.

Despite their promise, questions remain regarding the comparative effectiveness and safety of second- and third-generation TKIs versus first-generation TKIs. This systematic review and meta-analysis aimed to comprehensively evaluate and compare the clinical efficacy, safety, and cost-effectiveness of second- and third-generation TKIs with first-generation TKIs both alone and in combination with chemotherapy or antiangiogenic agents, in patients with advanced NSCLC harboring sensitizing EGFR mutations.

Recommendations

The use of second and third generation Tyrosine Kinase Inhibitor (TKI) is ***recommended*** rather than first generation TKI for patients with advanced Non-Small Cell Lung Cancer (NSCLC) harbouring sensitizing Epidermal Growth Factor Receptor (EGFR) mutations.

Strength: Conditional

Certainty of evidence – High for efficacy & Low for side effects

Rationale/Justification

Evidence shows moderate desirable effects and small undesirable effects with overall balance of effects favors the use of second- and third-generation TKI therapy. However, resource requirements are large, and although current cost-effectiveness analyses probably favor the comparison, they are likely to reduce equity due to high costs and limited accessibility.

Hence a conditional recommendation was made for patients in whom therapy is accessible through any available financing mechanism (self-payment, patient-assistance programs, insurance, health schemes etc)

Summary of Evidence

Key Question

In patients with advanced NSCLC harbouring sensitizing EGFR mutations, how effective are 2nd and 3rd generation TKI in comparison to first generation TKI with or without chemotherapy/antiangiogenic agents?

Included Studies

A total of 812 records from electronic databases were identified till 31st May 2024. Of the 812 articles, 408 duplicate articles were removed. Further 344 articles were excluded after screening. Full text examination was done for 60 articles and all were available. A set of 43 articles were further excluded as they were not relevant pertaining to the study design, intervention and outcome of the PICO. Finally, 17 articles were included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with advanced NSCLC and harbouring sensitizing EGFR mutations. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effect 2nd & 3rd generation TKI immunotherapy over 1st generation TKI immunotherapy in patients with advanced NSCLC.

Subgroups:

1. Type of mutation
2. Metastatic sites
3. Gender
4. Smoking status

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

1. Overall survival (*6 studies*)
2. Adverse effects (*5 studies*)
3. Progression free survival (*6 studies*)
4. Response Rate (*4 studies*)
5. Quality of life (*4 studies*)
6. Cost (*4 studies*)

Key question in PICO format

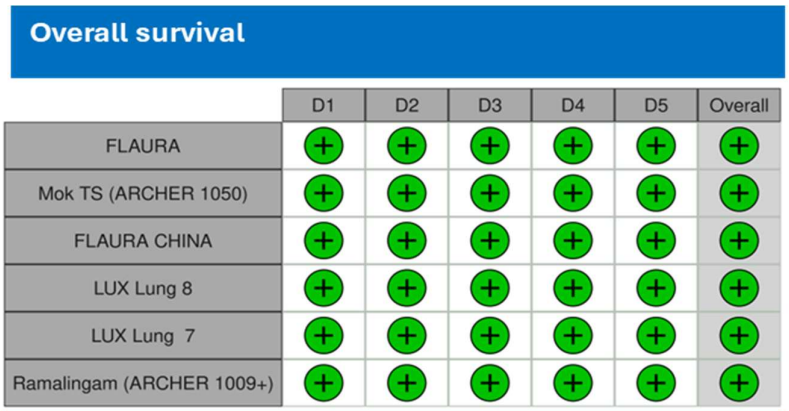
In patients with advanced NSCLC harbouring sensitizing EGFR mutations, how effective are 2nd and 3rd generation TKI in comparison to first generation TKI with or without chemotherapy/antiangiogenic agents?

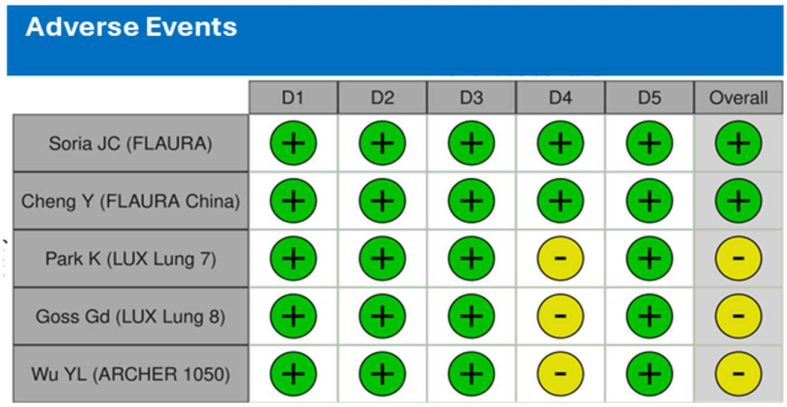
Framework	Inclusion criteria
Population	Patients with advanced NSCLC harboring sensitizing EGFR mutation *Subgroup*: 1. Type of mutation 2. Metastatic sites 3. Gender 4. Smoking status
Intervention	2nd & 3rd gen. TKI (Subgroup: Afatanib/Dacomitinib/ Osimertinib)
Comparator	1st gen TKI 1. Geftinib/Erlotinib 2. Geftinib/Erlotinib with chemotherapy 3. Geftinib/Erlotinib with antiangiogenic agents (Bevacizumab/ Ramucirumab)
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Progression free survival (*Important outcome*) • Response rate (*Important Outcome*) • Quality of life (*Important Outcome*) • Cost (*Important Outcome*)

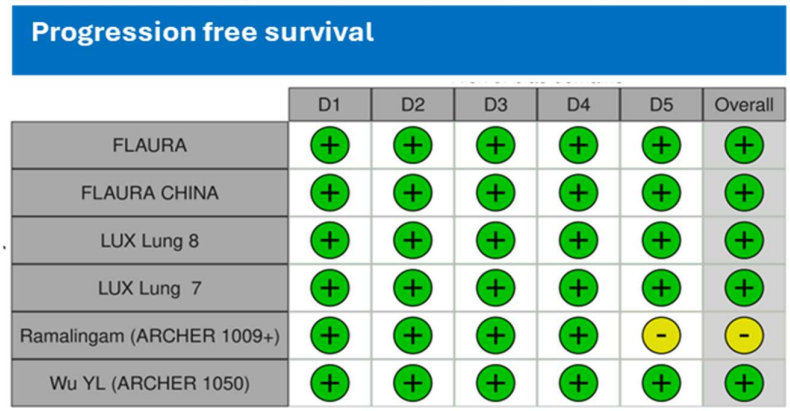
Critical Outcome reviewed and their MCID provided by GDG

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)	5% at 2 years
		OS (Proportion increase in median survival)	6 months
2	Adverse events	Proportion difference in grade 3 or higher AEs	10%

Risk of Bias Assessment







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**

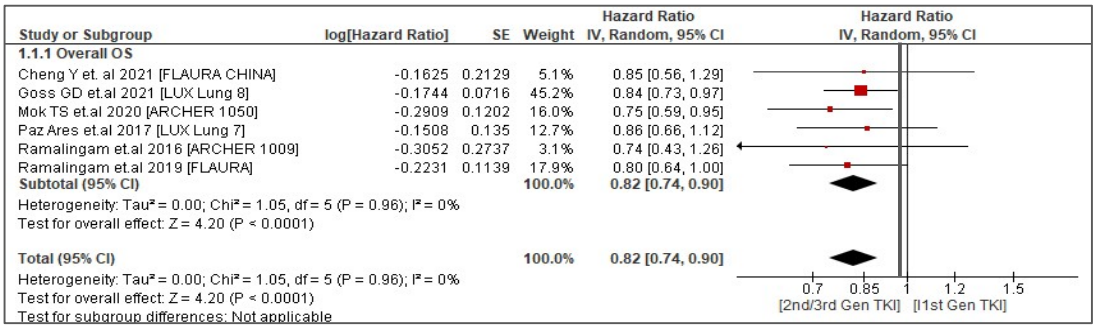
-

Forest Plot: Desirable Effects

Overall Survival

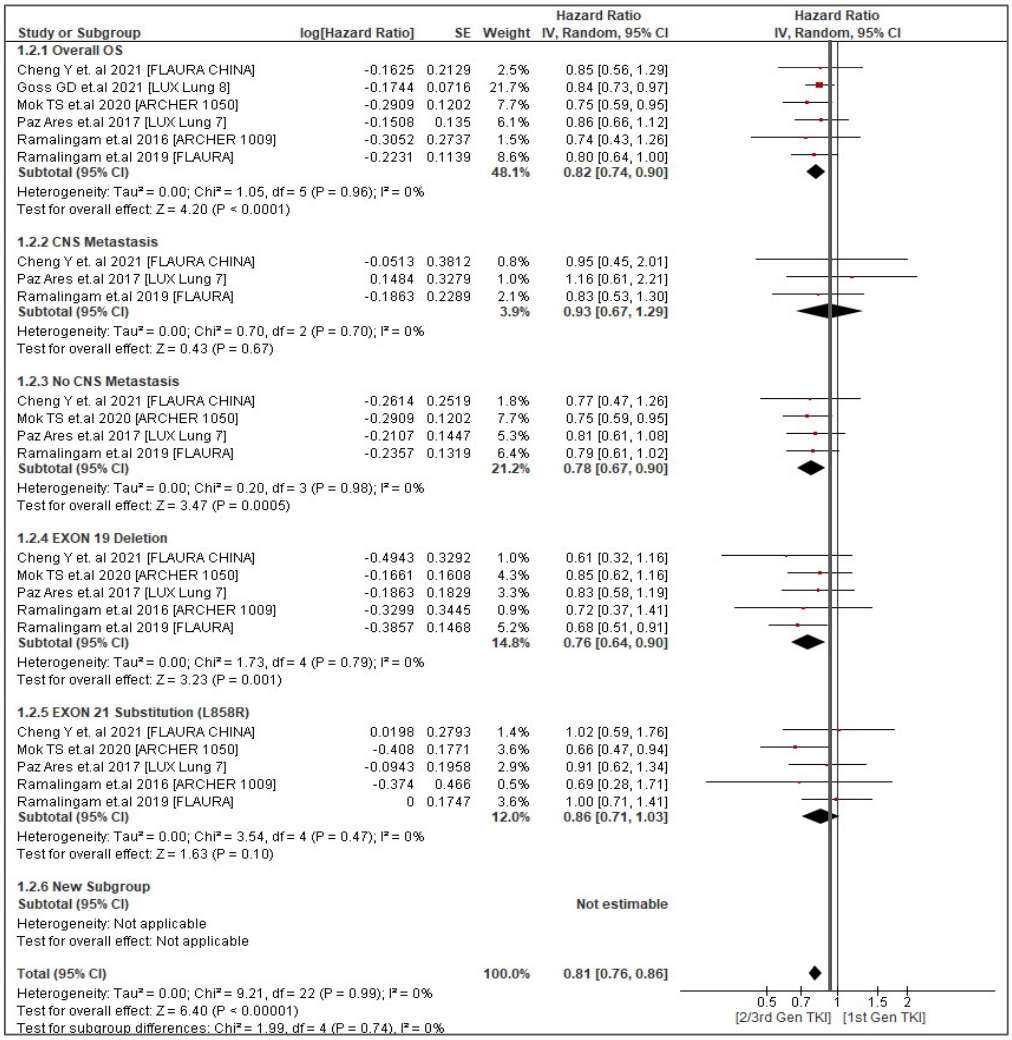
A pooled analysis of 6 randomized controlled trials shows a statistically significant and clinically meaningful improvement in overall survival with second- and third-generation EGFR TKIs compared with first-generation TKIs (with or without chemotherapy/anti-angiogenic agents): HR 0.82 (95% CI 0.74–0.90; p < 0.0001), corresponding to 18% relative reduction in mortality. This benefit exceeds the expert-defined minimum clinically important difference (MCID) of 5% and is therefore likely to be clinically important.

Figure 1: Overall survival (OS) using HR



MCID line is in red (-)

Figure 2: Subgroup analysis; CNS metastasis & type of mutation



MCID line is in red (-)

Undesirable Effects

Pooled results from 5 RCTs demonstrate a statistically significant increase in adverse effects with second- and third-generation TKIs compared with first-generation TKIs, with a pooled odds ratio of 1.53 (95% CI 1.28–1.83; p < 0.00001). However, there was substantial heterogeneity (I^2 = 88%), reflecting variability in toxicity profiles between agents. Notably, Soria et al. (FLAURA), which evaluated the third-generation TKI Osimertinib, reported fewer Grade ≥3 adverse events in the intervention group compared to first-generation TKIs. Most adverse effects were manageable and not considered serious, with the majority being diarrhoea and rash, typically controlled with dose adjustments and supportive care. Soria et al., commonly reported events with first-generation TKIs included rash/acne (19 cases), vomiting (4 cases), and elevations in AST (12 cases) and ALT (21 cases).

