# 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**

# CONTENTS

# 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 |

# 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, 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.<br><br>**Strength:** Strong<br>**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 (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.<br><br>**Strength**: Strong<br>**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 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?**<br>(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.<br><br>**Strength**: Conditional<br>**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 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.<br><br>**Strength**: Strong<br>**Certainty of evidence:** 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 low certainty of evidence. |

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| **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***.<br><br>**Strength**: Conditional<br>**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.<br><br>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. |
| **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).<br><br>**Strength**: Conditional<br>**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. |

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| **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.<br><br>**Strength**: Conditional<br>**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 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.<br><br>**Strength**: Strong<br>**Certainty of evidence** – High for efficacy and very low for side effects | 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.<br><br>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. |

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| **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<br><br>**Strength:** Conditional<br>**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.<br>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.<br><br>**Strength**: Conditional<br>**Certainty of evidence** – Low | 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.<br>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. |

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| **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***.<br><br>**Strength:** Conditional<br>**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.<br><br>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).<br><br>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. |

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| **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.<br><br>**Strength:** Conditional<br>**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.<br><br>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. |

# 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?**

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## 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.

**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<br>**Subgroup:**<br>• Surgical approach (Open vs minimally invasive)<br>• Type of surgery (lobectomy vs pneumonectomy)<br>• Pre-existing cardiopulmonary comorbidities / poor performance status |
| **Intervention** | Prehabilitation |
| **Comparator** | Standard of care |
| **Outcome** | • Perioperative outcomes (Critical outcome)<br>• Mortality (Critical outcome)<br>• Quality of life (Critical outcome)<br>• Length of hospital stay (Important outcome)<br>• Surgical complications (Important outcome)<br>• 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<br>3% at 5 years |
| | | Proportion increase 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

| Study ID | Experimental | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|
| 1 | Benzo et al | ! | + | ! | + | + | - |
| 2 | Chen et al | + | ! | + | + | + | ! |
| 3 | Garcia et al | + | ! | - | + | + | - |
| 4 | Han et al | + | ! | ! | ! | + | - |
| 5 | Huang et al | ! | ! | + | + | + | - |
| 6 | Karenovics et al | + | ! | ! | + | + | - |
| 7 | Kaya et al | ! | ! | ! | ! | + | - |
| 8 | Lai et al | ! | ! | + | + | + | - |
| 9 | Lai et al | ! | ! | + | + | + | - |
| 10 | Lai et al | + | ! | + | + | + | ! |
| 11 | Laurent et al | ! | ! | + | ! | + | - |
| 12 | Liu et al | + | ! | + | + | + | ! |
| 13 | Liu et al | + | ! | + | + | + | ! |
| 14 | Machado et al | + | ! | + | + | + | ! |
| 15 | Morano et al | + | ! | + | + | + | ! |
| 16 | Pehlivan et al | - | ! | + | ! | + | - |
| 17 | Stefanelli et al | ! | ! | + | ! | + | - |
| 18 | Tenconi et al | + | ! | ! | ! | + | - |
| 19 | Wang et al | + | ! | + | + | + | ! |
| 20 | Yao et al | ! | ! | + | ! | + | - |
| 21 | Zhou et al | + | ! | + | ! | + | - |
| 22 | Zou et al | ! | ! | + | + | + | - |

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

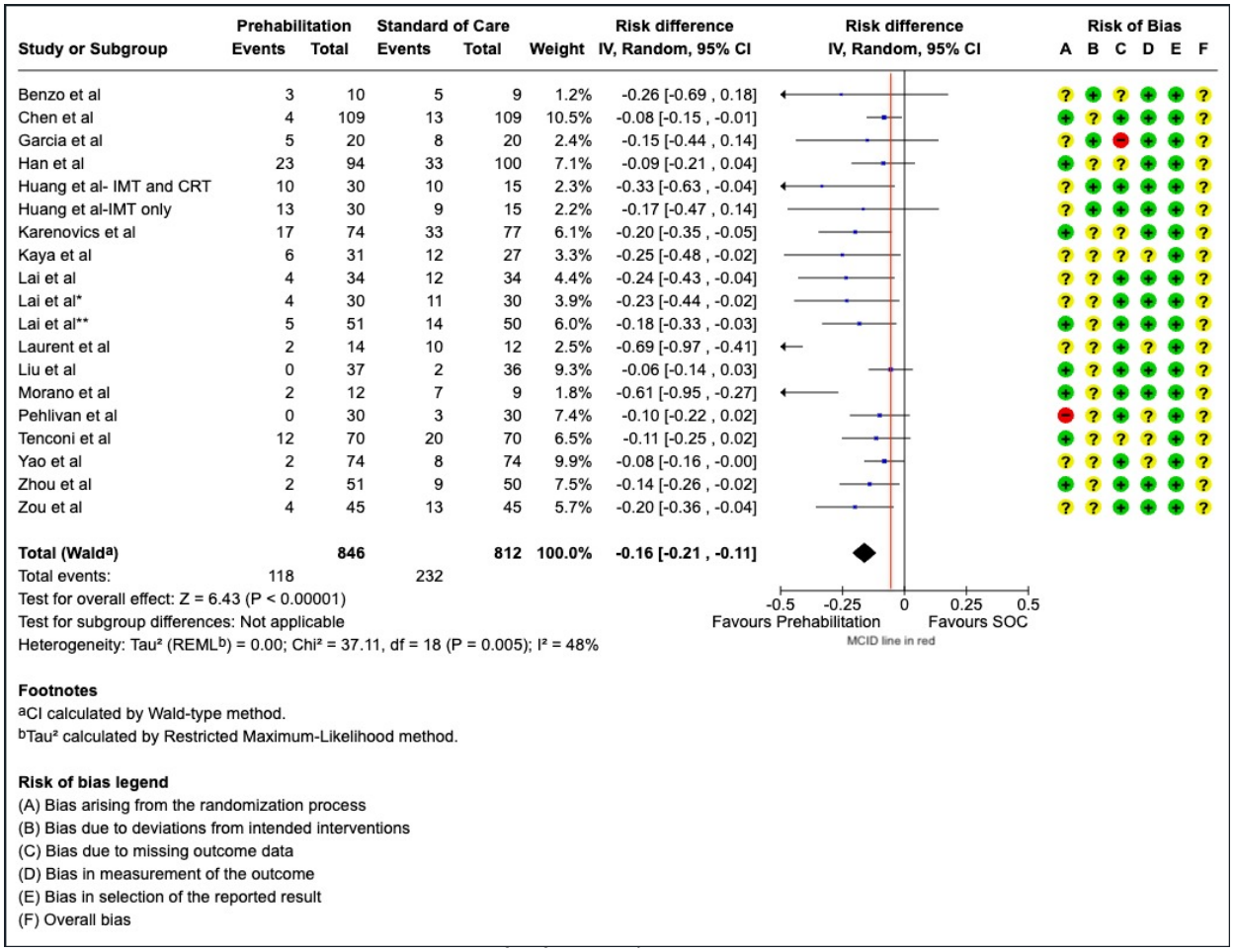
| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

## 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.

3.1 (a): Forest plot - Pulmonary complications

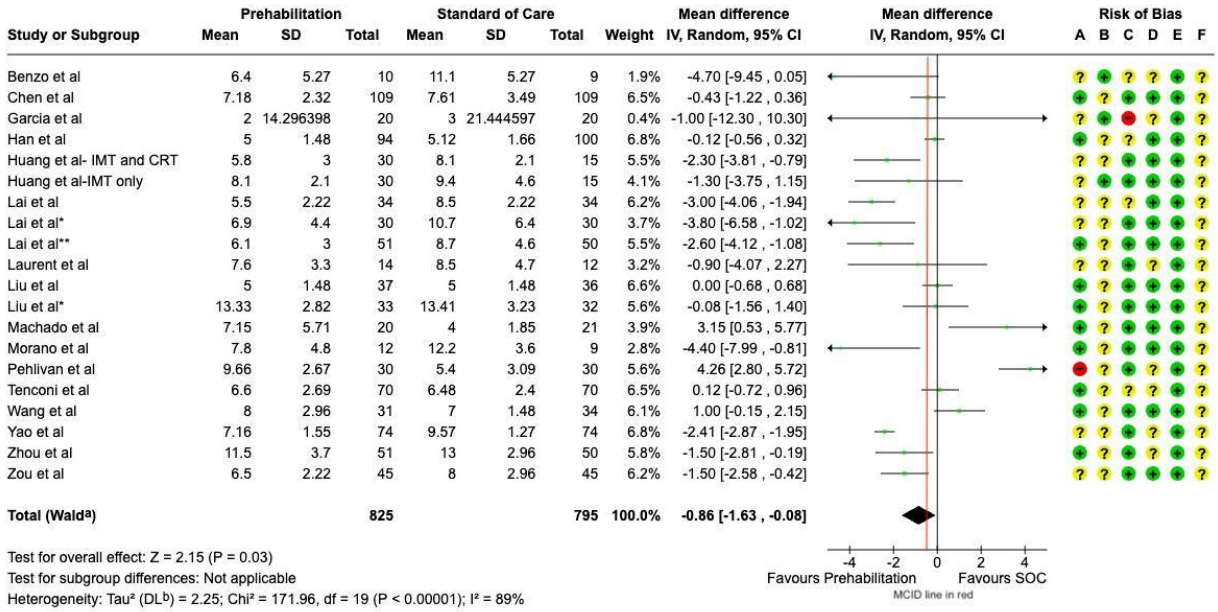



*- Orange line shows MCID given by GDG

**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)

3.1 (b): Forest Plot - Hospital Stays



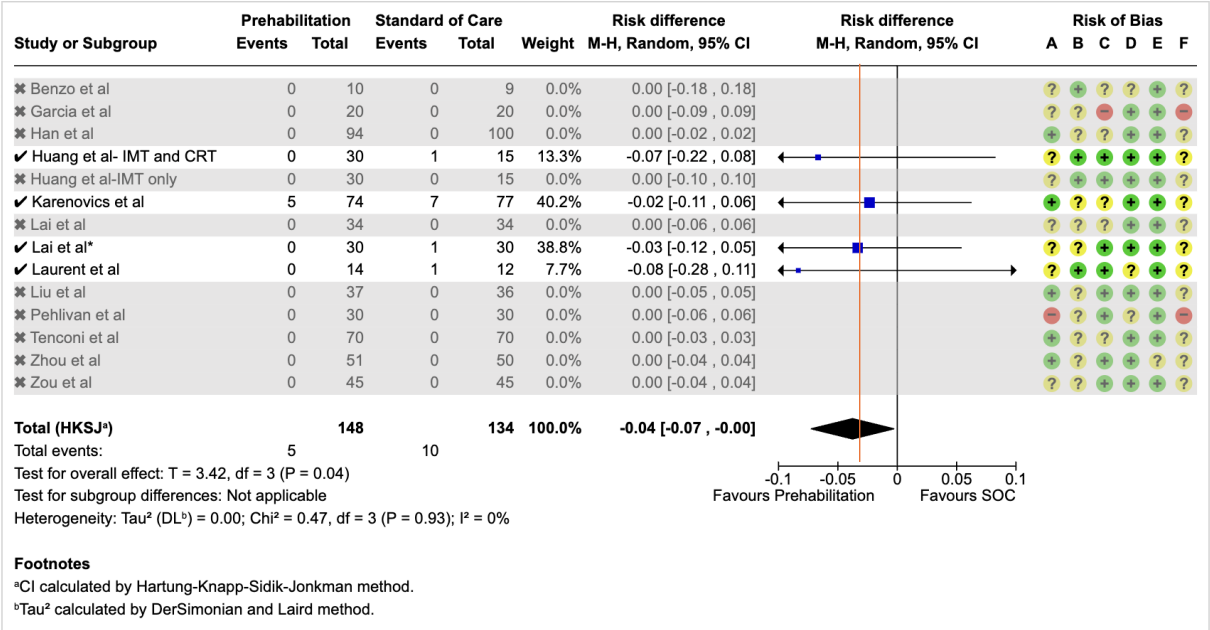

Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 2.25; Chi² = 171.96, df = 19 (P < 0.00001); I² = 89%

*- 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.

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.

## 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

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

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

**Setting:** Tertiary Care Hospitals

**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

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

## Explanations

a. *Downgraded by two levels for risk of bias as less than 1/3rd studies (by weight) were at low risk of bias*
b. *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

**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
Subgroups: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1 5. Smoking status
**Setting:** Tertiary Care Hospitals
**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.<br><br>**Strength:** Strong<br><br>**Certainty of Evidence**: Very low | |

### RESEARCH PRIORITIES:

Given the absence of India-specific evidence on cost-effectiveness, equity, feasibility, and acceptability of prehabilitation versus standard care for lung-cancer surgery, the following research priorities are recommended:

**Health Economic Evaluations:** Perform formal cost–effectiveness and cost–utility analyses of prehabilitation versus standard care, incorporating Indian cost data for personnel (physiotherapists, dietitians, psychologists), programme delivery modalities (in-person, remote, hybrid), hospital resource use (ICU days, readmissions), and estimating QALYs gained to inform policymakers and payers.

**Equity-Focused Research:** Investigate disparities in access to and benefits from prehabilitation—examining urban–rural differences, socioeconomic strata, and public versus private centre capabilities—through observational studies or secondary data analyses to identify structural, financial, and geographic barriers to equitable uptake.

**Feasibility & Acceptability Studies:** Use mixed-method and implementation research designs to (a) assess institutional readiness, workforce capacity, and infrastructure requirements for delivering prehabilitation across diverse Indian settings, and (b) explore patient, caregiver, and clinician perspectives on programme burden, cultural fit, and perceived value to guide tailored, scalable implementa

**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

## 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). [1,2]

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.

**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)<br>**Subgroups:** 1. T stage 2. Nodal involvement 3. Histology 4. PDL1<br>5. Smoking status |
| **Intervention** | Mediastinal lymph nodal dissection |
| **Comparator** | Systematic mediastinal lymph node sampling |
| **Outcome** | • Overall survival **(Critical outcome)**<br>• Surgery/surgical procedure related complications **(Critical outcome)**<br>• Disease free survival **(Important outcome)**<br>• Length of hospital stay **(Important outcome)**<br>• 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<br>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

| Outcome 1 – Overall Survival (Critical Outcome) | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Izbicki et al 1994 | ! | + | - | + | + | - |
| Sugi et al 1998 | ! | + | + | + | + | ! |
| Izbicki et al 1998 | ! | + | + | + | + | ! |
| Darling et al 2011 | ! | + | + | + | + | ! |
| Zhang et al 2013 | ! | + | + | + | + | ! |
| Wu et al 2002 | ! | + | + | + | + | ! |
| **Outcome 2 – Surgical Procedure related Complications** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Izbicki et al 1994 | ! | + | - | + | + | - |
| Sugi et al 1998 | ! | + | + | + | + | ! |
| Allen at al 2006 | ! | + | + | + | + | ! |
| Zhang et al 2013 | ! | + | + | + | + | ! |
| **Outcome 3 – Disease free survival** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Izbicki et al 1998 | ! | + | - | + | + | - |
| Darling et al 2011 | ! | + | + | + | + | ! |
| **Outcome 4: Length of Hospital Stay** | | | | | | |
| Izbicki et al 1994 | ! | + | + | + | + | ! |
| Sugi et al 1998 | ! | + | + | + | + | ! |
| Allen at al 2006 | ! | + | + | + | + | ! |

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

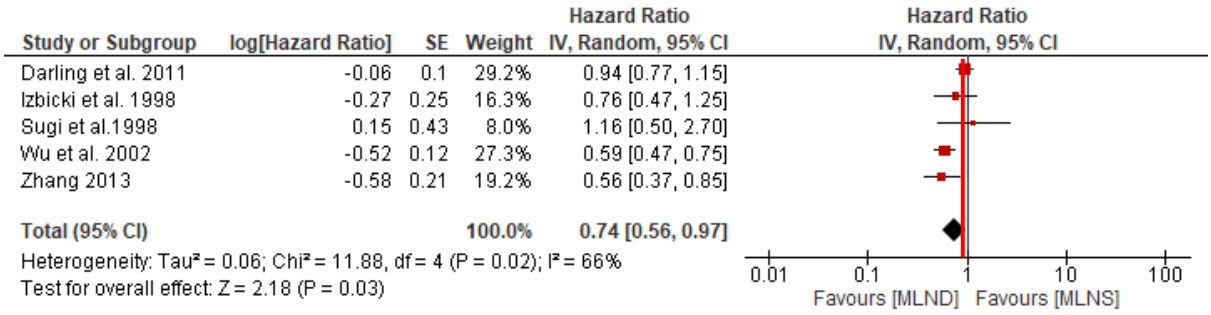
| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