Figure 3: Grade 3 and above adverse events

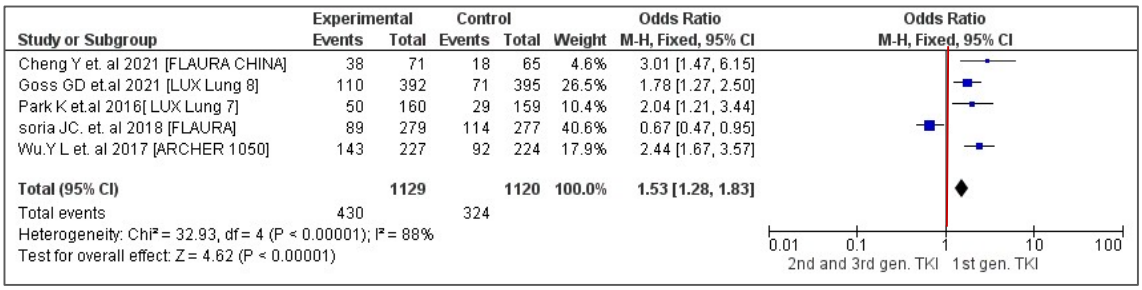
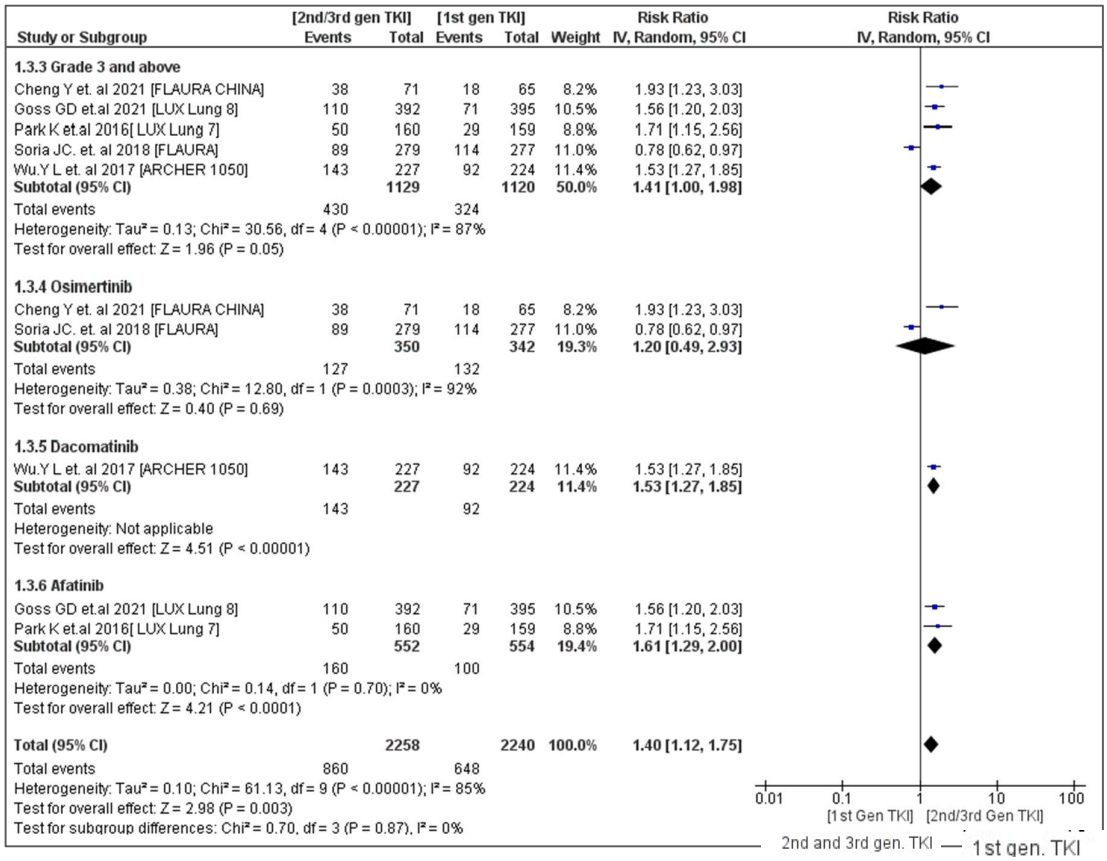


Figure 4: Subgroup analysis based on type of TKIs



Summary of Findings Table

2nd/3rg gen. TKI compared to 1st gen TKI for NSCLC with EGFR mutation

Patient or population: NSCLC with EGFR mutation
Intervention: 2nd/3rg gen. TKI
Comparison: 1st gen TKI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 1st gen TKI	Risk with 2nd/3rg gen. TKI				
OS Using HR	62% *(range 40 to 75%) FU 26 to 48 months	-	**HR 0.82** (0.74 to 0.90)	2359 (6 RCTs)	⊕⊕⊕⊕ High	
Adverse events grade 3 or more	289 per 1,000	**384 per 1,000** (343 to 427)	**OR 1.53** (1.28 to 1.83)	2249 (5 RCTs)	⊕⊕◯◯ Low[a,b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **HR:** Hazard Ratio; **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.

Explanation:

a. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 88%*

***Calculation of Absolute Effects**
When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Evidence Profile Table

2nd/3rg gen. TKI compared to 1st gen TKI for NSCLC with EGFR mutation

Patient or population: NSCLC with EGFR mutation
Intervention: 2nd/3rg gen. TKI
Comparison: 1st gen TKI

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	2nd/3rg gen. TKI	1st gen TKI	**Relative (95% CI)**	**Absolute (95% CI)**		
OS Using HR												
6	randomised trials	not serious	not serious	not serious	not serious	none	-	62% *(range 40 to 75%) FU 26 to 48 months	**HR 0.82** (0.74 to 0.90)	**72 fewer per 1,000** (from 109 fewer to 39 fewer)	⊕⊕⊕⊕ High	
Adverse Event: Grade 3 and above												
5	randomised trials	serious[a]	serious[b]	not serious	not serious	none	384 per 1,000 (38.4%)	289 per 1,000 (28.9%)	**OR 1.53** (1.28 to 1.83)	**94 more per 1,000** (from 53 more to 138 more)	⊕⊕◯◯ Low[a,b]	

CI: Confidence Interval; **HR:** Hazard Ratio; **MD:** Mean Difference; **RR:** Risk Ratio

Explanations:

a. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 88%*

Summary of judgements:

Problem	Yes
Desirable Effects	Moderate
Undesirable Effects	Small
Certainty of evidence	High for efficacy & low for side effects
Values	Probably no important uncertainty or variability
Balance of effects	Favors the intervention
Resources required	Large cost
Certainty of evidence of required resources	Low
Cost effectiveness	Probably favors the comparison
Equity	Reduced
Acceptability	Probably yes
Feasibility	Probably no
Recommendation: The use of second and third generation Tyrosine Kinase Inhibitor (TKI) is ***recommended*** rather than first generation TKI for patients with advanced Non-Small Cell Lung Cancer (NSCLC) harbouring sensitizing Epidermal Growth Factor Receptor (EGFR) mutations **Strength:** Conditional **Certainty of evidence** – High for efficacy & Low for side effects	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

There is a lack of cost-effectiveness evidence comparing second- and third-generation EGFR tyrosine kinase inhibitors with first-generation TKIs, with or without chemotherapy or anti-angiogenic agents, in patients with advanced NSCLC harbouring sensitizing EGFR mutations.

IN PATIENTS WITH ADVANCED NSCLC AND NO ONCOGENIC DRIVER ALTERATION, DOES IMMUNOTHERAPY (IMMUNE CHECK POINT INHIBITORS) EITHER ALONE OR IN COMBINATION IMPROVE OVERALL SURVIVAL AS COMPARED TO CHEMOTHERAPY ALONE?

Table of Contents

1. **Background**..... **145**
2. **Recommendations**..... **145**
3. **Rationale/Justification**..... **145**
4. **Summary of Evidence**..... **145**
5. **Key question in PICO format**..... **146**
6. **Risk of Bias**..... **148**
7. **Forest Plot**..... **150**
8. **Summary of Findings Table**..... **155**
9. **Evidence Profile Table**..... **157**
10. **Summary of Judgements**..... **159**
11. **Caveats in Existing Evidence**..... **159**

Background

Lung cancer is a leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and accounts for 85% of all lung cancers. It comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. It commonly occurs in adults, and smoking is associated with > 80% of NSCLC cases. Advanced NSCLC without actionable oncogenic driver alterations represents a major clinical challenge because treatment options are limited and prognosis remains poor. Over the past decade, the development of immune checkpoint inhibitors has transformed the management of advanced NSCLC by targeting programmed cell death pathways and enhancing antitumor immune responses. Several large randomized trials have shown that immunotherapy can offer durable responses in a subset of patients, contrasting with the typically transient benefits of chemotherapy. However, the magnitude of benefit varies widely and depends on factors such as PD-L1 expression levels and other tumor microenvironment characteristics. Immunotherapy is a newer kind of treatment that can be given by itself or with chemotherapy by blocking immune-checkpoint proteins (PD-1 or PD-L1), which normally act as brakes on T-cells. By releasing this brake, they allow T-cells to recognize and attack lung cancer cells more effectively. If a driver mutation is absent or unknown, immunotherapy (pembrolizumab, atezolizumab, etc.) is considered alone or in combination with chemotherapy. This review assessed the efficacy and safety of immunotherapy (alone or in combination with chemotherapy) compared to chemotherapy alone for treating advanced NSCLC.

Recommendation

Immunotherapy ((immune check point inhibitors) either alone or in combination is ***recommended*** rather than chemotherapy alone for patients with advanced non-small cell lung cancer (NSCLC) and no oncogenic driver alteration.

Strength: Conditional

Certainty of evidence – Low

Rationale/Justification

Evidence shows a large desirable effect and moderate undesirable due to increased immune-related toxicities that are generally manageable when recognised early. However, the cost of the immunotherapy is large thereby reducing the equity.

Hence, a conditional recommendation was made in favour of immunotherapy, for patients who can afford treatment (self-payment, patient-assistance programs, insurance, CGHS etc) and access to centres capable of monitoring and managing immune-related adverse events.

Summary of Evidence

Key Question

In patients with advanced NSCLC and no oncogenic driver alteration, does immunotherapy either alone or in combination improve overall survival as compared to chemotherapy alone?

Included Studies

A total of 3509 records from electronic databases were identified till 25th oct 2024. Of the 3509 articles, 703 duplicate articles were removed. Further 1692 articles were excluded after title and abstract screening because they were not relevant. Full text examination was done for 1114 articles. After application of inclusion and exclusion criteria, 23 articles-60 reports were included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with advanced NSCLC and no oncogenic driver alteration. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effect of Immunotherapy with/without chemotherapy (platinum-based doublet chemotherapy) in conjunction with chemotherapy alone (Platinum-based doublet chemotherapy) in patients with advanced NSCLC and no oncogenic driver alteration.

Subgroups:

1. Histology
2. PD-L1 status
3. Age
4. Smoking status

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

1. Overall survival (*22 studies*)
2. Adverse effects (*23 studies*)
3. Progression free survival (*22 studies*)
4. Response Rate (*23 studies*)
5. Quality of life (*11 studies*)
6. Cost (*No studies*)

PICO

Framework	Inclusion criteria
Population	Patients with advanced NSCLC and no oncogenic driver alteration *Subgroups*: Histology, PD-L1 status, Age, Smoking status
Intervention	Immunotherapy with/without chemotherapy (platinum-based doublet chemotherapy) *Subgroups*: 1. Combination immunochemotherapy vs. Mono-immunotherapy 2. Immunotherapy drugs (Pembrolizumab, Atezolizumab, Nivolumab, and Durvalumab) 3. Dual Immunotherapy combinations (a. Nivolumab and Ipilimumab b. Durvalumab and Tremelimumab

Comparator	Chemotherapy alone (Platinum-based doublet chemotherapy)
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Progression-free survival (*Important Outcome*) • Response rate (*Important Outcome*) • Quality of life (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

Sr. No	Critical outcome reviewed	What does it measure	MCID decided by GDG
1	Overall Survival	Absolute survival gain	5%
		OS (Proportion increase in median survival)	6 months
2	Adverse events	Proportion difference in grade 3 or higher AEs	10%

Risk of Bias Assessment

Overall survival

	D1	D2	D3	D4	D5	Overall
CHECKMATE 26, 2017	+	+	+	+	+	+
CHECKMATE-227, 2019	+	+	+	+	+	+
CHECKMATE 9LA, 2021	+	+	+	+	+	+
CHOICE-01, 2023	+	+	+	+	+	+
EMPOWER-Lung3, 2022	+	+	+	+	+	+
GEMSTONE-302, 2022	+	+	+	+	+	+
Govindan 2017	+	+	+	+	+	+
IMPOWER-110, 2020	+	+	+	+	+	+
IMPOWER-130, 2019	+	+	+	+	+	+
NEPTUNE , 2023	+	+	+	+	+	+
MYSTIC, 2020	+	+	+	+	+	+
KEYNOTE-407 2018	+	+	+	+	+	+
KEYNOTE-189, 2018	+	+	+	+	+	+
KEYNOTE-042, 2019	+	+	+	+	+	+
KEYNOTE-024, 2021	+	+	+	+	+	+
KEYNOTE-021, 2020	+	+	+	+	+	+
IMPOWER-132, 2020	+	+	+	+	+	+
CameL, 2023	+	+	+	+	+	+
CameL-Sq, 2022	+	+	+	+	+	+
RATIONALE 304, 2021	+	+	+	+	+	+
POSEIDON, 2022	+	+	+	+	+	+
ORIENT-11, 2022	+	+	+	+	+	+

Progression free survival

	D1	D2	D3	D4	D5	Overall
CHECKMATE 26, 2017	+	+	+	+	+	+
CHECKMATE-227, 2019	+	+	+	+	+	+
CHECKMATE 9LA, 2021	+	+	+	+	+	+
CHOICE-01, 2023	+	+	+	+	+	+
EMPOWER-Lung3, 2022	+	+	+	+	+	+
GEMSTONE-302, 2022	+	+	+	+	+	+
Govindan 2017	+	+	+	+	+	+
IMPOWER-110, 2020	+	+	+	-	-	+
IMPOWER-130, 2019	+	+	+	+	+	+
NEPTUNE , 2023	+	+	+	-	+	+
MYSTIC, 2020	+	+	+	-	+	+
KEYNOTE-407 2018	+	+	+	-	+	+
KEYNOTE-189, 2018	+	+	+	+	+	+
KEYNOTE-042, 2019	+	+	+	-	+	+
KEYNOTE-024, 2021	+	+	-	+	+	+
KEYNOTE-021, 2020	+	+	+	-	+	+
IMPOWER-132, 2020	+	+	+	+	+	+
CameL, 2023	+	+	+	+	+	+
CameL-Sq, 2022	+	+	+	+	+	+
RATIONALE 304, 2021	+	+	+	+	+	+
POSEIDON, 2022	+	+	+	+	+	+
ORIENT-11, 2022	+	+	+	+	+	+

Response rate

	D1	D2	D3	D4	D5	Overall
CHECKMATE 26, 2017	+	+	+	+	+	+
CHECKMATE-227, 2019	+	+	+	+	+	+
CHECKMATE 9LA, 2021	+	+	+	+	+	+
CHOICE-01, 2023	+	+	+	+	+	+
EMPOWER-Lung3, 2022	+	+	+	+	+	+
GEMSTONE-302, 2022	+	+	+	+	+	+
Govindan 2017	+	+	+	+	+	+
IMPOWER-110, 2020	+	+	+	+	+	+
IMPOWER-130, 2019	+	+	+	+	+	+
NEPTUNE , 2023	+	+	+	+	+	+
MYSTIC, 2020	+	+	+	+	+	+
KEYNOTE-407 2018	+	+	+	+	+	+
KEYNOTE-189, 2018	+	+	+	+	+	+
KEYNOTE-042, 2019	+	+	+	+	+	+
KEYNOTE-024, 2021	+	+	+	+	+	+
KEYNOTE-021, 2020	+	+	+	+	+	+
IMPOWER-132, 2020	+	+	+	+	+	+
CameL, 2023	+	+	+	+	+	+
CameL-Sq, 2022	+	+	+	+	+	+
Zou J, 2022	-	+	+	-	-	X
RATIONALE 304, 2021	+	+	+	+	+	+
POSEIDON, 2022	+	+	+	+	+	+
ORIENT-11, 2022	+	+	+	+	+	+

Adverse events

	D1	D2	D3	D4	D5	Overall
CHECKMATE 26, 2017	+	+	+	+	+	+
CHECKMATE-227, 2019	+	+	+	+	+	+
CHECKMATE 9LA, 2021	+	+	+	+	+	+
CHOICE-01, 2023	+	+	+	+	+	+
EMPOWER-Lung3, 2022	+	+	+	+	+	+
GEMSTONE-302, 2022	+	+	+	+	+	+
Govindan 2017	+	+	+	+	+	+
IMPOWER-110, 2020	+	+	+	+	+	+
IMPOWER-130, 2019	+	+	+	+	+	+
NEPTUNE , 2023	+	+	+	+	+	+
MYSTIC, 2020	+	+	+	+	+	+
KEYNOTE-407 2018	+	+	+	+	+	+
KEYNOTE-189, 2018	+	+	+	+	+	+
KEYNOTE-042, 2019	+	+	+	+	+	+
KEYNOTE-024, 2021	+	+	+	+	+	+
KEYNOTE-021, 2020	+	+	+	+	+	+
IMPOWER-132, 2020	+	+	+	+	+	+
CameL, 2023	+	+	+	+	+	+
CameL-Sq, 2022	+	+	+	+	+	+
Zou J, 2022	-	+	+	-	-	X
RATIONALE 304, 2021	+	+	+	+	+	+
POSEIDON, 2022	+	+	+	+	+	+
ORIENT-11, 2022	+	+	+	+	+	+

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

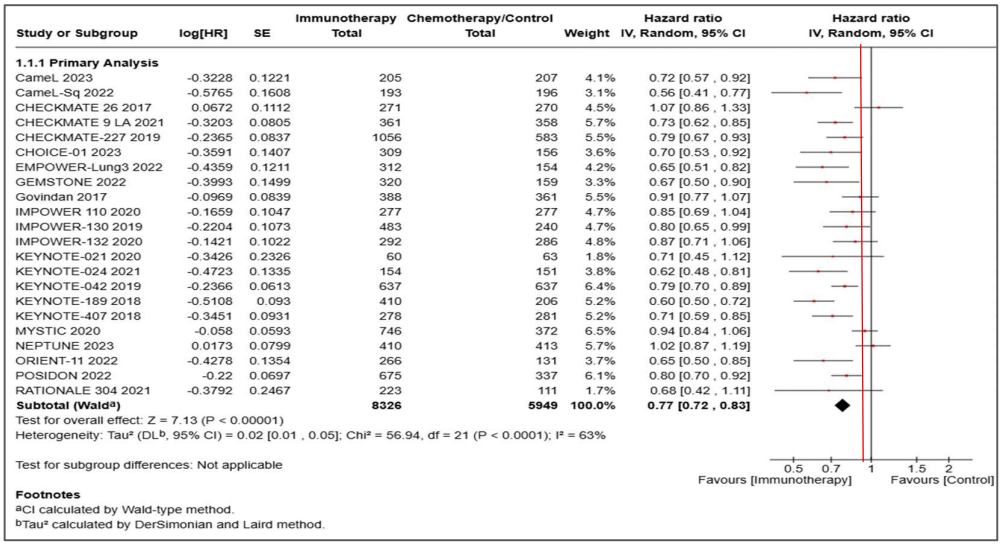
	**Low risk**
	**Some concerns**
	**High risk**

Forest Plot: Desirable Effects

Overall Survival

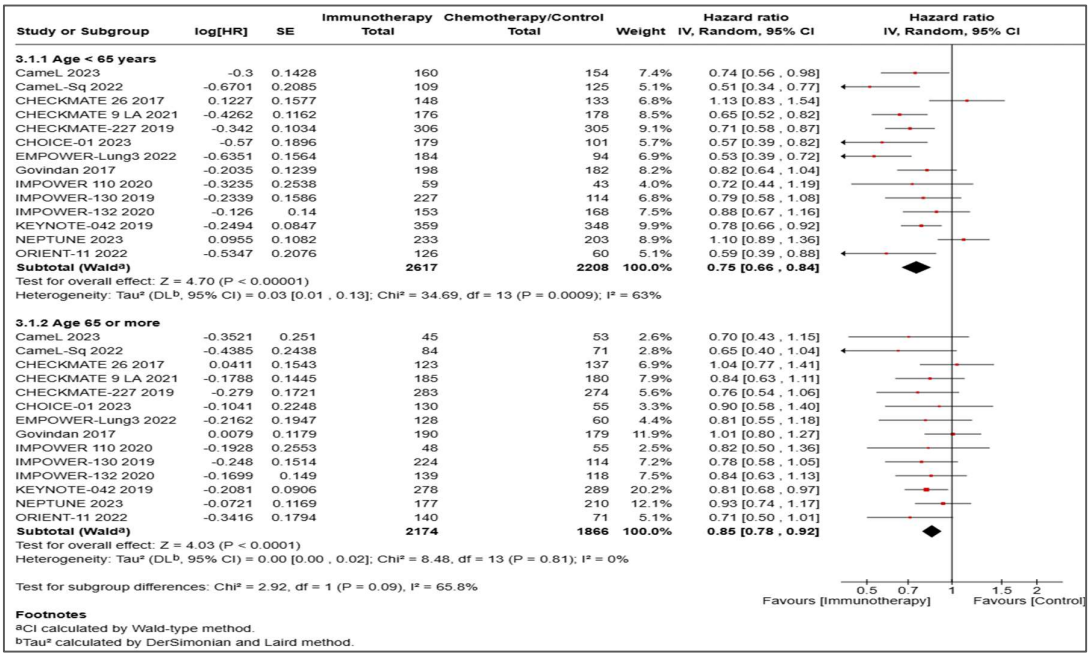
The pooled evidence from 23 randomized controlled trials shows that immunotherapy (alone or combined with chemotherapy) significantly improves overall survival in patients with advanced NSCLC without oncogenic driver alterations, producing a 23% relative reduction in the hazard of death compared with chemotherapy alone (HR 0.77, 95% CI 0.72–0.83). Using the GDG's MCID of 5%, the observed relative effect clearly exceeds the threshold for clinical importance.

Figure 1: Forest plot: Overall survival (OS) using HR



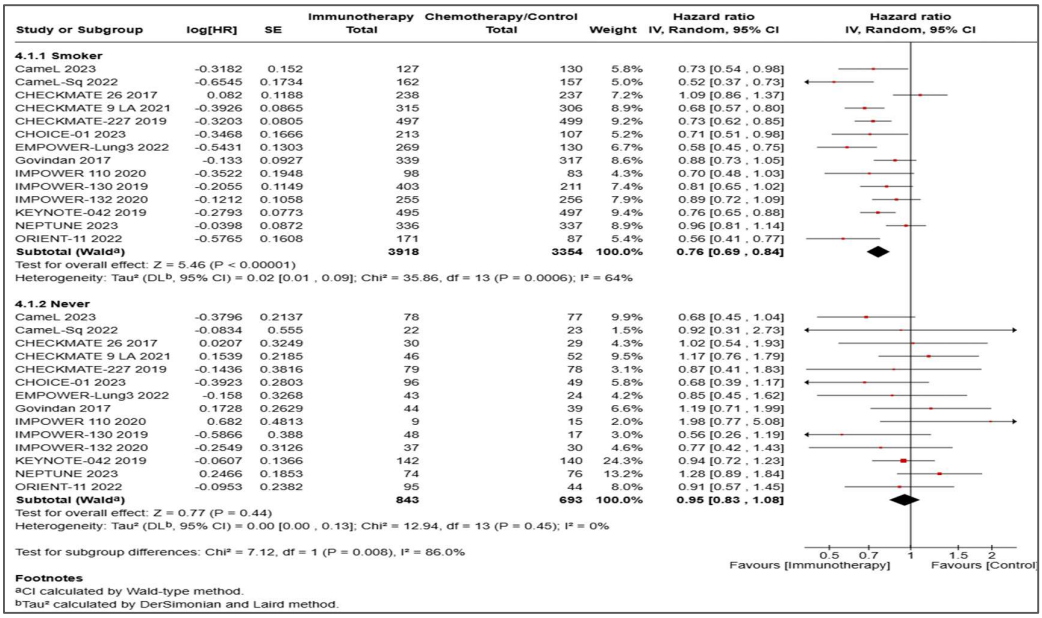
Red line indicated MCID provided by GDG (5%)

Figure 2: Overall survival (hazard ratio) Subgroup for age (<65 years *vs.* > 65 years)



Both age groups (<65 years and ≥65 years) experienced a statistically significant survival benefit with immunotherapy; however, the effect appeared slightly larger in younger patients (HR 0.75, 95% CI 0.66–0.84) compared with older adults (HR 0.85, 95% CI 0.78–0.92). Although the test for subgroup differences was not statistically significant (p = 0.09), the direction of effect suggests a modest attenuation of benefit with increasing age.

Figure 3: Overall survival (hazard ratio) Subgroup for Smoking status



A significant subgroup effect was observed between smokers and never-smokers (p = 0.008), with smokers demonstrating a larger survival benefit (HR 0.76, 95% CI 0.69–0.84) compared with never-smokers (HR 0.95, 95% CI 0.83–1.08).