## 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



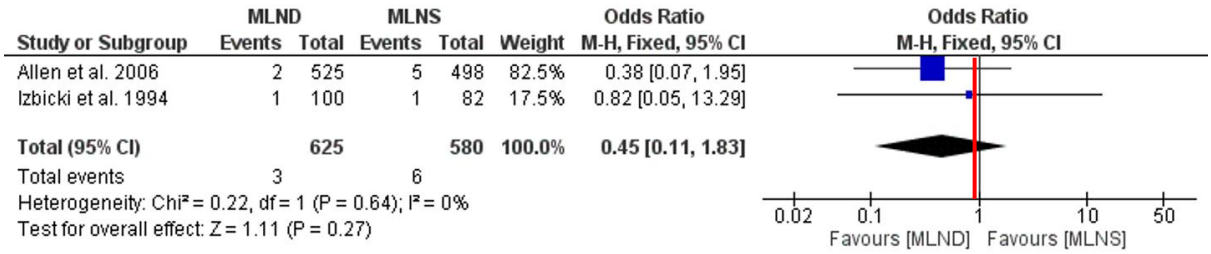

*- Red line shows MCID given by GDG

## 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

Fig 4.1 – Forest Plot: Acute respiratory distress syndrome




*- Red line shows MCID given by GDG

Fig 4.2 – Forest Plot: Atelectasis

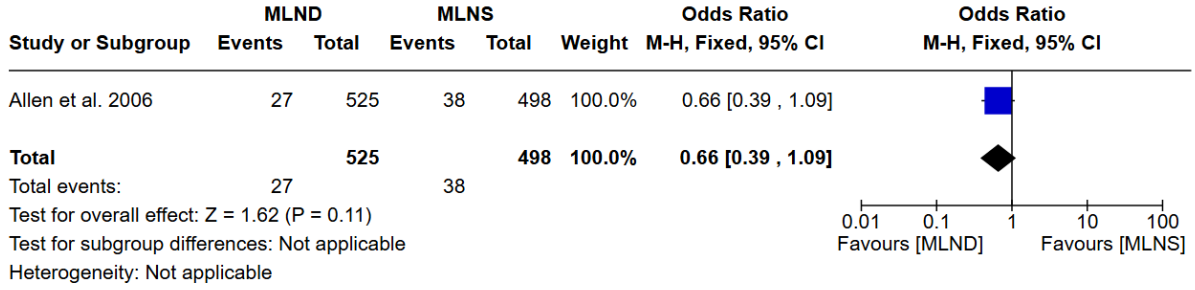



Fig 4.3 – Forest Plot: Atrial fibrillation

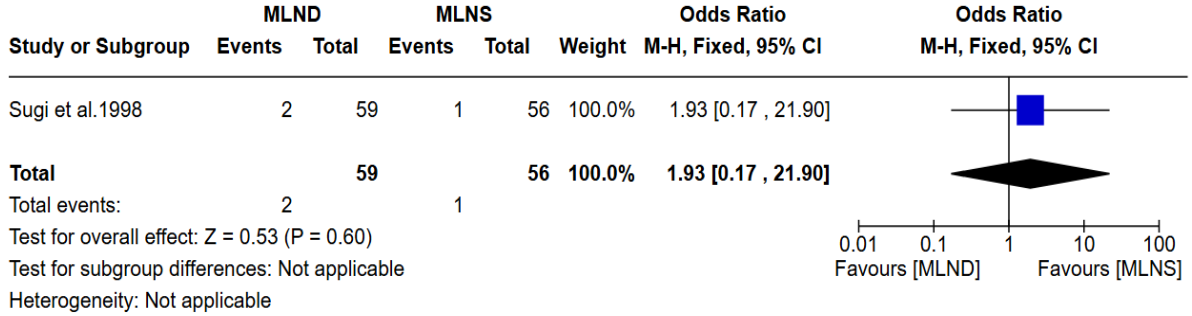


Fig 4.4 – Forest Plot: Air leaks

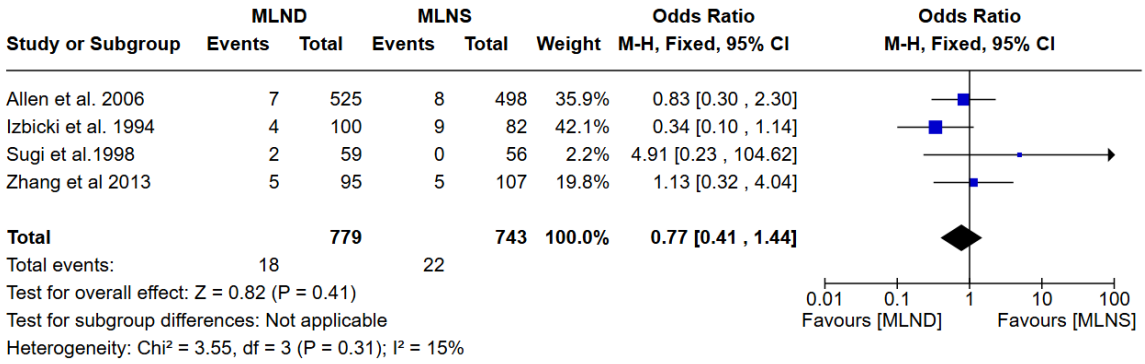



Fig 4.5 – Forest Plot: Broncho pleural fistula

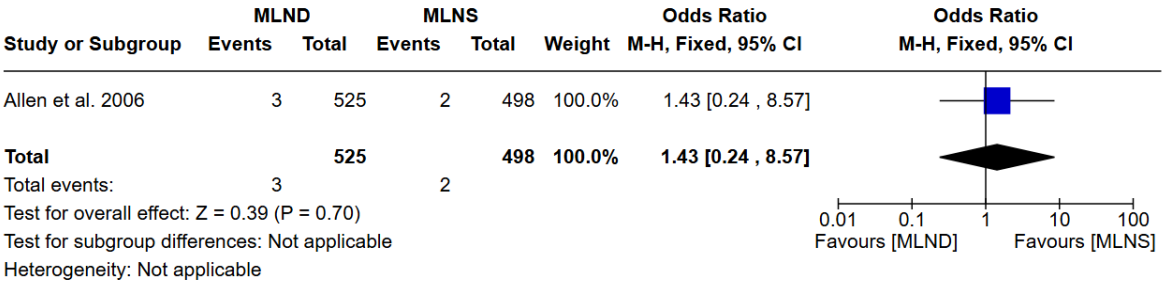



Fig 4.6 – Forest Plot: Chylothorax

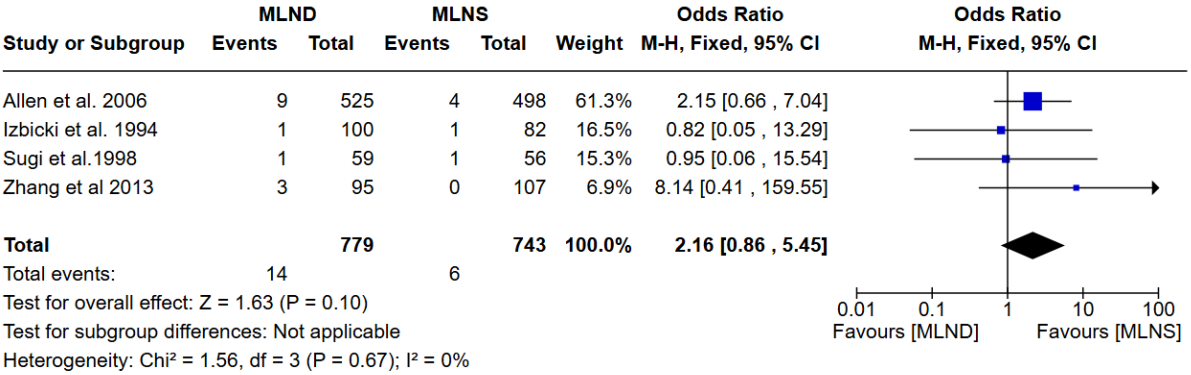


Fig 4.7 – Forest Plot: Haemorrhage

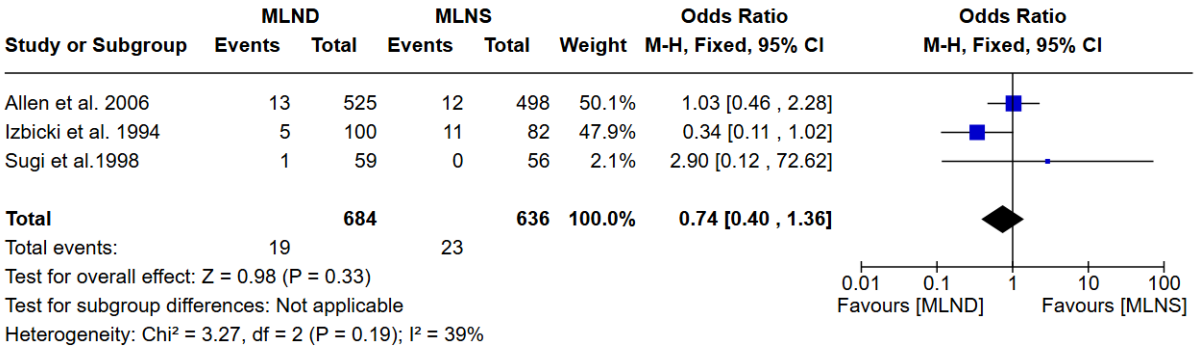
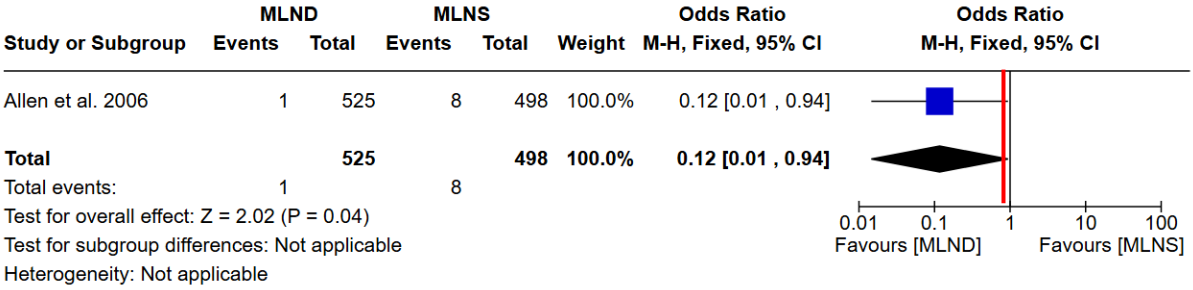



Fig 4.8 – Forest Plot: Myocardial Infarction




*- Red line shows MCID given by GDG

Fig 4.9 – Forest Plot: Pneumonia

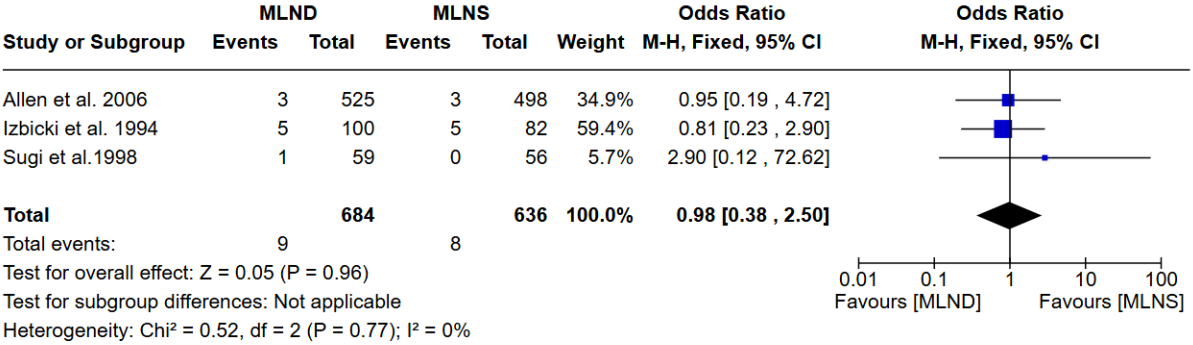



Fig 4.10 – Forest Plot: Recurrent nerve injury

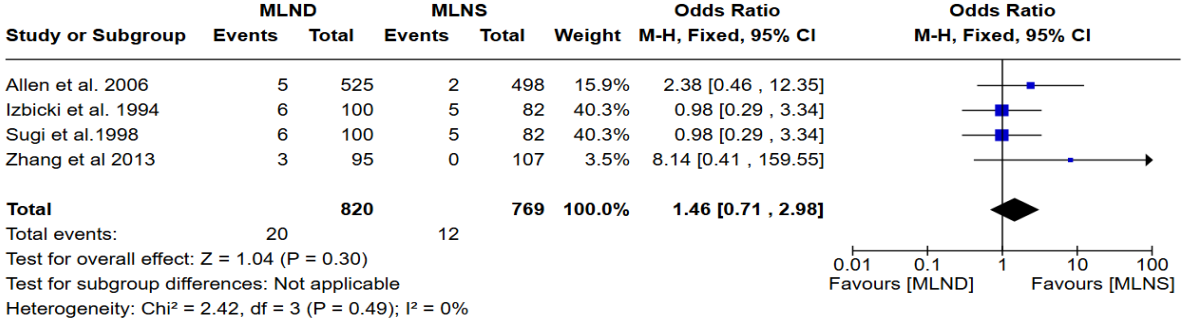


Fig 4.11 – Forest Plot: Respiratory failure

| Study or Subgroup | MLND Events | MLND Total | MLNS Events | MLNS Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Allen et al. 2006 | 22 | 525 | 34 | 498 | 100.0% | 0.60 [0.34 , 1.04] |
| **Total** | | **525** | | **498** | **100.0%** | **0.60 [0.34 , 1.04]** |
| Total events: | 22 | | 34 | | | |

Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

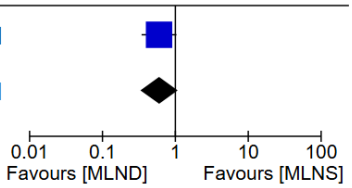
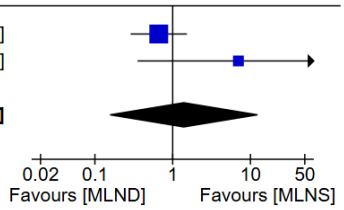



Fig 4.12 – Forest Plot: Retained bronchial secretion

| Study or Subgroup | MLND Events | MLND Total | MLNS Events | MLNS Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Izbicki et al. 1994 | 12 | 100 | 14 | 82 | 68.6% | 0.66 [0.29 , 1.52] |
| Sugi et al.1998 | 3 | 59 | 0 | 56 | 31.4% | 7.00 [0.35 , 138.65] |
| **Total (Wald[a])** | | **159** | | **138** | **100.0%** | **1.39 [0.16 , 12.31]** |
| Total events: | 15 | | 14 | | | |

Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 1.63; Chi² = 2.30, df = 1 (P = 0.13); I² = 57%

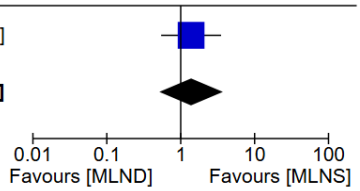



**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Fig 4.13 – Forest Plot: Sero pneumothorax

| Study or Subgroup | MLND Events | MLND Total | MLNS Events | MLNS Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Izbicki et al. 1994 | 13 | 100 | 8 | 82 | 100.0% | 1.38 [0.54 , 3.52] |
| **Total** | | **100** | | **82** | **100.0%** | **1.38 [0.54 , 3.52]** |
| Total events: | 13 | | 8 | | | |

Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



## Summary of Findings

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

**Patient or population:** Operable Non-Small Cell Lung Cancer

**Setting:** Tertiary Care Hospital

**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 %<br>(range 16.1 to 62)<br>Fu (3.9 to 6.5 yrs) | - | **HR 0.74**<br>(0.56 to 0.97) | 1980<br>(5 RCTs) | ⊕◯◯◯<br>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

**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. *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
**Setting:** Tertiary Care Hospital
**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 | Mediastinal lymph node dissection | lymph node sampling | Relative (95% CI) | Absolute (95% CI) | | |
| **Overall survival** | | | | | | | | | | | | |
| 5 | randomised trials | Not serious | serious[b] | not serious | serious[c] | none | 485/1000 (48.46%) | - | **HR 0.74** (0.56 to 0.97) | | ⊕◯◯◯ Very low[a,b,c] | |
| **ARDS** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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) | ⊕⊕◯◯ Low[a,d] | |
| **Atelactasis** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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] | |
| **Atrial fibrillation** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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) | ⊕⊕◯◯ Low[a,d] | |
| **Air leaks** | | | | | | | | | | | | |
| 4 | randomised trials | serious[a] | not serious | not serious | serious[d] | none | 18/779 (2.3%) | 22/743 (3.0%) | **OR 0.77** (0.41 to 1.44) | **7 fewer per 1,000** (from 17 fewer to 12 more) | ⊕⊕◯◯ Low[a,d] | |
| **Bronchopleural fistula** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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,d] | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Chylothorax** | | | | | | | | | | | | |
| 4 | randomised trials | serious[a] | 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] | |
| **Haemorrhage** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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[a,d] | |
| **MI** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | not serious | 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) | ⊕⊕⊕◯ Moderate[a] | |
| **Pneumonia** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | serious[d] | none | 9/684 (1.3%) | 8/636 (1.3%) | **OR 0.98** (0.38 to 2.50) | **0 fewer per 1,000** (from 8 | ⊕⊕◯◯ Low[a,d] | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 18 more) | | |
| **Recurrent nerve injury** | | | | | | | | | | | | |
| 4 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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[a,d] | |
| **Retained bronchial secretion** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | serious[d] | none | 15/159 (9.4%) | 14/138 (10.1%) | **OR 1.39** (0.16 to 12.31) | **34 more per 1,000** (from 84 fewer to 480 more) | ⊕⊕◯◯ Low[a,d] | |
| **Respiratory failure** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[d] | 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) | ⊕⊕◯◯ Low[a,d] | |
| **Seropneumothorax** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious [a] | not serious | not serious | serious[d] | 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) | ⊕⊕◯◯ Low[a,d] | |

**Disease free survival**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | serious [a] | not serious | not serious | serious[d] | none | -/0 | -/0 | **HR 0.95** (0.79 to 1.16) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⊕⊕◯◯ Low[a,d] | |

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. 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 MCID*

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

*f. Optimal Information Size (OIS) not met*

*g. Downgraded one level for risk of bias as less than 2/3rd studies (by weight) were at low risk of bias*

## 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.<br><br>**Strength**: Strong<br>**Certainty of evidence**: Very low | |

# RESEARCH PRIORITIES

Given the absence of direct evidence on cost-effectiveness, equity, feasibility, and acceptability for mediastinal lymph node dissection (MLND) versus sampling (MLNS) in operable NSCLC, the following research priorities are recommended:

**Health Economic Evaluations** Conduct formal cost–effectiveness and cost–utility analyses comparing MLND versus MLNS, incorporating Indian unit-cost data (operative time, hospital stay, complication management, and training/upskilling costs) and estimating QALY or life-year gains to inform resource-allocation decisions.