Figure 4: Overall survival (hazard ratio) Subgroup for Histology

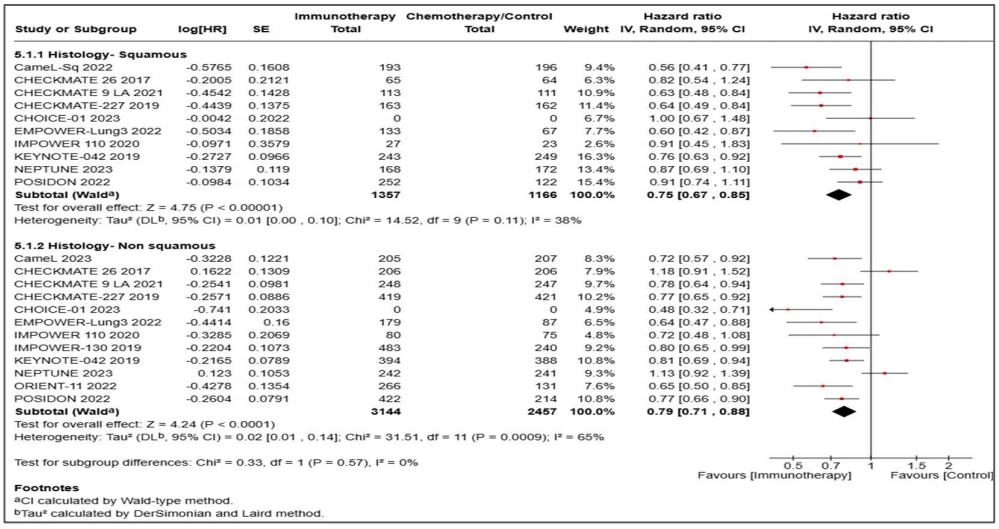


Figure 5: Overall survival (hazard ratio) Subgroup for PD-L1 status

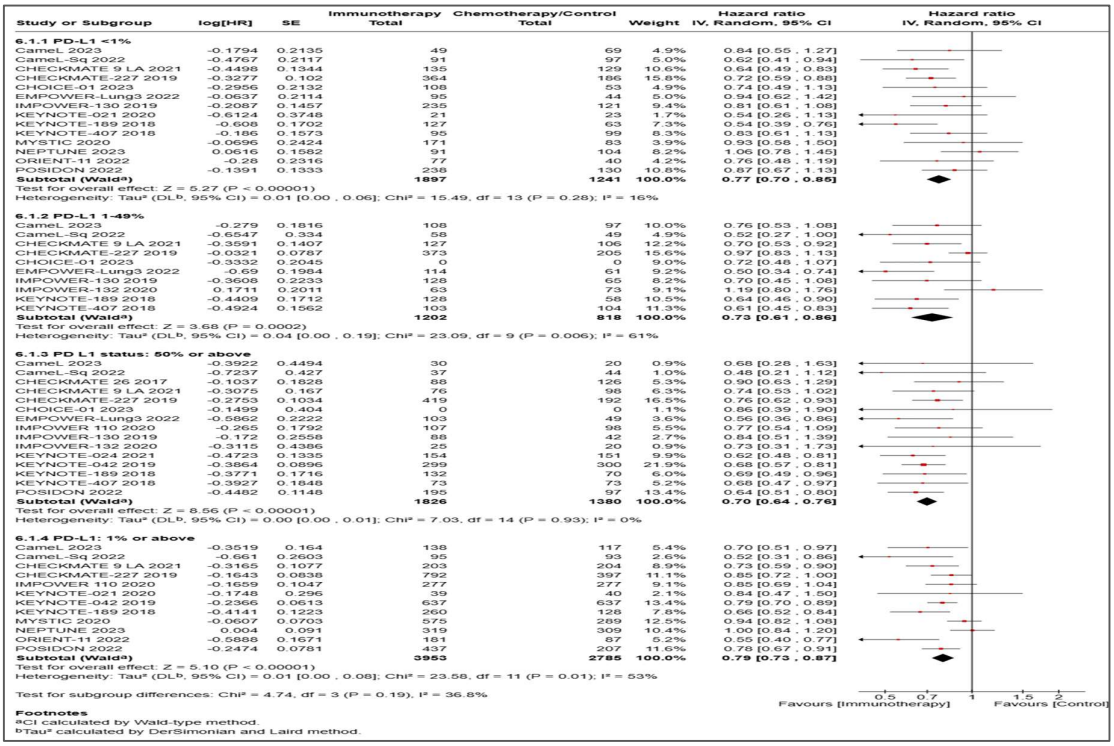
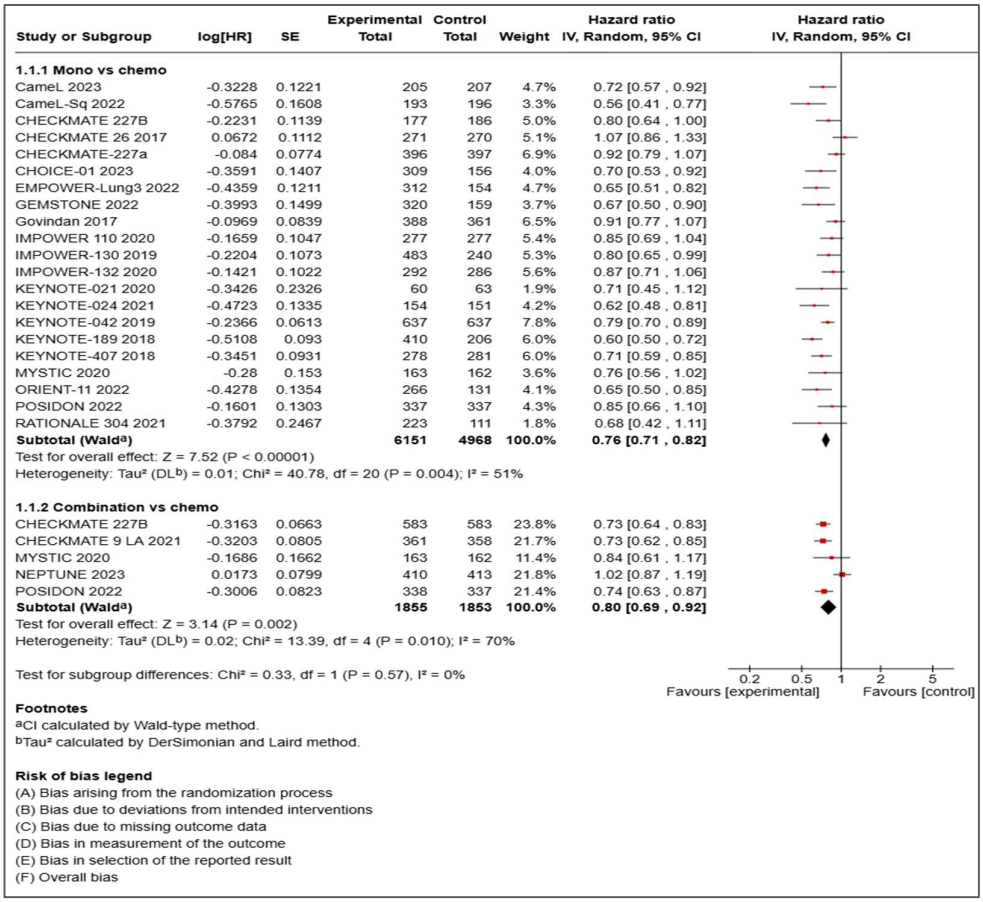


Figure 6: Subgroup analysis exploring various combinations (Mono-immunotherapy versus Combination immunotherapy)

Overall Survival



Study or Subgroup	log[HR]	SE	Experimental Total	Control Total	Weight	Hazard ratio IV, Random, 95% CI
1.1.1 Mono vs chemo						
CameL 2023	-0.3228	0.1221	205	207	4.7%	0.72 [0.57 , 0.92]
CameL-Sq 2022	-0.5765	0.1608	193	196	3.3%	0.56 [0.41 , 0.77]
CHECKMATE 227B	-0.2231	0.1139	177	186	5.0%	0.80 [0.64 , 1.00]
CHECKMATE 26 2017	0.0672	0.1112	271	270	5.1%	1.07 [0.86 , 1.33]
CHECKMATE-227a	-0.084	0.0774	396	397	6.9%	0.92 [0.79 , 1.07]
CHOICE-01 2023	-0.3591	0.1407	309	156	4.0%	0.70 [0.53 , 0.92]
EMPOWER-Lung3 2022	-0.4359	0.1211	312	154	4.7%	0.65 [0.51 , 0.82]
GEMSTONE 2022	-0.3993	0.1499	320	159	3.7%	0.67 [0.50 , 0.90]
Govindan 2017	-0.0969	0.0839	388	361	6.5%	0.91 [0.77 , 1.07]
IMPOWER 110 2020	-0.1659	0.1047	277	277	5.4%	0.85 [0.69 , 1.04]
IMPOWER-130 2019	-0.2204	0.1073	483	240	5.3%	0.80 [0.65 , 0.99]
IMPOWER-132 2020	-0.1421	0.1022	292	286	5.6%	0.87 [0.71 , 1.06]
KEYNOTE-021 2020	-0.3426	0.2326	60	63	1.9%	0.71 [0.45 , 1.12]
KEYNOTE-024 2021	-0.4723	0.1335	154	151	4.2%	0.62 [0.48 , 0.81]
KEYNOTE-042 2019	-0.2366	0.0613	637	637	7.8%	0.79 [0.70 , 0.89]
KEYNOTE-189 2018	-0.5108	0.093	410	206	6.0%	0.60 [0.50 , 0.72]
KEYNOTE-407 2018	-0.3451	0.0931	278	281	6.0%	0.71 [0.59 , 0.85]
MYSTIC 2020	-0.28	0.153	163	162	3.6%	0.76 [0.56 , 1.02]
ORIENT-11 2022	-0.4278	0.1354	266	131	4.1%	0.65 [0.50 , 0.85]
POSIDON 2022	-0.1601	0.1303	337	337	4.3%	0.85 [0.66 , 1.10]
RATIONALE 304 2021	-0.3792	0.2467	223	111	1.8%	0.68 [0.42 , 1.11]
Subtotal (Wald[a])			**6151**	**4968**	**100.0%**	**0.76 [0.71 , 0.82]**
Test for overall effect: Z = 7.52 (P < 0.00001)						
Heterogeneity: Tau² (DL[b]) = 0.01; Chi² = 40.78, df = 20 (P = 0.004); I² = 51%						
1.1.2 Combination vs chemo						
CHECKMATE 227B	-0.3163	0.0663	583	583	23.8%	0.73 [0.64 , 0.83]
CHECKMATE 9 LA 2021	-0.3203	0.0805	361	358	21.7%	0.73 [0.62 , 0.85]
MYSTIC 2020	-0.1686	0.1662	163	162	11.4%	0.84 [0.61 , 1.17]
NEPTUNE 2023	0.0173	0.0799	410	413	21.8%	1.02 [0.87 , 1.19]
POSIDON 2022	-0.3006	0.0823	338	337	21.4%	0.74 [0.63 , 0.87]
Subtotal (Wald[a])			**1855**	**1853**	**100.0%**	**0.80 [0.69 , 0.92]**
Test for overall effect: Z = 3.14 (P = 0.002)						
Heterogeneity: Tau² (DL[b]) = 0.02; Chi² = 13.39, df = 4 (P = 0.010); I² = 70%						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Undesirable Effects

The pooled analysis of 23 randomized controlled trials demonstrated no significant difference in the risk of serious adverse events (Grade ≥3) between immunotherapy (alone or in combination) and chemotherapy alone (OR 0.99, 95% CI 0.89–1.10; p = 0.79). Immune-related adverse events were substantially more common with immunotherapy than with chemotherapy alone, with a pooled odds ratio of 5.58 (95% CI 3.58–8.70; p < 0.00001), indicating more than a fivefold increase in risk. The most common immune related adverse events were skin rashes, mild endocrine changes, and low-grade GI events.

Figure 1: Forest plot: Adverse events (Grade ≥3)

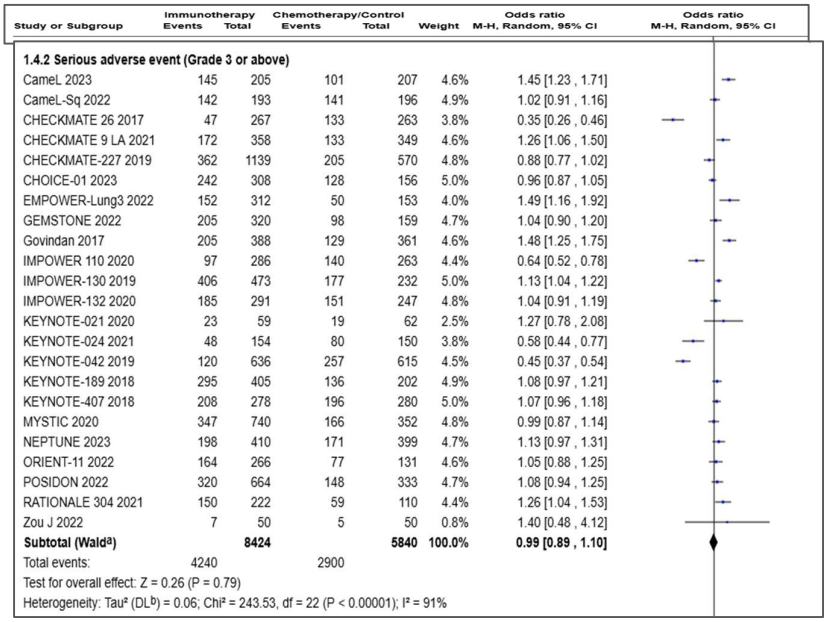
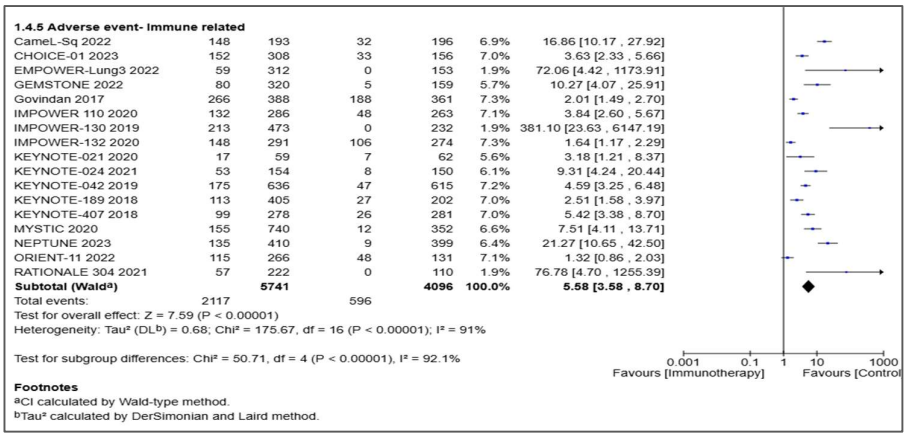


Figure 2: Forest plot: Adverse events (immune related)



Summary of Findings Table

Immunotherapy Vs chemotherapy alone in completely resected NSCLC patients with no oncogenic driver alteration

Patient or population: Patients with advanced NSCLC and no oncogenic driver alteration
Intervention: Immunotherapy either alone or in combination
Comparison: Chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with Immunotherapy				
Overall survival (hazard ratio)	54.75% *(range 27.2 – 88.7%) FU (1 to 5.4 yr)	-	**HR 0.77** (0.72 to 0.83)	14375 (23 RCTs)	⊕⊕◯◯ Low[a,b]	
Overall survival-Smokers (OS-Smokers) assessed with: Hazard Ratio		-	**HR 0.76** (0.69 to 0.84)	7272 (14 RCTs)	⊕⊕◯◯ Low[a,b]	
Overall survival-non-smokers assessed with: Hazard ratio		-	**HR 0.95** (0.83 to 1.04)	1536 (14 RCTs)	⊕⊕◯◯ low[b,c]	
Adverse events - Serious adverse event (Grade 3 or above)	497 per 1,000	492 per 1,000 (442 to 547)	**RR 0.99** (0.89 to 1.10)	14264 (23 RCTs)	⊕⊕◯◯ low[c,a]	
Adverse events – immune related	146 per 1,000	488 per 1,000 (359 to 642)	**RR 5.58** (3.58 to 8.70)	9,837 (17 RCTs)	⊕⊕⊕◯ moderate[a]	

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence Interval; **HR:** Hazard Ratio; **MD:** Mean Difference; **RR:** Risk 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.

Explanation:

a. Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with high I^2
b. Publication bias strongly suspected, downgraded by one level (funnel plot provided below)
c. Downgraded one level for imprecision as the 95% CI crossed the null effect line

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Evidence Profile Table

Immunotherapy Vs chemotherapy alone in completely resected NSCLC patients with no oncogenic driver alteration

Patient or population: Patients with advanced NSCLC and no oncogenic driver alteration
Intervention: Immunotherapy either alone or in combination
Comparison: Chemotherapy alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	POCRT	POCT	Relative (95% CI)	Absolute (95% CI)		
OS Using HR												
23	randomised trials	not serious	serious[a]	not serious	not serious	*Publication bias strongly suspected[b]	8426	5949	**HR 0.77** (0.72 to 0.83)	54.75% *(range 27.2 – 88.7%) FU (1 to 5.4 yr)	⊕⊕◯◯ Low[a,b]	CRITICAL
Overall survival-Smokers (assessed with: Hazard Ratio)												
14	randomised trials	not serious	serious[a]	not serious	not serious	publication bias strongly suspected[b]	3918	3354	**HR 0.76** (0.69 to 0.84)	**-- per 1,000** (from -- to --)	⊕⊕◯◯ Low[a,b]	CRITICAL
Overall survival-non-smokers (assessed with: Hazard ratio)												
14	randomised trials	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	843	693	**HR 0.95** (0.83 to 1.04)	**-- per 1,000** (from -- to --)	⊕⊕◯◯ low[b,c]	CRITICAL
Adverse events (Grade 3 or more)												

23	randomised trials	not serious	serious[a]	not serious	serious[c]	none	4240/8424 (50.3%)	2900/5840 (49.7%)	**RR 0.99** (0.89 to 1.10)	**5 fewer per 1,000** (from 55 fewer to 50 more)	⊕⊕◯◯ low[c,a]	CRITICAL
Adverse events – immune related												
17	randomised trials	not serious	serious[a]	not serious	not serious	none	146 per 1,000	488 per 1,000 (359 to 642)	RR 5.58 (3.58 to 8.70)	**342 more per 1,000** (213 more to 496 more)	⊕⊕⊕◯ moderate[a]	CRITICAL

CI: Confidence Interval; **HR:** Hazard Ratio; **MD:** Mean Difference; **RR:** Risk Ratio

Explanations:

a. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with high I^2*
b. *Publication bias strongly suspected, downgraded by one level (funnel plot provided below)*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

Summary of Judgements

Problem	Yes
Desirable Effects	Large
Undesirable Effects	Moderate
Certainty of evidence	Low
Values	Probably no important uncertainty or variability
Balance of effects	Favours the intervention
Resources required	Large cost
Certainty of evidence of required resources	No included studies
Cost effectiveness	Varies
Equity	Reduced
Acceptability	Varies
Feasibility	Varies
Recommendation: Immunotherapy ((immune check point inhibitors) either alone or in combination is ***recommended*** rather than chemotherapy alone for patients with advanced non-small cell lung cancer (NSCLC) and no oncogenic driver alteration. **Strength**: Conditional **Certainty of evidence** – Low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

There is a lack of cost-effectiveness evidence evaluating immunotherapy (alone or in combination) compared with chemotherapy alone in patients with advanced NSCLC without oncogenic driver alterations, limiting informed decisions on value for money and resource allocation.

IN PATIENTS WITH NSCLC, HOW EFFECTIVE IS IMMUNOTHERAPY (IMMUNE CHECKPOINT INHIBITORS) DELIVERED AS INDIVIDUALIZED DOSING REGIMEN (LOW DOSE) COMPARED TO STANDARD FULL DOSE IMMUNOTHERAPY?

Table of Contents

1. **Background**..... **163**
2. **Recommendations**..... **163**
3. **Rationale/Justification**..... **163**
4. **Summary of Evidence**..... **164**
5. **Key question in PICO format**..... **165**
6. **Risk of Bias**..... **166**
7. **Forest Plot**..... **167**
8. **Summary of Findings Table**..... **169**
9. **Evidence Profile Table**..... **170**
10. **Summary of Judgements**..... **172**
11. **Caveats in Existing Evidence**..... **172**

Background

Lung cancer remains the leading cause of cancer-related mortality globally, responsible for 1.8 million deaths and 18.7% of the total cancer deaths. Despite advancements in early detection and multimodal treatment approaches, outcomes remain suboptimal, particularly in operable NSCLC where recurrence and mortality risks persist. Of the various management options immunotherapy, especially immune checkpoint inhibitors such as nivolumab and pembrolizumab, has emerged as a paradigm shift in the treatment of NSCLC. These agents, are conventionally administered at fixed standard doses, irrespective of patient-specific characteristics like body weight or surface area. However, these regimens result in high per-patient costs, raising concerns over the financial sustainability of widespread immunotherapy use in publicly funded health systems. Emerging clinical pharmacokinetic evidence suggests that lower or weight-based dosing may achieve similar therapeutic outcomes while significantly reducing drug expenditure. By synthesizing available data on costs and clinical outcomes associated with standard versus individualized immunotherapy dosing in operable NSCLC cost reduction may be achieved.

Recommendations

In patients with advanced NSCLC without driver mutations, lower-dose pembrolizumab (100 mg) may be considered on an individual basis when the standard dose (200 mg) is unaffordable or unavailable. Such use should occur after documenting the rationale for dose modification, and obtaining informed consent outlining the uncertain efficacy and associated evidence limitations.

Strength: Conditional

Certainty of evidence: Very low

Rationale/Justification

The desirable and undesirable effects of reduced dosage was comparable to the standard full-dose regimen, with very low-certainty evidence supporting comparable clinical outcomes rather than superiority. Given the moderate resource savings, probable cost-effectiveness, and potential to improve equity, alongside the intervention's acceptability and likely feasibility, the panel judged the balance of effects to probably favour individualized dosing.

The available evidence for reduced-dose pembrolizumab is derived solely from non-randomized cohort studies, which carry a high risk of confounding and selection bias. In view of the methodological limitations and the uncertainty around comparative efficacy, any consideration of a lower dose should be undertaken cautiously and restricted to settings where the standard dose is not feasible.

Summary of Evidence

Key Question

Should Individualized dosing regimen vs. Standard fixed full dose indefinite dosing schedule be used for patients with NSCLC, eligible for immune checkpoint inhibitors?

Included Studies

A total of 4,111 records up to 31 December 2024 were identified. After removing 1,100 duplicates and excluding 2,996 records on title/abstract screening, 15 full texts were reviewed. Applying our inclusion and exclusion criteria resulted in eight observational studies entering the systematic review; no RCTs were eligible. All studies examined pembrolizumab as first-line therapy. Because the DCGI endorses a fixed 200 mg pembrolizumab dose in India, the dose-comparison recommendation was limited to trials evaluating fixed doses (100 mg vs 200 mg every 3 weeks); only **two studies** fulfilled this requirement and were included in the dose-comparison analysis.

Population and Study Characteristics

All the studies included patients NSCLC patients eligible for immune checkpoint inhibitors. The review includes adults of all ages and genders where the intervention was individualized (weight-based or reduced) dosing and the comparator was fixed standard dosing for treatment of patients with NSCLC, eligible for immune checkpoint inhibitors

Subgroups:

1. Stage
2. Histology
3. PD-L1 status
4. Age
5. Smoking status

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

1. Overall survival (*2 studies*)
2. Side effects (*1 study*)
3. Quality of life (*No studies*)
4. Progression free survival (*2 studies*)
5. Response rate (*2 studies*)
6. Cost (*2 studies*)

PICO

Framework	Description
Population	Patients with NSCLC being considered / eligible for immune checkpoint inhibitors *Subgroups*: 1. Stage 2. Histology 3. PD-L1 status 4. age 5. Smoking status
Intervention	Individualized dosing regimen (low dose or reduced frequency) *Subgroups*: reduced frequency dosing schedule/reduced dose and reduced frequency
Comparator	Standard fixed full dose indefinite dosing schedule
Outcome	• Overall survival (*Critical Outcome*) • Side effects (*Critical Outcome*) • Quality of life (*Critical Outcome*) • Progression free survival (*Important Outcome*) • Response rate (*Important Outcome*) • Cost (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

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)	Non-inferiority within 5%
		OS (Proportion increase in median survival)	-2 to +2 months
2	Adverse events	Proportion difference in grade 3 or higher AEs	10%
4	Quality of life	Point change on the 0–100 scale	10-point change

Risk of Bias/ Quality Assessment for non-randomized studies

National Institute of Health (NIH) quality assessment

Observational Studies

Study id	1. Was the research question or objective clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate ≥50%?	4. Were subjects from same/similar population & criteria applied uniformly?	5. Was a sample size justification/power calculation provided?	6. Were exposures measured before outcomes?	7. Was the timeframe sufficient to detect association?	8. Did the study examine different levels of exposure?	9. Were exposure measures clearly defined and valid?	10. Was the exposure assessed more than once over time?	11. Were the outcome measures clearly defined, valid, and reliable?	12. Were outcome assessors blinded to exposure?	13. Was loss to follow-up ≤20%?	14. Were confounders measured and adjusted statistically?	Overall score
Grit et al.,2024	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Other	Yes	Yes	12/14
Low et al.,2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	11/14

The National Institute of Health (NIH) Quality Assessment Tool quality assessment. Study quality was rated as 0 for poor (0-4 out of 14 questions), i for fair (5-10 out of 14 questions), or ii for good (11-14 out of 14 questions)

Desirable Effects

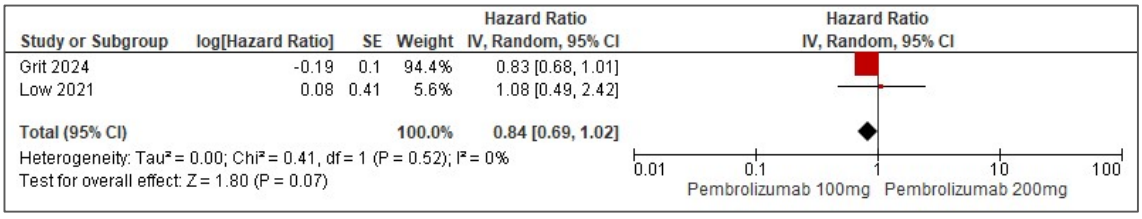
Overall Survival

Evidence from pooled analyses comparing individualized or lower-dose pembrolizumab regimens with the standard fixed full-dose schedule in NSCLC shows no meaningful difference in overall survival. For the 100 mg versus 200 mg every-3-weeks comparison, the pooled HR was 0.84 (95% CI 0.69–1.02; n = 2,026; p = 0.07). The confidence intervals crossed the null and the effects were not statistically significant. Overall, the evidence suggests that individualized or reduced-dose pembrolizumab regimens yield survival outcomes comparable to those achieved with standard full-dose fixed dosing.