**Equity-Focused Research** Investigate disparities in access to MLND, examining geographic (urban–rural), institutional (tertiary vs. district hospitals), and socioeconomic factors that influence whether patients receive systematic dissection versus sampling and identify strategies to ensure equitable staging.

**Feasibility & Training Requirement Studies** Use implementation and hybrid effectiveness, implementation designs to assess the real-world practicability of MLND in diverse Indian surgical settings, focusing on: a. Infrastructure and workflow: perioperative support services b. Surgeon training needs: baseline skill assessment, upskilling programs, competency benchmarks c. Long-term sustainability: integration into routine practice, continuing professional development pathways.

**Acceptability Studies** Undertake qualitative or mixed-method research with patients, caregivers, and thoracic surgeons to explore perceptions, preferred trade-offs (survival benefit vs. morbidity), and potential barriers or facilitators to adopting MLND over MLNS in routine practice.

**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

## 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.

**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<br>**Subgroups:**<br>• Single metastatic sites vs more than one metastatic sites<br>• Site(s) of metastasis(es) |
| **Intervention** | Radical local treatment in addition to systemic therapy (chemo /immune /targeted)<br>**Subgroups:**<br>• Surgery<br>• Radiation<br>• Upfront/delayed |
| **Comparator** | Systemic therapy (chemo/immune/targeted) alone |
| **Outcome** | • Overall survival (Critical outcome)<br>• Adverse effects (Critical outcome)<br>• Quality of life (Critical outcome)<br>• Progression free survival (Important outcome)<br>• Response rate (Important outcome)<br>• 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<br>3% at 5 years |
| | | Proportion increase 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

| Outcome 1 – Overall Survival (Critical Outcome) | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Gomez et al., 2019 | + | + | + | + | + | + |
| Peng et al., 2023 | + | + | + | + | + | + |
| Lim et al., 2014 | ! | + | + | + | + | ! |
| Theelen at al., 2019 | ! | + | + | + | + | ! |
| Wang et al.,2022 | + | + | + | + | + | + |
| **Outcome 2 – Progression of free survival (Important Outcome)** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Welsh et al., 2020 (SBRT) | + | + | + | + | + | + |
| Welsh et al., 2020 (Traditional RT) | + | + | + | + | + | + |
| Peng et al., 2023 | + | + | + | + | + | + |
| Iyengar et al., 2018 | ! | + | + | + | + | ! |
| Tsai et al., 2023 | + | + | + | + | + | + |
| Theelen et al., 2019 | ! | + | + | + | + | ! |
| Wang et al., 2022 | + | + | + | + | + | + |
| **Outcome 3 – Overall Response rate** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Welsh et al,. 2020 (SBRT) | + | + | + | + | + | + |
| Welsh et al.,2020 (Traditional RT) | + | + | + | + | + | + |
| Shan et al., 2021 | ! | + | + | + | + | ! |
| Lim et al.,2014 | ! | + | + | + | + | ! |
| Theelen et al., 2019 | ! | + | + | + | + | + |

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

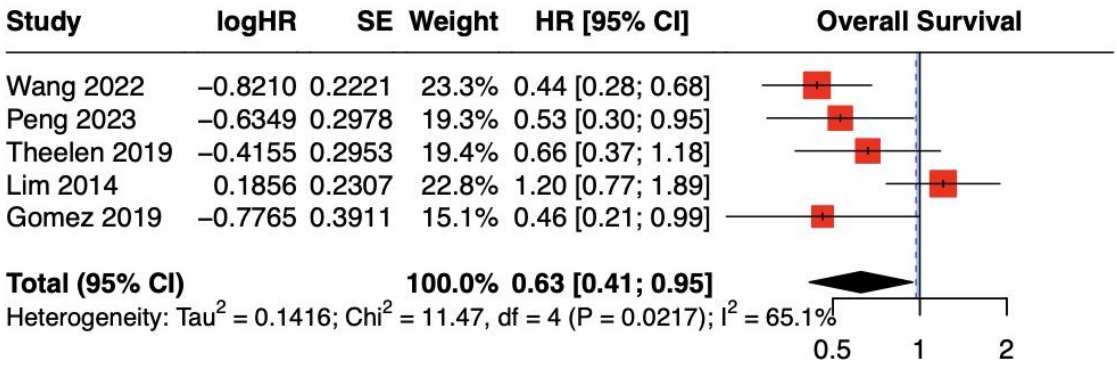
| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

## 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

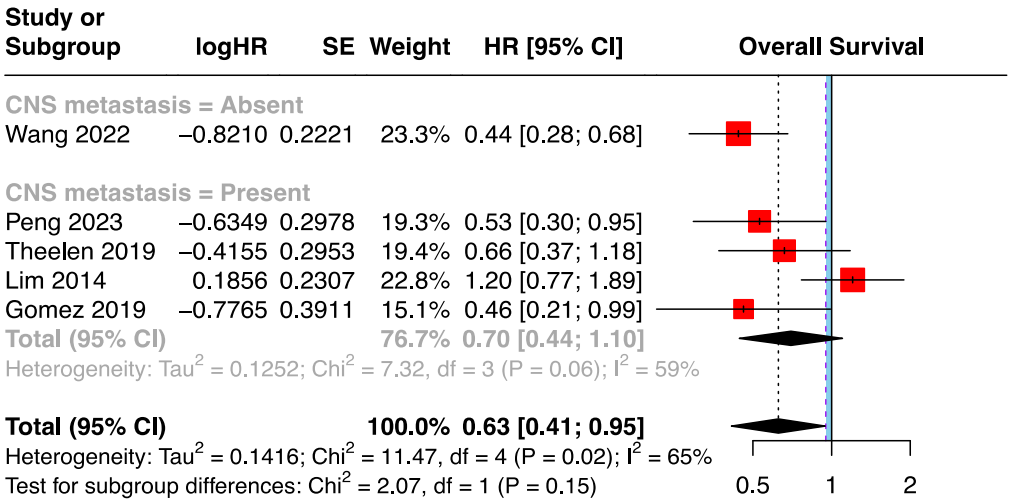
3.1 – Forest Plot – Overall Survival




*- 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.

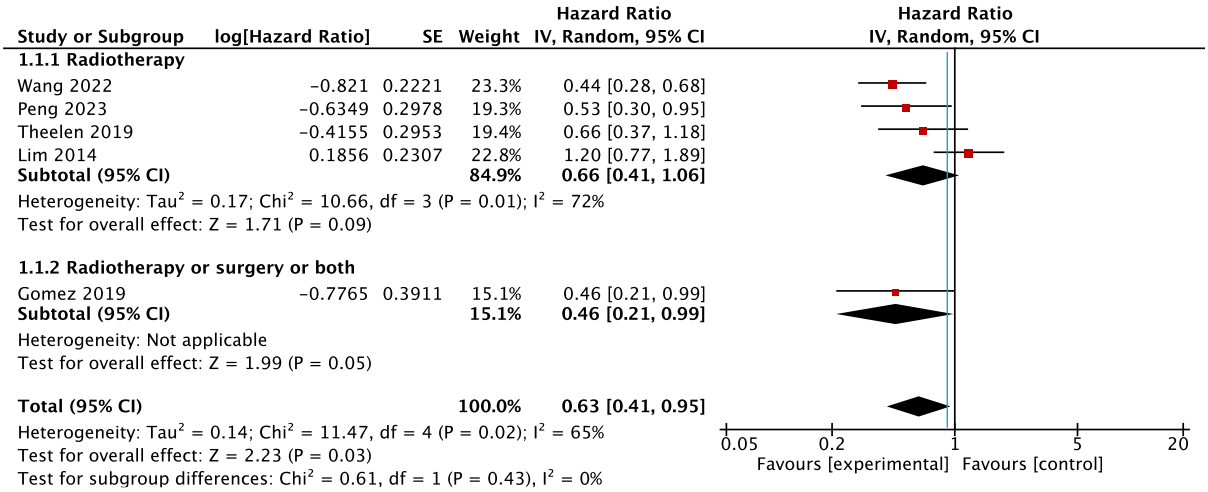
3.2 Forest Plot – with subgroup - metastasis




*- 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 ($\chi^2$ = 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.

3.3 Forest Plot – Subgroup – type of therapy



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

*- No distinction made between intervention and control group

## Summary of findings

**Radical local therapy compared to control for NSCLC**

**Patient or population:** Patients with Oligometastatic Non-small cell Lung cancer
Subgroups: Single metastatic sites vs more than one metastatic sites
Site(s) of metastasis(es)
**Setting:** Tertiary Care Hospitals
**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) | ⊕⊕◯◯ Low[a,b,c,d,e] |
| | 640 per 1,000 | **755 per 1,000** (654 to 833) | | | |
| OS - Radiotherapy follow-up: 1 years | **Control risk (pooled using eligible studies)** | | **HR 0.66** (0.41 to 1.06) | 383 (4 RCTs) | ⊕◯◯◯ Very low[a,b,c,e,f] |
| | 640 per 1,000 | **745 per 1,000** (623 to 833) | | | |
| | **Control risk (pooled using eligible studies)** | | | | |

| | | | | | |
|---|---|---|---|---|---|
| OS - radiotherapy or surgery or both follow-up: 1 years | 620 per 1,000 | **803 per 1,000** (623 to 904) | **HR 0.46** (0.21 to 0.99) | 49 (1 RCT) | ⊕⊕◯◯ Low[c,e,g,h] |
| OS - CNS Metastasis present follow-up: 1 years | **Control risk (pooled using eligible studies)** | | **HR 0.70** (0.44 to 1.10) | 299 (4 RCTs) | ⊕◯◯◯ Very low[a,b,f] |
| | 560 per 1,000 | **666 per 1,000** (528 to 775) | | | |
| OS - CNS Metastasis absent follow-up: 1 years | **Control risk (pooled using eligible studies)** | | **HR 0.44** (0.28 to 0.68) | 133 (1 RCT) | ⊕⊕◯◯ Low[h] |
| | 850 per 1,000 | **931 per 1,000** (895 to 956) | | | |
| PFS follow-up: 1 years | **Control risk (pooled using eligible studies)** | | **HR 0.51** (0.33 to 0.79) | 568 (7 RCTs) | ⊕⊕⊕◯ Moderate[c,d,e,i] |
| | 250 per 1,000 | **493 per 1,000** (334 to 633) | | | |
| | **Control risk (pooled using eligible studies)** | | | | |

| | | | | | |
|---|---|---|---|---|---|
| PFS- CNS Metastasis present follow-up: 1 years | 200 per 1,000 | **381 per 1,000** (259 to 501) | **HR 0.60** (0.43 to 0.84) | 435 (6 RCTs) | ⊕⊕⊕◯ Moderate[d] |
| PFS - CNS Metastasis absent follow-up: 1 years | **Control risk (pooled using eligible studies)** | | **HR 0.28** (0.17 to 0.46) | 133 (1 RCT) | ⊕⊕◯◯ Low[h] |
| | 430 per 1,000 | **790 per 1,000** (678 to 866) | | | |
| Response rate | 390 per 1,000 | **554 per 1,000** (386 to 796) | **RR 1.42** (0.99 to 2.04) | 321 (5 RCTs) | ⊕◯◯◯ Very low[a,c,e,f,j] |

*__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. 1/3 rd to 2/3 rd of studies are at low risk of bias, so we have downgraded by one level.
b. Point estimates are on opposite sides. All confidence intervals are not overlapping. Substantial heterogeneity is present as per I^2. However excluding one study (Lim et al., 2014 due to all patient having CNS metastasis, the study being old, and regimen changes) resolved the inconsistency. So, evidence is downgraded by two levels.
c. The evidence matches the research question.
d. Confidence interval excludes the null value. The sample size is within 50% - 100% of the optimal information size. So, we have downgraded by one point.
e. There are less than 10 studies. So, publication bias could not be assessed.
f. Confidence interval includes the null value, but the two boundaries do not suggest very different inferences. The sample size is within 30% - 50% of the optimal information size. So, we have downgraded by two point.
g. There is only one study, so inconsistency could not be assessed.
h. Confidence interval excludes null value. The sample size is less than 30% of the optimal information size. So, we have downgraded by two point.
i. Inconsistency is explainable by excluding Wang et al., 2022, as it is the only study excluding patients with CNS metastasis
j. Point estimates are on same side. All confidence intervals are overlapping. Heterogeneity is low as per I^2. So, evidence is not downgraded.