All included studies evaluated pembrolizumab as first-line therapy and specifically compared fixed 100 mg versus 200 mg every-3-weeks regimens; consequently, the recommendation applies only to first-line pembrolizumab and is framed against the Indian regulatory context, where the DCGI has approved a fixed 200 mg dose rather than weight-based dosing.

The MCID was set at a non-inferiority margin of 5%, and although the survival difference did not reach statistical significance, it was clinically meaningful because the reduced-dose intervention demonstrated effects comparable to the standard comparator.

Figure 1: Comparison of impact of 100mg Vs 200mg every 3 weeks Pembrolizumab on Overall survival of NSCLC patients.



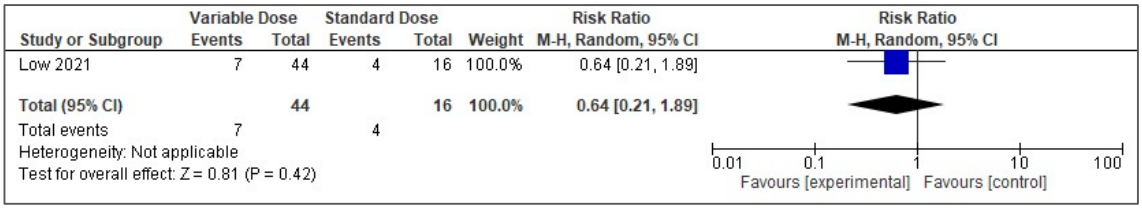
Quality of Life

No studies reported for the mentioned outcome in the meta-analysis for this review.

Undesirable Effects

Across the available studies, individualized or reduced-dose pembrolizumab regimens demonstrated statistically non-significant differences in adverse events compared with standard fixed dosing. In the 100 mg versus 200 mg comparison suggested a nonsignificant reduction in adverse events (RR 0.64, 95% CI 0.21–1.89; n = 60). Overall, the evidence indicates no meaningful difference in the risk of adverse events between individualized and standard dosing strategies, and the certainty of evidence is low due to imprecision.

Figure 1: Comparison of Grade 3 or more side-effects in 100mg Vs 200mg every 3 weeks Pembrolizumab on NSCLC patient



Summary of Findings Table

Pembrolizumab 100mg compared to 200 mg every 3 weeks for patients with NSCLC

Patient or population: patients with NSCLC

Intervention: Pembrolizumab 100mg every 3 weeks

Comparison: 200 mg every 3 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with 200 mg every 3 weeks	Risk with Pembrolizumab 100mg every 3 weeks			
Overall Survival	44.71%* (range 39.4-50) follow-up 2 to 4 yrs	-	**HR 0.84** (0.69 to 1.02)	2026 (2 non-randomised studies)	⨁◯◯◯ very low[a,b]
Grade 3 or more adverse events	250 per 1,000	**160 per 1,000** (53 to 473)	**RR 0.64** (0.21 to 1.89)	60 (1 non-randomised study)	⨁◯◯◯ very low[c,a,d]

Explanation:

a. *Intervention of interest was immune checkpoint inhibitors, but all included studies evaluated only pembrolizumab*
b. *Optimal information size (OIS) not met*
c. *Single study was downgraded one level for inconsistency as it was in evaluable*
d. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

Evidence Profile Table

Individualized dosing regimen vs. Standard fixed full dose indefinite dosing schedule for patients with NSCLC, eligible for immune checkpoint inhibitors

Patient or population: patients with NSCLC, eligible for immune checkpoint inhibitors

Intervention: Pembrolizumab 100mg every 3 weeks

Comparison: 200 mg every 3 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pembrolizumab 100mg every 3 weeks	200 mg every 3 weeks	Relative (95% CI)	Absolute (95% CI)		
Overall Survival												
2	non-randomised studies	not serious	not serious	serious[a]	serious[b]	none	26%	40%	**HR 0.84** (0.69 to 1.02)	**55 fewer per 1,000** (from 112 fewer to 6 more)	⊕◯◯◯ very low[a,b]	
Grade 3 or more adverse events												
1	non-randomised studies	not serious	serious[c]	serious[a]	serious[d]	none	7/44 (15.9%)	4/16 (25.0%)	**RR 0.64** (0.21 to 1.89)	**90 fewer per 1,000** (from 198	⊕◯◯◯ very low[c,a,d]	

										fewer to 222 more)		

Explanation:

a. *Intervention of interest was immune checkpoint inhibitors, but all included studies evaluated only pembrolizumab*
b. *Optimal information size (OIS) not met*
c. *Single study was downgraded one level for inconsistency as it was in evaluable*
d. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Summary of Judgements

Problem	Yes
Desirable Effects	Trivial
Undesirable Effects	Trivial
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Probably favors the intervention
Resources required	Moderate savings
Certainty of evidence of required resources	Very Low
Cost effectiveness	Favors the intervention
Equity	Probably increased
Acceptability	Probably yes
Feasibility	Probably yes
Recommendation: In patients with advanced NSCLC without driver mutations, lower-dose pembrolizumab (100 mg) may be considered on an individual basis when the standard dose (200 mg) is unaffordable or unavailable. Such use should occur after documenting the rationale for dose modification, and obtaining informed consent outlining the uncertain efficacy and associated evidence limitations. **Strength**: Conditional **Certainty of evidence**: Very low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

There is a lack of high-quality randomized controlled trials evaluating individualized dosing regimens of immunotherapy compared with standard full-dose schedules in NSCLC, and although this represents an important research question, the feasibility of conducting a well-powered trial may be constrained by substantial costs.

IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC), WHAT IS THE COMPARATIVE EFFECTIVENESS OF PROPHYLACTIC CRANIAL IRRADIATION (PCI) AS COMPARED TO PATIENTS WHO DID NOT RECEIVE PCI?

Table of Contents

1. **Background**..... **175**
2. **Recommendations**..... **175**
3. **Rationale/Justification**..... **175**
4. **Summary of Evidence**..... **175**
5. **Key question in PICO format**..... **176**
6. **Risk of Bias**..... **178**
7. **Forest Plot**..... **179**
8. **Summary of Findings Table**..... **180**
9. **Evidence Profile Table**..... **182**
10. **Summary of Judgements**..... **184**
11. **Caveats in Existing Evidence**..... **184**

Background

Small cell lung carcinoma (SCLC) is a rapidly growing tumour of lung with high rate of metastasis especially intracranial metastasis. About 10-15% of patients with SCLC present with intracranial metastasis at the time of diagnosis and nearly 50% will have risk of developing brain metastasis within 2 years. Despite advances in systemic treatment, prognosis for patients with SCLC remains poor particularly in patients with extensive stage (ES) disease compared to limited stage (LS) disease.

Previous studies have suggested that PCI improves overall survival (OS) and decreases the incidence of intracranial metastases (IMD) in patients with limited stage (LS) and extensive stage (ES) disease compared to observation alone. However, much of this evidence was gathered in an era when routine brain imaging wasn't standard practice. For instance, the pivotal trial by the European Organisation for Research and Treatment of Cancer (EORTC) that demonstrated the efficacy of PCI in ES SCLC did not incorporate routine brain imaging into patient staging. Consequently, it's possible that a significant number of patients in the study had asymptomatic IMD. Recent trials and meta-analyses, which do include mandated brain imaging, have failed to show a survival benefit with PCI in ES disease, raising doubts about its current practice.

Similarly, the evidence supporting PCI in LS SCLC dates back over two decades. Recent studies suggest that in LS disease, where brain MRI staging is utilized, PCI might not lower the risk of IMD or improve OS. Furthermore, while PCI may reduce IMD incidence, it's also linked to notable neurocognitive decline, a factor gaining importance as systemic treatments progress and survival rates improve in SCLC.

Several meta-analyses have attempted to reassess PCI's role in SCLC, but they've been limited by stringent eligibility criteria, which have restricted the inclusion of trials. This underscores the need for updated research to inform clinical decision-making in the modern era of SCLC treatment.

Recommendations

Prophylactic Cranial Irradiation (PCI) is ***recommended*** as compared to no PCI, for treatment of patients with small cell lung cancer.

Strength: Strong

Certainty of evidence: very low

Rationale/Justification

The evidence shows moderate desirable effects and moderate undesirable effects with balance of effects favouring prophylactic cranial irradiation. The intervention was feasible and acceptable with probably no impact on equity, and therefore the recommendation is strong in favour of prophylactic cranial irradiation despite very low certainty of evidence.

Summary of Evidence

Key Question

In patients with Small Cell Lung Cancer (SCLC), what is the comparative effectiveness of Prophylactic Cranial Irradiation (PCI) as compared to patients who did not receive PCI?

Included Studies

A total of 4757 records from electronic databases were identified August 2024. Of the 4757 articles, 2641 duplicate articles were removed. Further 2556 articles were removed after title and abstract screening because they were not relevant. Full text review was done for 21 articles after removing 64 studies during full text screening with reasons. After application of inclusion and exclusion criteria, 21 articles were selected for systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with small cell lung carcinoma. The review includes adults of all ages and genders. Eligible studies are those that evaluate the effectiveness of Chemotherapy with or without radiation with Prophylactic Cranial Irradiation for treating small cell lung carcinoma

Subgroups:

1. MRI Surveillance
2. Observation (no brain imaging)

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

1. Overall survival (*Seven studies*)
2. Quality of life (*No studies*)
3. Adverse Effects (*Two Studies*)
4. Brain metastasis rates (*Twenty Studies*)
5. Neurocognitive Function (*One Study*)
6. Cost (*No studies*)
7. Treatment non-compliance rates (*Two studies*)

Key question in PICO format

In patients with Small Cell Lung Cancer (SCLC), what is the comparative effectiveness of Prophylactic Cranial Irradiation (PCI) as compared to patients who did not receive PCI)?

Framework	Description
Population	Patients with SCLC *Subgroups*: 1. Limited and extensive 2. Age 3. Response to treatment (chemoradiation/chemotherapy)
Intervention	(Chemotherapy with or without radiation) with Prophylactic Cranial Irradiation (PCI) *Subgroups*: 1. with or without hippocampal avoidance
Comparator	(Chemotherapy with or without radiation) without PCI *Subgroups*: 1. MRI surveillance 2. Observation (No brain imaging)
Outcome	• Overall survival (*Critical Outcome*) • Quality of life (*Critical Outcome*)

	• Adverse effects (*Critical Outcome*) • Brain metastasis rates (*Important Outcome*) • Neurocognitive function (*Important Outcome*) • Cost (*Important Outcome*) • Treatment non-compliance rates (*Important Outcome*)

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)	2 years overall survival – 5%
		OS (Proportion increase in median survival)	2 months
2	Adverse Events	Proportion difference in grade 3 or higher AEs	5%
3	Quality of Life	Point of change on the 0-100 scale	10 Points

Risk of Bias Assessment

Overall survival

	D1	D2	D3	D4	D5	Overall
Gregor et al 1997	+	+	+	+	+	+
Schild et al 2012	X	-	+	+	+	X
Slotman et al 2007	+	+	+	+	+	+

Incidence of adverse events

	D1	D2	D3	D4	D5	Overall
Schild et al 2012	X	-	+	-	+	X

Brain metastasis

Aisner et al 1982	+	+	+	-	+	-
Arriagada et al 1995	+	+	+	-	+	-
Arriagada et al 2001	+	+	+	-	+	-
Beiler et al 1979	-	-	+	-	-	-
Cao et al 2005	+	+	+	-	+	-
Cox et al 1978	-	-	+	-	-	-
Danish/NCI	-	-	-	-	-	-
Eagan et al 1981	-	X	+	X	-	X
Hansen et al 1980	+	+	+	-	+	-
Jackson et al 1977	-	-	+	X	-	X
Jat et al 2019	-	-	+	X	-	X
Laplanche et al 1998	+	+	+	-	-	-
Maurer et al 1980	+	+	+	+	+	+
Niiranen et al 1989	-	-	+	-	-	-
Ohonoshi et al 1993	-	-	+	-	-	-
Seydel et al 1985	+	-	-	-	-	-
Slotman et al 2007	+	+	+	+	+	+
Wagner et al 1996	-	-	-	-	-	-

Brain metastasis-HR

	D1	D2	D3	D4	D5	Overall
Gregor et al 1997	+	+	+	-	-	-

Neurocognitive function

	D1	D2	D3	D4	D5	Overall
Gregor et al 1997	+	+	X	-	-	X

Treatment Non Compliance Rates

	D1	D2	D3	D4	D5	Overall
Arrigada et al 1995	+	+	+	-	+	-
Arrigada et al 2001	+	+	+	-	+	-

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

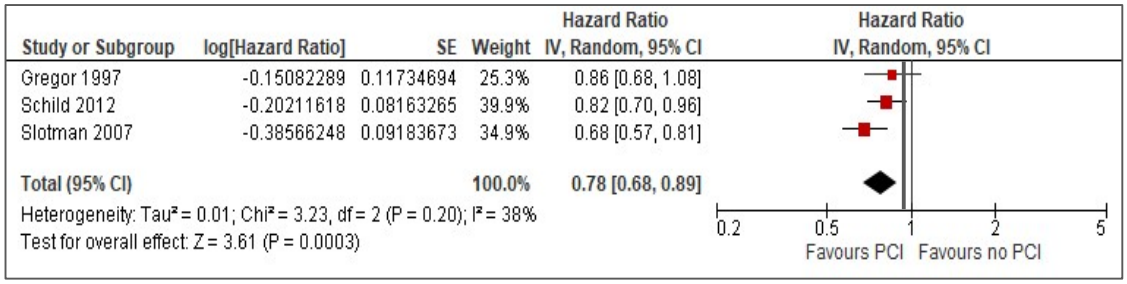
+	**Low risk**
-	**Some concerns**
X	**High risk**

Forest Plot: Desirable Effects

Overall Survival

Evidence suggests that PCI provides a statistically significant survival benefit when overall survival is reported as a hazard ratio (HR 0.78, 95% CI: 0.68–0.89). In contrast, when overall survival is reported as a risk ratio, no statistically significant or clinically meaningful difference is observed between PCI and no PCI (RR 1.26, 95% CI: 0.89–1.78). The Takahashi et al. (2017) trial was excluded from this analysis because patients underwent scheduled MRI surveillance every three months after treatment, which could have influenced and potentially confounded survival outcomes.