## Evidence Profile

**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
Subgroups: Single metastatic sites vs more than one metastatic sites
Site(s) of metastasis(es)
**Setting:** Tertiary Care Hospitals
**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] | not serious[b] | not serious[c] | serious[d] | none[e] | 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) | ⨁⨁◯◯ Low[a,b,c,d,e] | CRITICAL |

**OS - Radiotherapy (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | randomised trials | serious[a] | not serious[b] | not serious[c] | very serious[f] | none[e] | 144/183 (78.7%) | 64.0% | **HR 0.66** (0.41 to 1.06) | **105 more per 1,000** (from 17 fewer to 193 more) | ⊕◯◯◯ Very low[a,b,c,e,f] | CRITICAL |

**OS - radiotherapy or surgery or both (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | not serious | not serious[g] | not serious[c] | very serious[h] | none[e] | 21/25 (84.0%) | 62.0% | **HR 0.46** (0.21 to 0.99) | **183 more per 1,000** (from 3 more to 284 more) | ⊕⊕◯◯ Low[c,e,g,h] | CRITICAL |

**OS - CNS Metastasis present (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | randomised trials | serious[a] | not serious[b] | not serious | very serious[f] | none | 99/140 (70.7%) | 56.0% | **HR 0.70** (0.44 to 1.10) | **106 more per 1,000** (from | ⊕◯◯◯ Very low[a,b,f] | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 32 fewer to 215 more) | | |

**OS - CNS Metastasis absent (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | not serious | not serious | not serious | very serious[h] | none | 66/68 (97.1%) | 85.0% | **HR 0.44** (0.28 to 0.68) | **81 more per 1,000** (from 45 more to 106 more) | ⨁⨁◯◯ Low[h] | CRITICAL |

**PFS (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | randomised trials | not serious | not serious[i] | not serious[c] | serious[d] | none[e] | 100/286 (35.0%) | 25.0% | **HR 0.51** (0.33 to 0.79) | **243 more per 1,000** (from 84 more to 383 more) | ⨁⨁⨁◯ Moderate[c,d,e,i] | IMPORTANT |

**PFS- CNS Metastasis present (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | randomised trials | not serious | not serious | not serious | serious[d] | none | 40/218 (18.3%) | 20.0% | **HR 0.60** (0.43 to 0.84) | **181 more per 1,000** (from 59 more to 301 more) | ⊕⊕⊕◯ Moderate[d] | IMPORTANT |

**PFS - CNS Metastasis absent (follow-up: 1 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | not serious | not serious | not serious | very serious[h] | none | 60/68 (88.2%) | 43.0% | **HR 0.28** (0.17 to 0.46) | **360 more per 1,000** (from 248 more to 436 more) | ⊕⊕◯◯ Low[h] | IMPORTANT |

**Response rate**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | randomised trials | serious[a] | not serious[j] | not serious[c] | very serious[f] | none[e] | 87/157 (55.4%) | 64/164 (39.0%) | **RR 1.42** (0.99 to 2.04) | **164 more per 1,000** (from 4 fewer | ⊕◯◯◯ Very low[a,c,e,f,j] | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | to 406 more) | | |

CI: confidence interval; HR: hazard ratio; RR: risk ratio

***Explanations***

a. 1/3 rd to 2/3 rd of studies are at low risk of bias, so we have downgraded by one level.
b. Point estimates are on opposite sides. All confidence intervals are not overlapping. Substantial heterogeneity is present as per I^2. However excluding one study (Lim et al., 2014 due to all patient having CNS metastasis, the study being old, and regimen changes) resolved the inconsistency. So, evidence is downgraded by two levels.
c. The evidence matches the research question.
d. Confidence interval excludes the null value. The sample size is within 50% - 100% of the optimal information size. So, we have downgraded by one point.
e. There are less than 10 studies. So, publication bias could not be assessed.
f. Confidence interval includes the null value, but the two boundaries do not suggest very different inferences. The sample size is within 30% - 50% of the optimal information size. So, we have downgraded by two point.
g. There is only one study, so inconsistency could not be assessed.
h. Confidence interval excludes null value. The sample size is less than 30% of the optimal information size. So, we have downgraded by two point.
i. Inconsistency is explainable by excluding Wang et al., 2022, as it is the only study excluding patients with CNS metastasis
j. Point estimates are on same side. All confidence intervals are overlapping. Heterogeneity is low as per I^2. So, evidence is not downgraded.

## 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.<br><br>**Strength**: Conditional<br>**Certainty of evidence**: Very low | |

## RESEARCH PRIORITIES

Given the absence of direct evidence on cost-effectiveness, equity, feasibility, and acceptability for radical local treatment in oligometastatic NSCLC, the following research priorities are recommended:

**Health Economic Evaluations:** Conduct formal cost-effectiveness analyses comparing radical local treatment plus systemic therapy versus systemic therapy alone, accounting for variations in health system resources and treatment settings.

**Equity-Focused Research:** Investigate disparities in access to radical local treatment, particularly examining geographic (urban–rural), socioeconomic, and health system–level factors that influence equitable delivery of care.

**Feasibility Studies:** Evaluate the implementation of SABR and other radical local treatments in diverse clinical settings, focusing on infrastructure requirements, workforce capacity, and institutional readiness.

**Acceptability Studies:** Assess patient and clinician perspectives on radical local treatment through qualitative or mixed-methods research to understand perceived benefits, burdens, and barriers to uptake.

**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)?**

## List of 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 |

# Table of Contents

## 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:** 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 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:

- Overall survival (Seven studies)
- Quality of life (No studies)
- Adverse Effects (Two Studies)
- Brain metastasis rates (Twenty Studies)
- Neurocognitive Function (One Study)
- Cost (No studies)
- Treatment non-compliance rates (Two studies)

### Intervention

Chemotherapy (with or without radiation) with Prophylactic Cranial Irradiation (PCI)

### Comparator

Chemotherapy (with or without radiation) without PCI

### Outcome

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

- 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)

**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<br>Subgroups: 1. Limited and extensive 2. Age 3. Response to treatment (chemoradiation/chemotherapy) |
| Intervention | (Chemotherapy with or without radiation) with Prophylactic Cranial Irradiation (PCI)<br>Subgroups: 1. with or without hippocampal avoidance |
| Comparator | (Chemotherapy with or without radiation) without PCI<br>Subgroups: 1. MRI surveillance 2. Observation (No brain imaging) |
| Outcome | Overall survival (Critical outcome)<br>Quality of life (Critical outcome)<br>Adverse effects (Critical outcome)<br>Brain metastasis rates (Important outcome)<br>Neurocognitive function (Important outcome)<br>Cost (Important outcome)<br>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

| Outcome 1 – Overall Survival (Outcome reported as Hazard Ratio) | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Gregor et al 1997 | + | + | + | + | + | + |
| Schild et al 2012 | - | ! | + | + | + | - |
| Slotman et al 2007 | + | + | + | + | + | + |
| **Outcome 2 – Incidence of Adverse events** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Schild et al 2012 | - | ! | + | ! | + | - |
| **Outcome 3A: Incidence of Brain Metastasis** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| 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 | ! | - | + | - | ! | - |
| Hansen et al 1980 | + | + | + | ! | + | ! |
| Jackson et al 1977 | ! | ! | + | - | ! | - |
| Jat et al 2019 | ! | ! | + | - | ! | - |
| Laplanche et al 1998 | + | + | + | ! | ! | ! |
| Maurer et al 1980 | + | + | + | + | + | + |
| Niiranen et al 1989 | ! | ! | + | ! | ! | - |
| Ohonoshi et al 1993 | ! | ! | + | ! | ! | - |

| | |
|---|---|
| + | 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 |

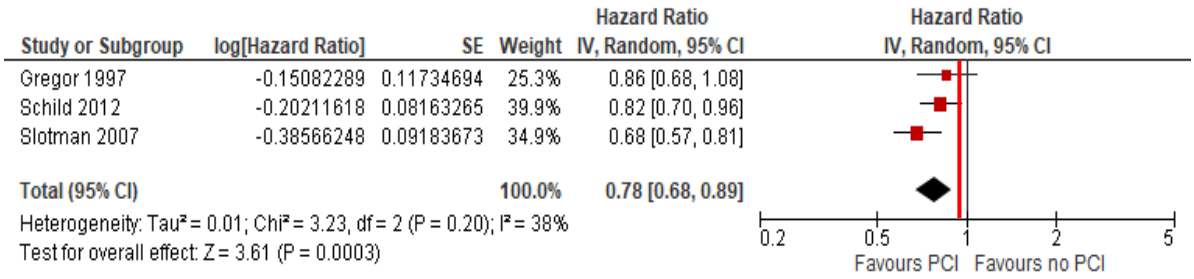
| | | | | | | |
|---|---|---|---|---|---|---|
| Seydel et al 1985 | + | ! | ! | ! | ! | - |
| Slotman et al 2007 | + | + | + | + | + | + |
| Wagner et al 1996 | ! | ! | ! | ! | ! | - |
| **Outcome 3B: Incidence of Brain metastasis (Outcome reported as HR)** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Gregor et al 1997 | + | + | + | ! | ! | ! |
| **Outcome 4: Neurocognitive function (Outcome reported as events)** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Gregor et al 1997 | + | + | - | ! | ! | - |
| **Outcome 5: Treatment Non Compliance Rates (Outcome reported as events)** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Arrigada et al 1995 | + | + | + | ! | + | ! |
| Arrigada et al 2001 | + | + | + | ! | + | ! |

## 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

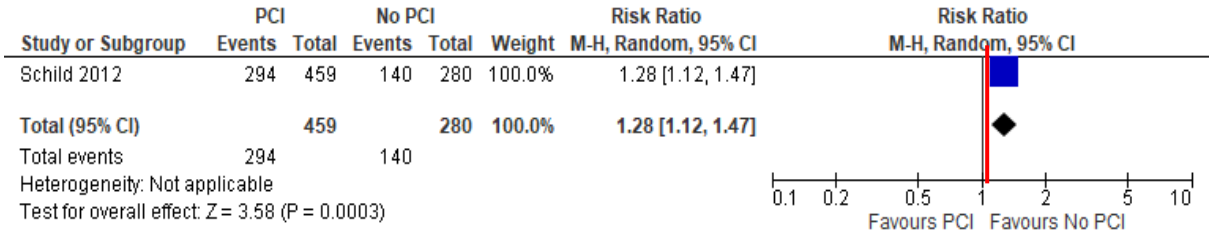
No studies reported for the mentioned outcome in the meta-analysis for this review.