Figure 3.1 – Forest plot: Overall survival (mortality reported as Hazard Ratio)



*- Orange line shows MCID given by GDG

Quality of Life

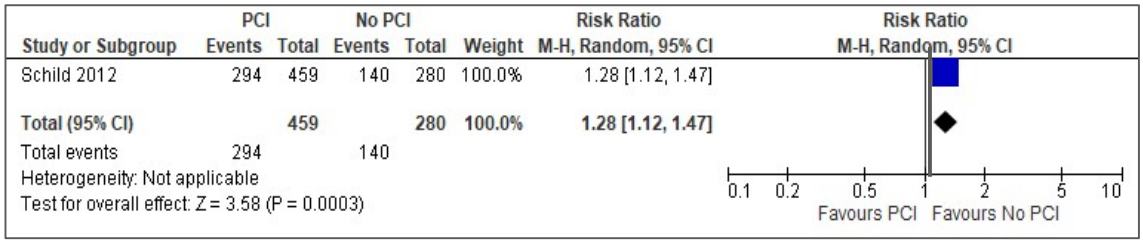
No studies reported for the mentioned outcome in the meta-analysis for this review.

Undesirable Effects

Adverse Effects

Evidence indicates a significantly higher risk of adverse events in the PCI group compared to the no-PCI group (RR 1.28, 95% CI: 1.12–1.47). This corresponds to an absolute increase from 500 per 1,000 patients in the no-PCI group to approximately 640 per 1,000 patients in the PCI group (range 560–735 per 1,000 based on the confidence interval). These findings suggest that PCI is associated with a 28% relative increase in adverse events.

Figure 3.2 - Forest Plot: Adverse events (outcome reported as events (RR))



Summary of Findings Table

Effectiveness of PCI in SCLC compared to placebo for health problem or population

Patient or population: Patients with SCLC
Intervention: Effectiveness of PCI in SCLC
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no PCI	Risk with Effectiveness of PCI in SCLC			
Overall Survival (mortality in HR)	72% * (range 61 to 87) Fu of one yr	-	**HR 0.78** (0.68 to 0.89)	1339 (3 RCTs)	⊕⊕◯◯ low[a,b]
Adverse events	500 per 1,000	640 per 1,000 (560 to 735)	**RR 1.28** (1.12 to 1.47)	739 (1 study)	⊕◯◯◯ very low[c,d,b]

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

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. *Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.*
b. *Optimal information size (OIS) not met*
c. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
d. *Single study was downgraded one level for inconsistency as it was in evaluable*

Evidence Profile Table

Effectiveness of PCI in SCLC compared to placebo for health problem or population

Patient or population: Patients with SCLC

Intervention: Effectiveness of PCI in SCLC

Comparison: Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylactic cranial irradiation (PCI)	No PCI	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (outcome reported as mortality in HR)												
3	randomised trials	not serious[a]	Not serious	not serious	serious[b]	none	-	72% risk (range 61 to 87)	**HR 0.78** (0.68 to 0.89)	-	⨁⨁◯◯ low[a,b]	CRITICAL
Adverse events												
1	randomised trials	Very Serious[c]	serious[d]	not serious	Serious[b]	none	294/459 (64.1%)	140/280 (50.0%)	**RR 1.28** (1.12 to	**140 more per 1,000** (from 210	⨁◯◯◯ very low[c,d,b]	CRITICAL

									1.47)	more to 70 more)		

Explanations:

a. Downgraded by one level for risk of bias as 1/3rd-2/3rd studies (by weight) were at low risk of bias.
b. Optimal information size (OIS) not met
c. Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias
d. Single study was downgraded one level for inconsistency as it was in evaluable

***Calculation of Absolute Effects**

When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available.

Summary of Judgements

Problem	Yes
Desirable Effects	Moderate
Undesirable Effects	Moderate
Certainty of evidence	Very low
Values	Probably No important uncertainty or variability
Balance of effects	Probably favors the intervention
Resources required	Moderate costs
Certainty of evidence of required resources	Very Low
Cost effectiveness	Probably favors the intervention
Equity	Probably no impact
Acceptability	Probably Yes
Feasibility	Yes
Recommendation: Prophylactic Cranial Irradiation (PCI) is ***recommended*** as compared to no PCI, for treatment of patients with small cell lung cancer. Strength: Strong Certainty of evidence: Low	

Caveats in Existing Evidence:

The GDG identified a key evidence gap regarding the continued net benefit of PCI in SCLC patients receiving contemporary systemic therapy (chemotherapy plus immunotherapy with or without thoracic radiotherapy), highlighting the lack of randomized comparisons between PCI and no PCI (or MRI surveillance with salvage therapy) incorporating modern baseline MRI, standardized neurocognitive assessments, and robust HRQoL and economic evaluations.

IN LIMITED STAGE SMALL CELL LUNG CANCER (SCLC), WHAT WOULD BE THE MOST EFFECTIVE TIMING AND FRACTIONATION OF RADIATION WITH CONCURRENT CHEMOTHERAPY THAT COULD SIGNIFICANTLY IMPACT PATIENT OUTCOME?

Table of Contents

1. **Background**..... **187**
2. **Recommendations**..... **187**
3. **Rationale/Justification**..... **187**
4. **Summary of Evidence**..... **187**
5. **Key question in PICO format**..... **188**
6. **Risk of Bias**..... **190**
7. **Forest Plot**..... **191**
8. **Summary of Findings Table**..... **193**
9. **Evidence Profile Table**..... **195**
10. **Summary of Judgements**..... **198**
11. **Caveats in Existing Evidence**..... **198**

Background

Limited-stage small-cell lung cancer (SCLC) is an aggressive malignancy characterized by rapid proliferation and early dissemination. Combined modality therapy: platinum-based chemotherapy with thoracic radiotherapy is the cornerstone of curative treatment, yet optimal sequencing remains uncertain. Early integration of radiotherapy (initiated concurrently with the first or second chemotherapy cycle) may enhance tumor cell kill during maximal chemosensitivity, potentially improving local control and overall survival. Conversely, delayed radiotherapy (after the third cycle) could allow for better systemic disease control and reduced toxicity. Defining the ideal timing and fractionation is therefore a high-priority question, as it directly influences treatment efficacy, toxicity profiles, and patient outcomes.

Recommendations

For patients with limited-stage small cell lung cancer, either early (with first or second cycle of chemotherapy) or late (with third cycle of chemotherapy or after) integration of thoracic radiotherapy with standard chemotherapy is ***recommended***.

Strength: Conditional

Certainty of evidence –Low

Rationale/Justification

The evidence showed trivial desirable effects with small undesirable effects, particularly a higher risk of acute esophagitis with early integration of radiotherapy. Resource requirements are similar with negligible cost differences, equity is probably not affected, and both approaches are considered probably acceptable and feasible.

The small differences in benefits and harms do not clearly favor one approach over the other, requiring individualized decision-making based on clinical judgment and patient preferences.

Summary of Evidence

Key Question

In limited stage small cell lung cancer (SCLC), what would be the most effective timing and fractionation of radiation with concurrent chemotherapy that could significantly impact patient outcome?

Included Studies

A total of 1337 records from electronic databases were identified till 31st May 2024. Of the 1337 articles, 99 duplicate articles were removed. Further 1183 articles were excluded after title and abstract screening because they were not relevant. Full text examination was done for 55 articles. After application of inclusion and exclusion criteria, 8 articles were included in the systematic review.

Population and Study Characteristics

All the studies included patients diagnosed with limited stage small cell lung cancer (SCLC)planned for concurrent radiotherapy along with ongoing chemotherapy. The review includes adults and both genders. Eligible studies are those that evaluate the effect of timing and fractionation of radiation with concurrent chemotherapy for treating limited stage small cell lung cancer (SCLC).

Subgroups:

Age, performance status

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

1. Overall survival (*8 Studies*)
2. Adverse effects (*8 Studies*)
3. Quality of life (*No study*)
4. Treatment non-compliance rates (*3 Studies*)

Key Question in PICO Format

In limited stage small cell lung cancer (SCLC), what would be the most effective timing and fractionation of radiation with concurrent chemotherapy that could significantly impact patient outcome?

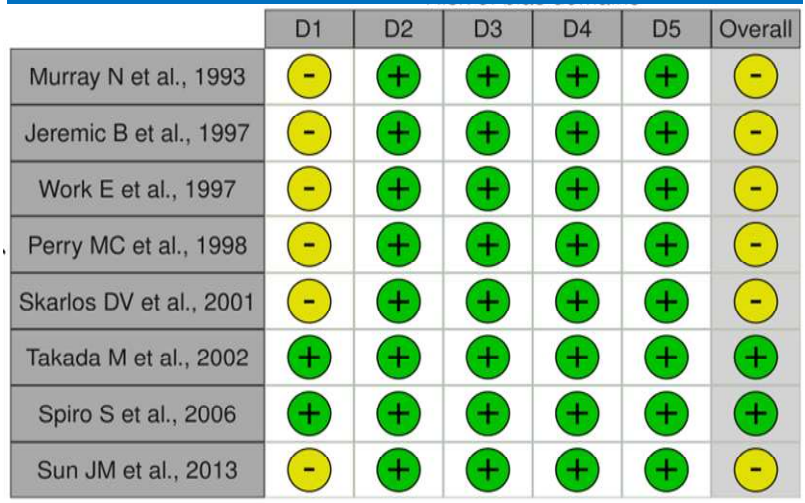
Framework	Inclusion criteria
Population	People with limited stage SCLC *Subgroups*: Age, performance status
Intervention	Early integration of radiation (with first or second cycle of chemotherapy) *Subgroup*: 1. Fractionation (once daily vs twice daily) 2. Days after starting chemotherapy (<30 days vs later)
Comparator	Radiation received with third cycle of chemotherapy or after *Subgroup*: Days after starting chemotherapy (>30 days vs>90 days)
Outcome	• Overall survival (*Critical Outcome*) • Adverse effects (*Critical Outcome*) • Quality of life (*Critical Outcome*) • Treatment non-compliance rates (*Important Outcome*)

Critical Outcome reviewed and their MCID provided by GDG

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)	5%
		OS (Proportion increase in median survival)	2 months
2	Adverse events	proportion difference in grade 3 or higher AEs	10%
3	Quality of life	point change on the 0–100 scale	10 points
		difference in the mean scores of QoL	

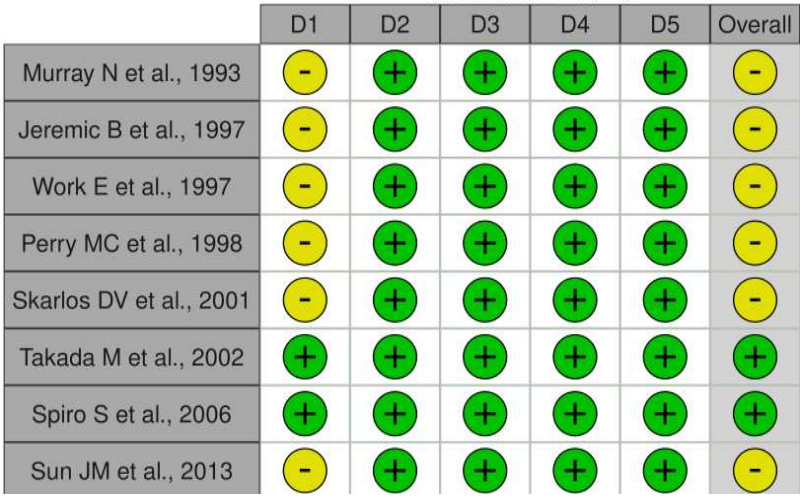
Risk of Bias Assessment

Overall survival



	D1	D2	D3	D4	D5	Overall
Murray N et al., 1993	-	+	+	+	+	-
Jeremic B et al., 1997	-	+	+	+	+	-
Work E et al., 1997	-	+	+	+	+	-
Perry MC et al., 1998	-	+	+	+	+	-
Skarlos DV et al., 2001	-	+	+	+	+	-
Takada M et al., 2002	+	+	+	+	+	+
Spiro S et al., 2006	+	+	+	+	+	+
Sun JM et al., 2013	-	+	+	+	+	-