## 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

**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) | ⨁⨁⨁◯ Moderate[a b,c,d] |
| Adverse events | 500 per 1,000 | 640 per 1,000 (560 to 735) | **RR 1.28** (1.12 to 1.47) | 739 (1 study) | ⨁⨁◯◯ Low[d,h,i,j] |

***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. Sub-group analysis was done for suspected parameters
b. The confidence interval of the pooled estimate has crossed the null value
c. High risk in one study and some concern in another study among four included studies
d. The I-square statistics is moderately high with a significant Chi-square test for heterogeneity
e. Sensitivity analysis was done for suspected parameters
f. High risk of bias in one out of two included studies
g. The I-square statistics is substantially high with a significant Chi-square test for heterogeneity
h. Indirectness in terms of study participants (mixture of limited and extensive disease patients)
i. The upper end of the confidence interval crossing 25% of the pooled estimate

## Evidence Profile

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

**Patient or population:** Patients with SCLC
**Setting:**
**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] | serious[e] | not serious[c] | not serious | none | - | 72% risk (range 61 to 87) | **HR 0.78** (0.68 to 0.89) | - | ⨁⨁⨁◯ Moderate[a, e, c] | CRITICAL |
| **Adverse events** | | | | | | | | | | | | |
| 1 | randomised trials | Serious[f] | not serious | not serious | serious[d] | none | 294/459 (64.1%) | 140/280 (50.0%) | **RR 1.28** (1.12 to 1.47) | **140 more per 1,000** (from 210 more to 70 more) | ⨁⨁◯◯ low[d, f] | CRITICAL |

**Explanations**

a. No concerns in most studies
b. The i-square is low with non-significant Chi-square test for heterogeneity
c. Sub-group analysis was done for suspected parameters
d. The optimal information size is not met
e. The I-square statistics is moderately high with a significant Chi-square test for heterogeneity
f. High risk of bias in the included study

## Summary of Judgements

| | |
|---|---|
| **Problem** | Yes |
| **Desirable Effects** | Moderate |
| **Undesirable Effects** | Moderate |
| **Certainty of evidence** | 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.<br><br>Strength: Strong<br>Certainty of evidence: Low | |

**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

## 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:

- Overall survival (8 Studies)
- Adverse effects (8 Studies)
- Quality of life (No study)
- Treatment non-compliance rates (3 Studies)

## 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

The following critical and important outcomes were evaluated:

- Overall survival (Critical Outcome)
- Adverse effects (Critical Outcome)
- Quality of life (Important 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 | |

## Review 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?

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

## 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** |
| - | **High risk** |

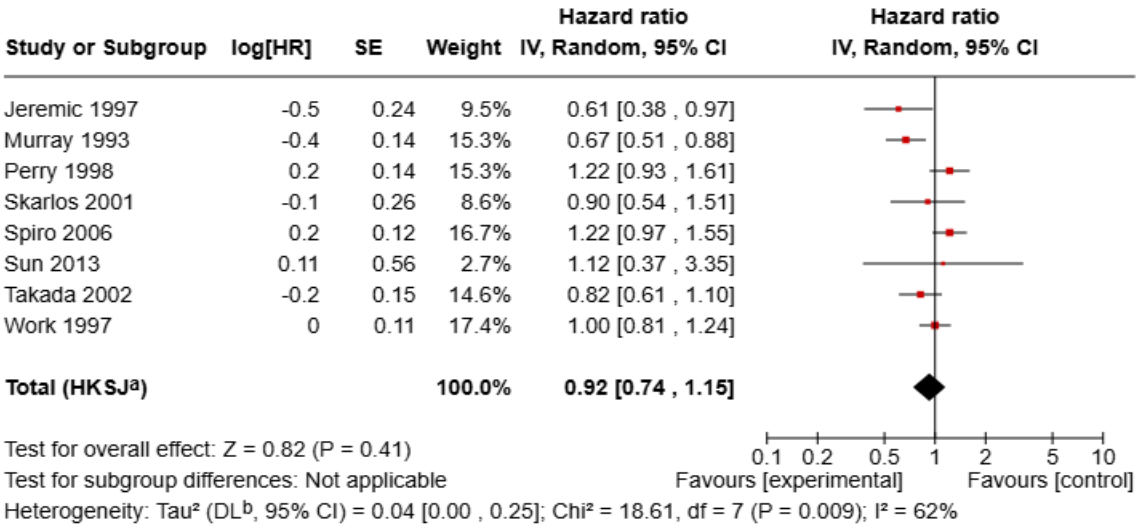
| | |
|---|---|
| **D1** | **Randomisation process** |
| **D2** | **Deviations from the intended interventions** |
| **D3** | **Missing outcome data** |
| **D4** | **Measurement of the outcome** |
| **D5** | **Selection of the reported result** |

## 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.

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




**Footnotes**

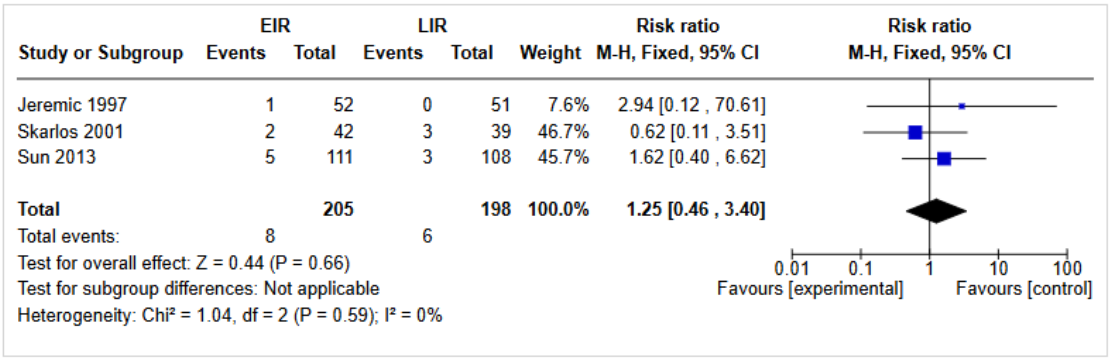
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by DerSimonian and Laird method.

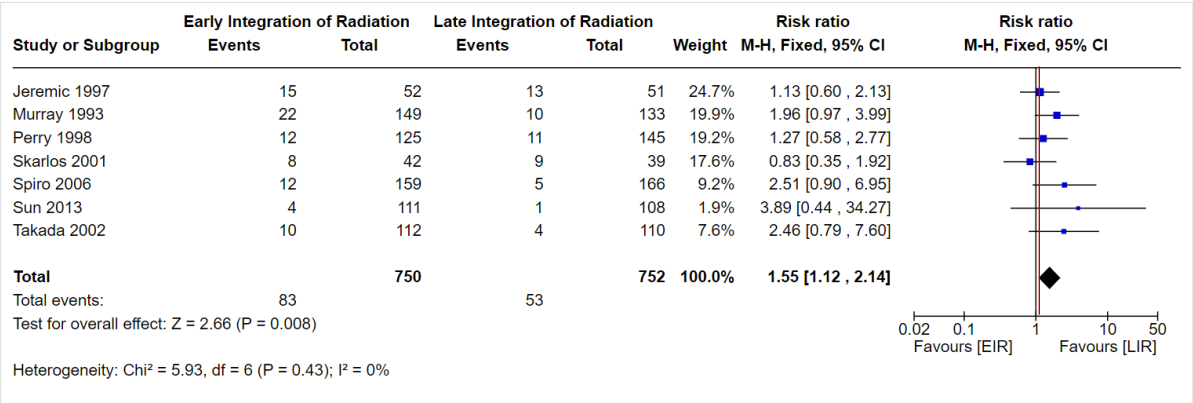
## Undesirable Effects

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 had 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.

### a. Pneumonitis




### b. Oesophagitis




*-Red line shows MCID given by GDG

## Summary of findings:

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

**Patient or population:** People with limited stage SCLC

**Setting:** India

**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) | ⊕⊕◯◯ Low[a,b] |
| **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) | ⊕⊕◯◯ Low[a,b] |
| Pneumonitis | 30 per 1,000 | **38 per 1,000** (14 to 103) | **RR 1.25** (0.46 to 3.40) | 403 (3 RCTs) | ⊕⊕⊕◯ Moderate |

| |
|---|
| *__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).<br><br>**CI:** confidence interval; **HR:** hazard ratio; **RR:** risk ratio |
| **GRADE Working Group grades of evidence**<br>**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.<br>**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.<br>**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.<br>**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. |

***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

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

**Patient or population:** People with limited stage SCLC
**Setting:** India
**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 | serious[a] | not serious | not serious | serious[b] | 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) | ⊕⊕◯◯ Low[a,b] | Critical |

a. all study except two has some concern in ROB

b. CI cross decision clinical decision threshold

**Evidence Profile**

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

**Patient or population:** People with limited stage SCLC

**Setting:** India

**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 | serious [a] | not serious | not serious | not serious | 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) | ⨁⨁⨁◯ Moderate [a] | Critical |

| **Pneumonitis** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | Serious[a] | not serious | not serious | Serious[b] | 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[a,c] | Critical |

**CI:** confidence interval

*Explanations*

a. All studies have overall "some concern" in ROB

c. CI crossing the null value

## 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.<br><br>**Strength**: Conditional<br>**Certainty of evidence** –Low | |

-

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

-

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## 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.

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## 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:

- T stage
- Nodal involvement
- Histology
- PDL1
- 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)

### Intervention

Post operative radiotherapy with adjuvant chemotherapy

### Comparator

Adjuvant chemotherapy alone

### Outcome

The following critical and important outcomes were evaluated:

1. Overall survival (Critical outcome)
2. Adverse effects (Critical outcome)
3. Quality of life (Critical outcome)
4. Disease free survival (Important outcome)

-

5. Cost (Important outcome)

## Critical Outcome reviewed and their MCID provided by GDG

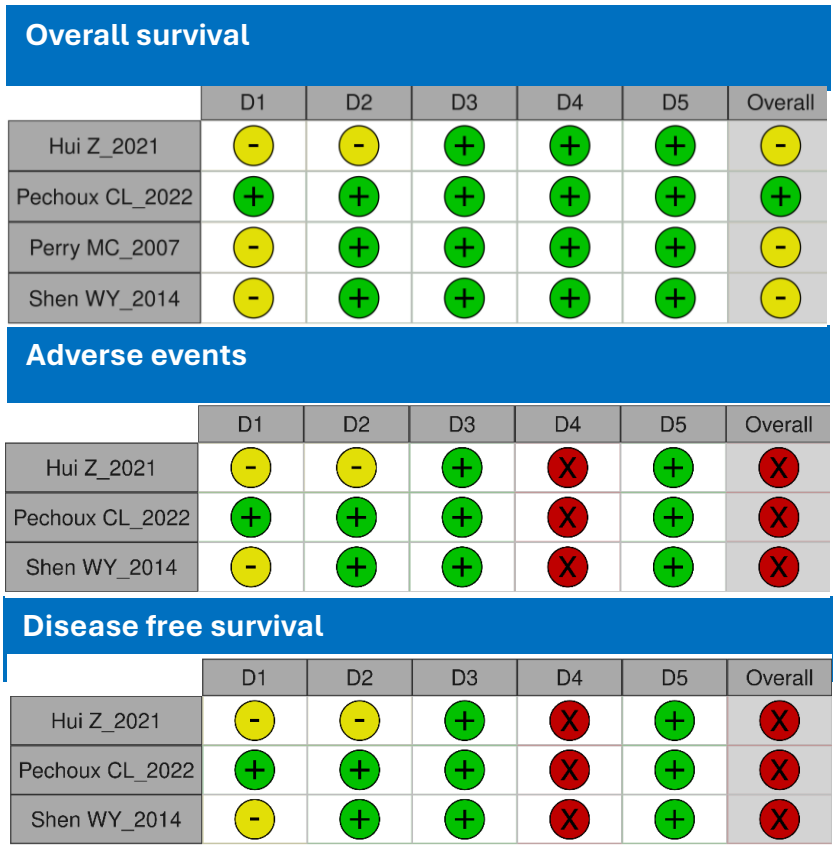
| Sr. No | Critical outcome reviewed | What does it measure | MCID decided by GDG |
|---|---|---|---|
| 1 | Overall Survival | OS (Proportion of people who have survived at a particular time point) | 5% |
| | | OS (Proportion increase in median survival) | 6 months |
| 2 | Adverse events | Adverse events | 10% |
| 3 | Quality of life (QoL) | Quality of life (difference in the mean scores of QoL) | 10 point change |

## PICO

| Framework | Inclusion criteria |
|---|---|
| Population | Patients with NSCLC with complete resection<br>Subgroups: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1<br>5. Smoking status |
| Intervention | Post op radiotherapy with adjuvant chemotherapy<br>Subgroups: i) 2D conformal<br>ii) 3D conformal |
| Comparator | Adjuvant chemotherapy alone |
| Outcome | Overall survival (Critical outcome)<br>Adverse effects (Critical outcome)<br>Quality of life (Critical outcome)<br>Disease free survival (Important outcome)<br>Cost (Important outcome) |

-

## 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 |

-

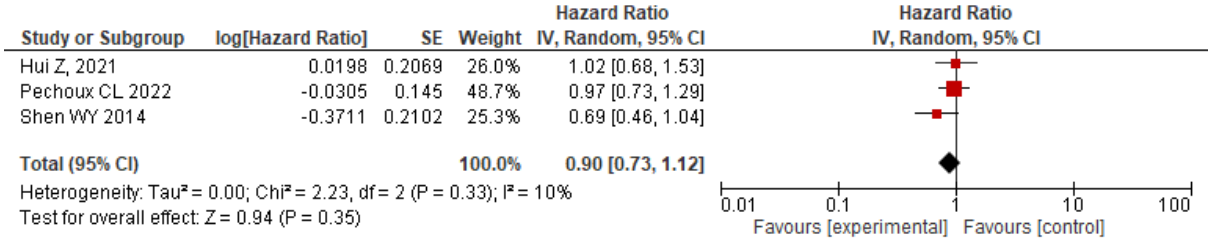
## Desirable Effects

### 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.

### Overall survival (OS) using HR



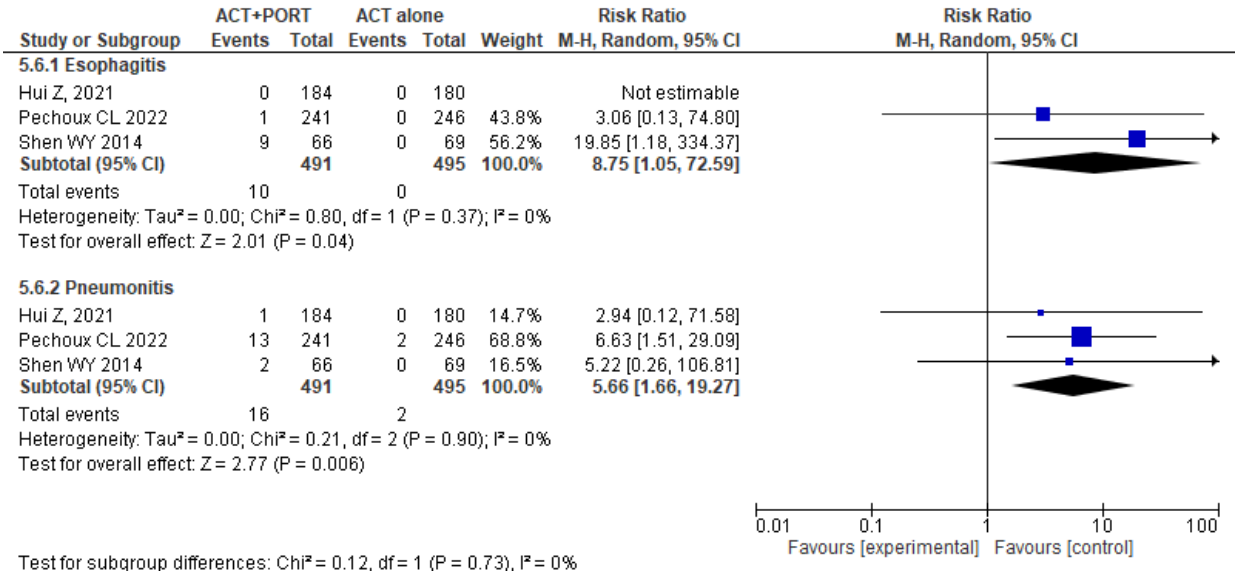

However, certain high-risk pathological features, notably positive (R1) or very close surgical margins and bulky or multi-station mediastinal (N2) nodal disease are consistently associated with higher locoregional recurrence and worse prognosis and therefore warrant individualised consideration of PORT.

(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.

Non hematologic adverse events of grade 3 or more is showed in figure

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## 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) | ⊕◯◯◯ Very 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,e,g] | 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,e] | 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.

-

***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

**Setting:** Tertiary Care Hospital

**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 | Very 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) | ⊕◯◯◯ Very low[a,b] | CRITICAL |
| Adverse Effects | | | | | | | | | | | | |
| **Esophagitis (AE Non-Hematologic Grade 3 or more)** | | | | | | | | | | | | |
| 3 | randomised trials | Very serious[c,e] | not serious | not serious | serious[g] | 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,e,g] | CRITICAL |
| **Pneumonitis (AE Non-Hematologic Grade 3 or more)** | | | | | | | | | | | | |

-

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | Very serious[c,e] | not serious | not serious | serious[h] | 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,e] | CRITICAL |

**CI:** confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

*Explanations*

a. As per SOP guidance, when less than one-third of the contributing weight comes from low-risk studies, a downgrade by two levels is warranted.
b. The pooled effect size crossed the null effect line
c. Less than one-third of the contributing weight comes from low-risk studies
d. Taking a MCID of 5%, the pooled effect size crossed MCID and line of null effect line both
e. High risk of bias in at least one domain in all included studies
f. Some concern in some domains
g. Taking a MCID of 10%, the pooled effect crossed MCID
h. OIS not met (OIS was calculated on the basis of RR)

-

## 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).<br><br>**Strength**: Conditional<br>**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

**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?**

List of Abbreviations

| Abbreviation | Full Form |
|---|---|
| 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 |

# Table of Contents

## 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:

- Overall survival (Two studies)
- Quality of life (Two studies)
- Adverse Effects (One Study)
- Disease free survival (One Study)
- Cost (No studies)

- Surgical outcomes (No studies)
- Post operative Pulmonary function (No studies)

### Intervention

Stereotactic Body Radiation Therapy (SBRT)

### Comparator

Lobectomy/ Limited lung resection/ Sub-lobar resection (Segmentectomy/Wedge resection)

### Outcome

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

- Overall survival (Critical outcome)
- Quality of life (Critical outcome)
- Adverse effects (Critical outcome)
- Disease free survival (Important outcome)
- Cost (Important outcome)
- Surgical outcomes (Important outcome)
- Post operative pulmonary function (Important outcome)

PICO question as provided by the secretariat:

| Framework | Description |
|---|---|
| Population | People with early stage operable non-small cell lung cancer (NSCLC)<br>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)<br>Adverse effects (Critical outcome)<br>Quality of life (Critical outcome)<br>Disease free survival (Important outcome)<br>Cost (Important outcome)<br>Surgical outcomes (Important outcome)<br>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

| Outcome 1A – 1 Year Overall Survival | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | + | + |
| **Outcome 1B – 18 Months Overall Survival** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Franks et al 2020 | ! | - | - | + | + | - |
| **Outcome 1C – 3 Year Overall Survival** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | + | + |
| **Outcome 2A - 6 Weeks Quality of Life** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Franks et al 2020 | ! | - | - | + | + | - |
| **Outcome 2B - 3 Months Quality of Life** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Franks et al 2020 | ! | - | - | + | + | - |
| **Outcome 2C - 6 Months Quality of Life** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Franks et al 2020 | ! | - | - | + | + | - |
| **Outcome 2D - Deterioration (TTD) in Global Health** | | | | | | |
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Louie et al 2015 | + | + | + | + | + | + |

| | |
|---|---|
| + | 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 |

| Outcome 3A - Grade 3 or 4 Adverse Events | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | + | + |

| Outcome 3B - Grade 3 Dyspnoea | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | + | + |

| Outcome 4A - 3 Years Recurrence Free Survival | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | ! | ! |

| Outcome 4B - 3 Years Local Recurrence Free Survival | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | ! | ! |

| Outcome 4C - 3 Years Regional Nodal Recurrence Free Survival | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | ! | ! |

| Outcome 4D - 3 Years Distance Metastasis Free Survival | | | | | | |
|---|---|---|---|---|---|---|
| Study ID | D1 | D2 | D3 | D4 | D5 | Overall |
| Chang et al 2015 | + | + | + | + | ! | ! |