Adverse events



	D1	D2	D3	D4	D5	Overall
Murray N et al., 1993	-	+	+	+	+	-
Jeremic B et al., 1997	-	+	+	+	+	-
Work E et al., 1997	-	+	+	+	+	-
Perry MC et al., 1998	-	+	+	+	+	-
Skarlos DV et al., 2001	-	+	+	+	+	-
Takada M et al., 2002	+	+	+	+	+	+
Spiro S et al., 2006	+	+	+	+	+	+
Sun JM et al., 2013	-	+	+	+	+	-

+	Low risk
-	Some concerns
X	High risk

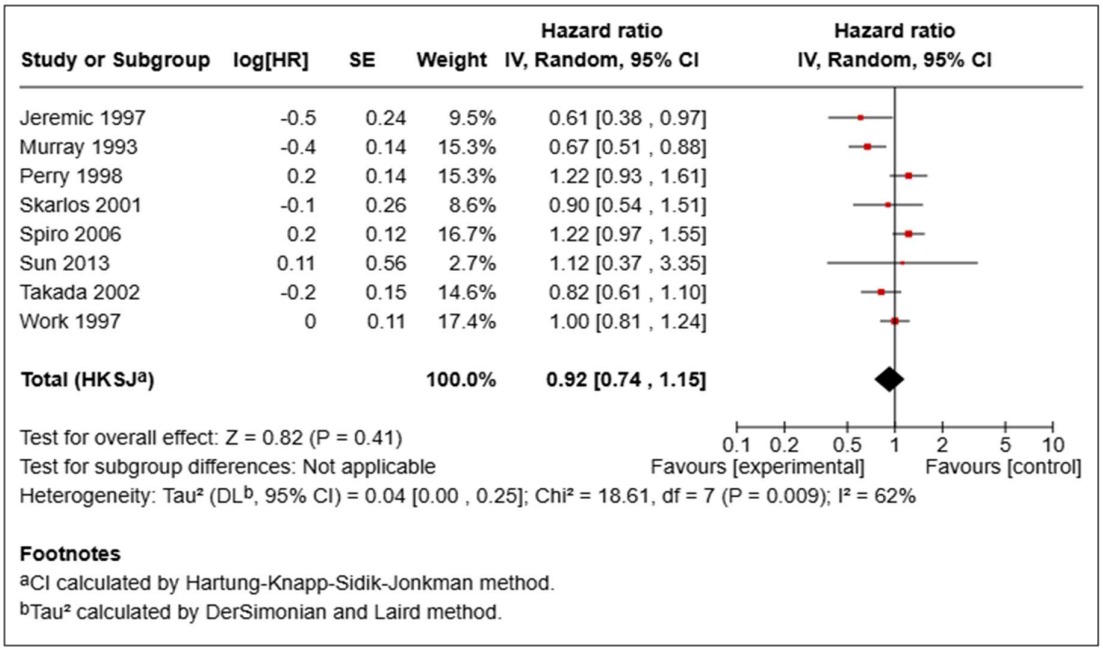
D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Forest Plot: Desirable Effects

Overall Survival

Evidence does not show a significant and clinically meaningful benefit of early integration of radiation in improving overall survival of patients with limited stage small cell lung cancer. The pooled analysis of eight studies comparing early integration of radiation (with first or second cycle of chemotherapy) to radiation received with third cycle of chemotherapy or after showed a hazard ratio of 0.92 (95% CI: 0.74 to 1.15), indicating a 8% relative reduction in the risk of death with early integration. This effect was not statistically significant with the confidence interval crossing the null value of 1. Moderate heterogeneity was observed across studies (I^2 = 62%, p = 0.009) for hazard ratio.

Figure 1: Outcome 1a. Overall survival: Hazard Ratio



Undesirable Effects

Moderately substantial undesirable effects in terms of adverse reactions were observed. It was observed that early integration of thoracic radiotherapy is associated with increased acute toxicity. Out of the vast list of side-effects observed in patients, oesophagitis (and pneumonitis were considered to be more critical and of special concern. The data showed a significantly increased risk for oesophagitis (RR 1.55, CI of 1.12 to 2.14, p=0.008) in intervention group. Pneumonitis however did not have any significantly different risk (RR 1.25 (0.46 to 3.40) between intervention and comparator group. Further incidences of other complications leukopenia, thrombocytopenia, neutropenia and nausea-vomiting did not differ significantly between the groups. Few adverse events-such as febrile neutropenia and infection however showed higher risk with intervention group.

Figure 2 (a): Pneumonitis

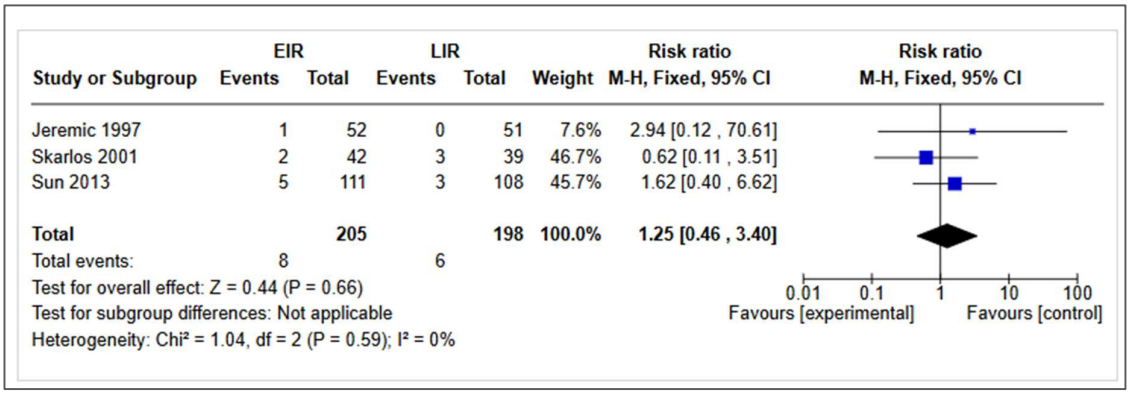
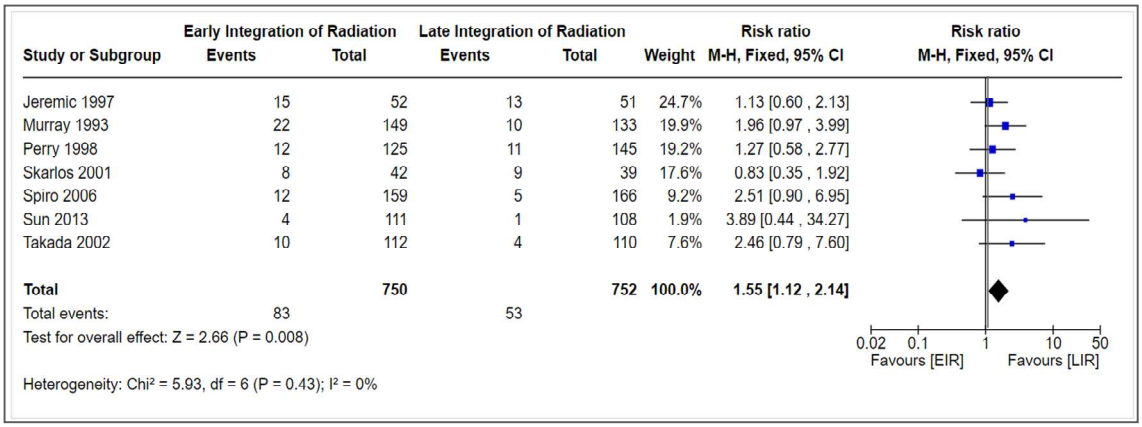


Figure 2 (b): Oesophagitis



*(-) Red line shows MCID given by GDG

Summary of Findings Table

Overall Survival of early integration of radiotherapy compared to late integration in limited stage SCLC

Patient or population: People with limited stage SCLC
Intervention: Early integration of radiation (with first or second cycle of chemotherapy)
Comparison: Radiation received with third cycle of chemotherapy or after

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with late integration	Risk with early integration			
Overall Survival (Hazard Ratio)	83.74% * (range 76-89 %) Follow-up 3 to 5yrs	-	**HR 0.92** (0.74 to 1.15)	1733 (8 RCTs)	very low[a,b,c]
Adverse reactions					
Oesophagitis	70 per 1,000	**109 per 1,000** (79 to 151)	**RR 1.55** (1.12 to 2.14)	1502 (7 RCTs)	⊕◯◯◯ very low[a,d]
Pneumonitis	30 per 1,000	**38 per 1,000** (14 to 103)	**RR 1.25** (0.46 to 3.40)	403 (3 RCTs)	⊕⊕◯◯ Low[e,c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **HR:** Hazard Ratio; **RR:** Risk 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.

Explanation:

a. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
b. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 62%*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
d. *Optimal information size (OIS) not met*
e. *Some concerns were identified in the study included for this outcome*

***Calculation of Absolute Effects**
When only hazard ratios (HRs) were reported, absolute effects for event-free patients were estimated using the following formula:

$$p_1 = exp(ln(p_0) \times HR) = p_0^{HR}$$

where:

- p_1 **= proportion of event-free patients in the intervention group at a specified time point**
- p_0 **= proportion of event-free patients in the control group at the same time point**
- HR **= hazard ratio comparing the hazard of the event between the intervention and control groups**

This approach assumes proportional hazards and allows estimation of absolute risks when only relative effect measures (HRs) are available

Evidence Profile Table

Overall Survival of early integration of radiotherapy compared to late integration in limited stage SCLC

Patient or population: People with limited stage SCLC
Intervention: Early integration of radiation (with first or second cycle of chemotherapy)
Comparison: Radiation received with third cycle of chemotherapy or after

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EIR	LIR	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (Hazard Ratio)												
8	randomised trials	Very serious[a]	serious[b]	not serious	serious[c]	none	-	83.74% *(range 76-89 %) Follow-up 3 to 5yrs	**HR 0.92** (0.74 to 1.15)	**26 per 1,000** (from 98 fewer to 39 more)	⊕◯◯◯ very low[a,b,c]	Critical

a. all study except two has some concern in ROB

b. CI cross decision clinical decision threshold

Evidence Profile Table

Overall Survival of early integration of radiotherapy compared to late integration in limited stage SCLC

Patient or population: People with limited stage SCLC
Intervention: Early integration of radiation (with first or second cycle of chemotherapy)
Comparison: Radiation received with third cycle of chemotherapy or after

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adverse events_ revised	[placebo]	Relative (95% CI)	Absolute (95% CI)		
Oesophagitis												
7	randomised trials	Very serious[a]	Not serious	not serious	Serious[d]	none	83/750 (11.1%)	53/752 (7.0%)	**RR 1.55** (1.12 to 2.14)	**39 more per 1,000** (from 8 more to 80 more)	⊕◯◯◯ very low[a,d]	Critical
Pneumonitis												
3	randomised trials	Serious[e]	not serious	not serious	Serious[c]	none	8/205 (3.9%)	6/198 (3.0%)	**RR 1.25** (0.46 to 3.40)	**8 more per 1,000** (from 16 fewer to 73 more)	⊕⊕◯◯ Low[e,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. *Downgraded one level as the point estimates vary widely across the studies and significant heterogeneity with I^2 of 62%*
c. *Downgraded one level for imprecision as the 95% CI crossed the null effect line*
d. *Optimal information size (OIS) not met*
e. *Some concerns were identified in the study included for this outcome*

Summary of Judgements

Problem	Yes
Desirable Effects	Trivial
Undesirable Effects	Small
Certainty of evidence	Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Negligible costs and savings
Certainty of evidence of required resources	No included studies
Cost effectiveness	No included studies
Equity	Probably no impact
Acceptability	Probably Yes
Feasibility	Probably Yes
Recommendations: For patients with limited-stage small cell lung cancer, either early (with first or second cycle of chemotherapy) or late (with third cycle of chemotherapy or after) integration of thoracic radiotherapy with standard chemotherapy is ***recommended***. **Strength**: Conditional **Certainty of evidence** –Low	

Caveats in Existing Evidence:

The GDG opined that the existing evidence had the following limitations:

- There is a lack of high-quality randomized controlled trials comparing clearly defined early versus late interventions using contemporary chemotherapy agents and modern radiation techniques, and the feasibility of conducting such trials remains unexplored.

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Neoadjuvant chemotherapy followed by surgery as compared to upfront surgery followed by adjuvant chemotherapy

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Addition of postoperative radiotherapy to standard therapy compared to standard therapy alone

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Immunotherapy (immune check point inhibitors) as compared to chemotherapy alone in advanced stage NSCLC

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Immunotherapy (immune checkpoint inhibitors) delivered as low dose compared to standard full dose immunotherapy

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