## 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

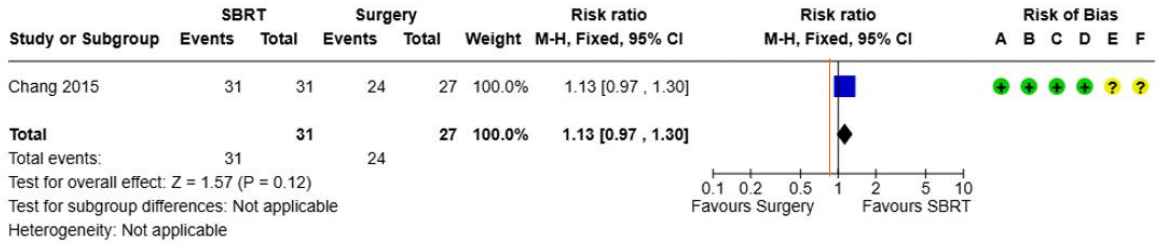



Figure 3.2 – Forest plot: 18 Months Overall survival

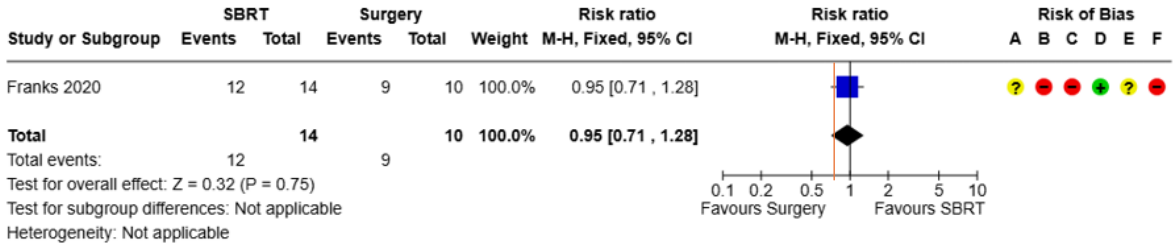



Figure 3.3 – Forest plot: 3 Years Overall survival

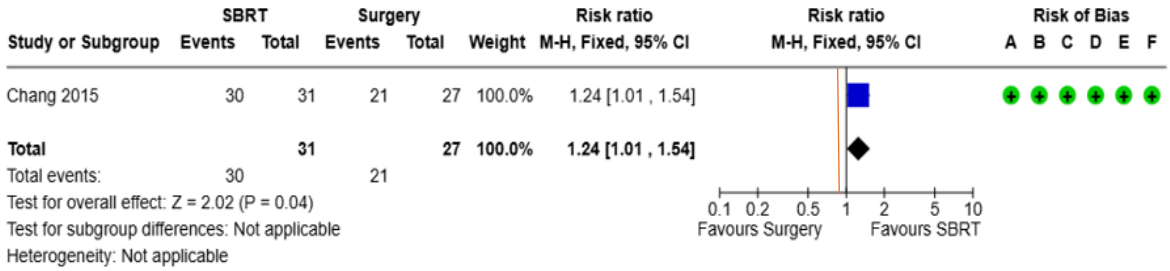
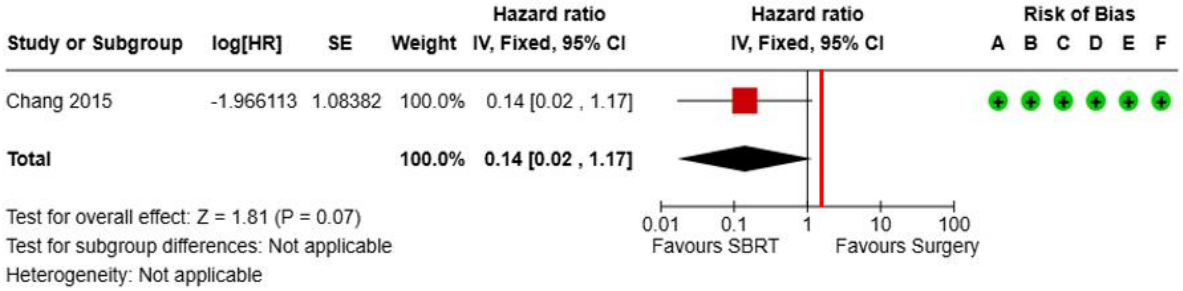
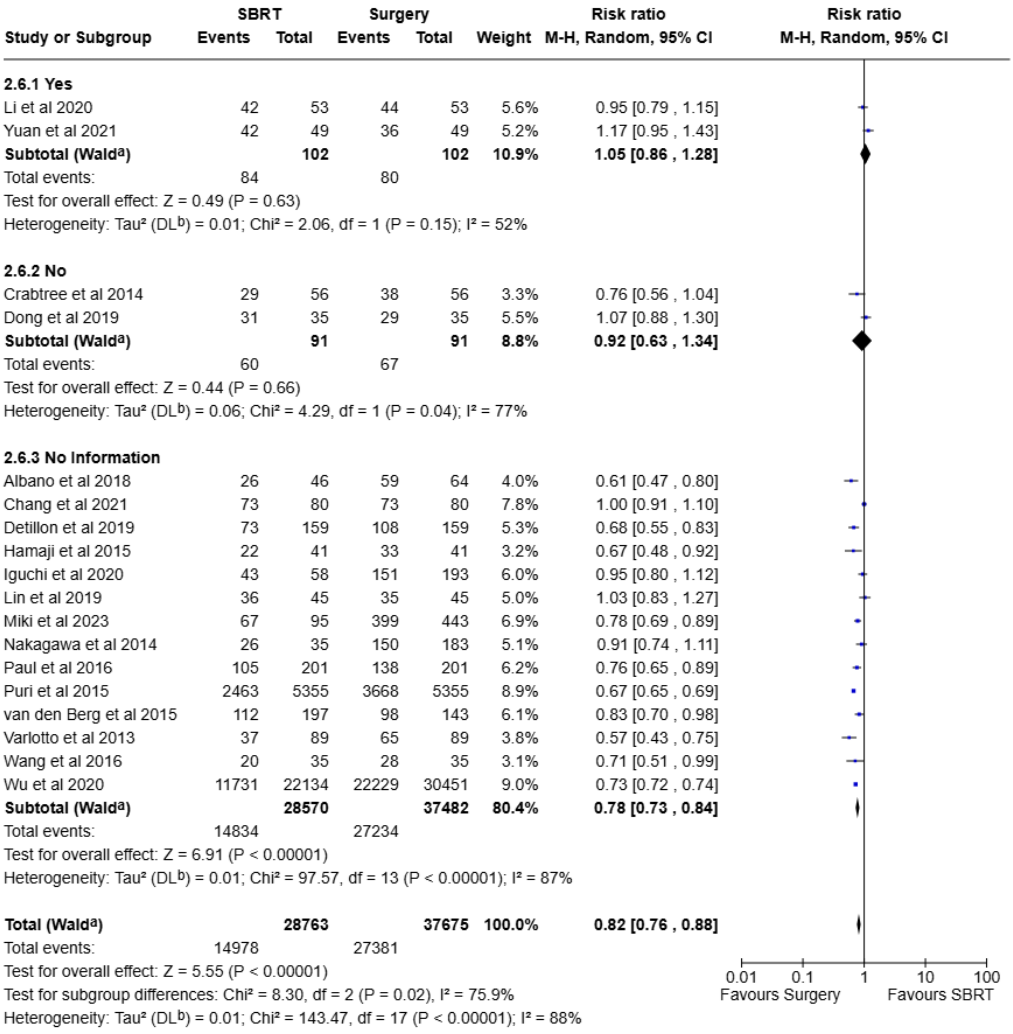


Figure 3.4 – Forest plot: 3 Years Overall survival (HR)




Forest plots from observational studies

***3-year overall survival***




**Footnotes**

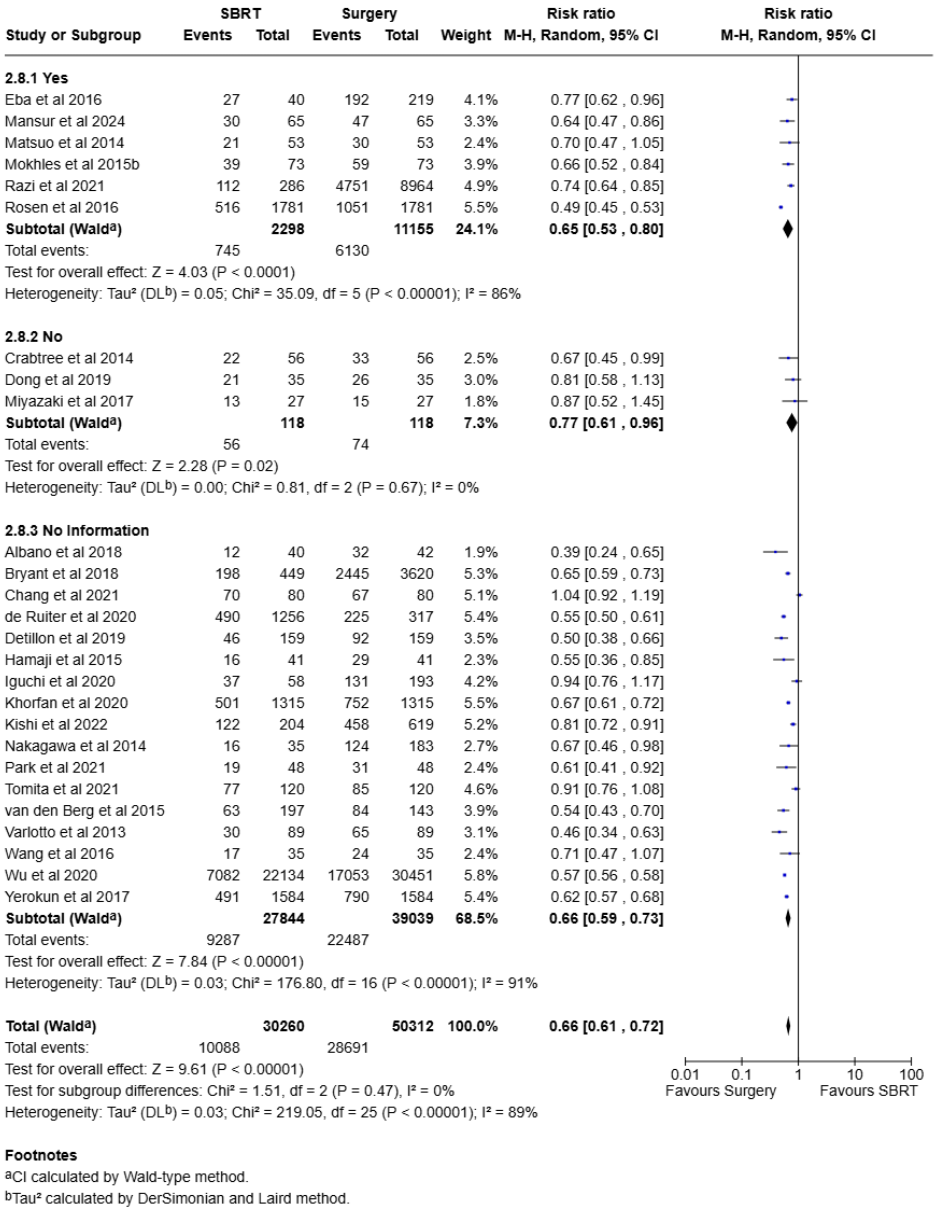
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## 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

## 5-year overall survival



| Study or Subgroup | SBRT Events | SBRT Total | Surgery Events | Surgery Total | Weight | Risk ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.8.1 Yes** | | | | | | |
| Eba et al 2016 | 27 | 40 | 192 | 219 | 4.1% | 0.77 [0.62 , 0.96] |
| Mansur et al 2024 | 30 | 65 | 47 | 65 | 3.3% | 0.64 [0.47 , 0.86] |
| Matsuo et al 2014 | 21 | 53 | 30 | 53 | 2.4% | 0.70 [0.47 , 1.05] |
| Mokhles et al 2015b | 39 | 73 | 59 | 73 | 3.9% | 0.66 [0.52 , 0.84] |
| Razi et al 2021 | 112 | 286 | 4751 | 8964 | 4.9% | 0.74 [0.64 , 0.85] |
| Rosen et al 2016 | 516 | 1781 | 1051 | 1781 | 5.5% | 0.49 [0.45 , 0.53] |
| **Subtotal (Wald[a])** | | **2298** | | **11155** | **24.1%** | **0.65 [0.53 , 0.80]** |
| Total events: | 745 | | 6130 | | | |
| Test for overall effect: Z = 4.03 (P < 0.0001) | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.05; Chi² = 35.09, df = 5 (P < 0.00001); I² = 86% | | | | | | |
| **2.8.2 No** | | | | | | |
| Crabtree et al 2014 | 22 | 56 | 33 | 56 | 2.5% | 0.67 [0.45 , 0.99] |
| Dong et al 2019 | 21 | 35 | 26 | 35 | 3.0% | 0.81 [0.58 , 1.13] |
| Miyazaki et al 2017 | 13 | 27 | 15 | 27 | 1.8% | 0.87 [0.52 , 1.45] |
| **Subtotal (Wald[a])** | | **118** | | **118** | **7.3%** | **0.77 [0.61 , 0.96]** |
| Total events: | 56 | | 74 | | | |
| Test for overall effect: Z = 2.28 (P = 0.02) | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0% | | | | | | |
| **2.8.3 No Information** | | | | | | |
| Albano et al 2018 | 12 | 40 | 32 | 42 | 1.9% | 0.39 [0.24 , 0.65] |
| Bryant et al 2018 | 198 | 449 | 2445 | 3620 | 5.3% | 0.65 [0.59 , 0.73] |
| Chang et al 2021 | 70 | 80 | 67 | 80 | 5.1% | 1.04 [0.92 , 1.19] |
| de Ruiter et al 2020 | 490 | 1256 | 225 | 317 | 5.4% | 0.55 [0.50 , 0.61] |
| Detillon et al 2019 | 46 | 159 | 92 | 159 | 3.5% | 0.50 [0.38 , 0.66] |
| Hamaji et al 2015 | 16 | 41 | 29 | 41 | 2.3% | 0.55 [0.36 , 0.85] |
| Iguchi et al 2020 | 37 | 58 | 131 | 193 | 4.2% | 0.94 [0.76 , 1.17] |
| Khorfan et al 2020 | 501 | 1315 | 752 | 1315 | 5.5% | 0.67 [0.61 , 0.72] |
| Kishi et al 2022 | 122 | 204 | 458 | 619 | 5.2% | 0.81 [0.72 , 0.91] |
| Nakagawa et al 2014 | 16 | 35 | 124 | 183 | 2.7% | 0.67 [0.46 , 0.98] |
| Park et al 2021 | 19 | 48 | 31 | 48 | 2.4% | 0.61 [0.41 , 0.92] |
| Tomita et al 2021 | 77 | 120 | 85 | 120 | 4.6% | 0.91 [0.76 , 1.08] |
| van den Berg et al 2015 | 63 | 197 | 84 | 143 | 3.9% | 0.54 [0.43 , 0.70] |
| Varlotto et al 2013 | 30 | 89 | 65 | 89 | 3.1% | 0.46 [0.34 , 0.63] |
| Wang et al 2016 | 17 | 35 | 24 | 35 | 2.4% | 0.71 [0.47 , 1.07] |
| Wu et al 2020 | 7082 | 22134 | 17053 | 30451 | 5.8% | 0.57 [0.56 , 0.58] |
| Yerokun et al 2017 | 491 | 1584 | 790 | 1584 | 5.4% | 0.62 [0.57 , 0.68] |
| **Subtotal (Wald[a])** | | **27844** | | **39039** | **68.5%** | **0.66 [0.59 , 0.73]** |
| Total events: | 9287 | | 22487 | | | |
| Test for overall effect: Z = 7.84 (P < 0.00001) | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.03; Chi² = 176.80, df = 16 (P < 0.00001); I² = 91% | | | | | | |
| **Total (Wald[a])** | | **30260** | | **50312** | **100.0%** | **0.66 [0.61 , 0.72]** |
| Total events: | 10088 | | 28691 | | | |
| Test for overall effect: Z = 9.61 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 1.51, df = 2 (P = 0.47), I² = 0% | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.03; Chi² = 219.05, df = 25 (P < 0.00001); I² = 89% | | | | | | |



**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

### 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 3.5 – Forest plot: 6 weeks Quality of Life

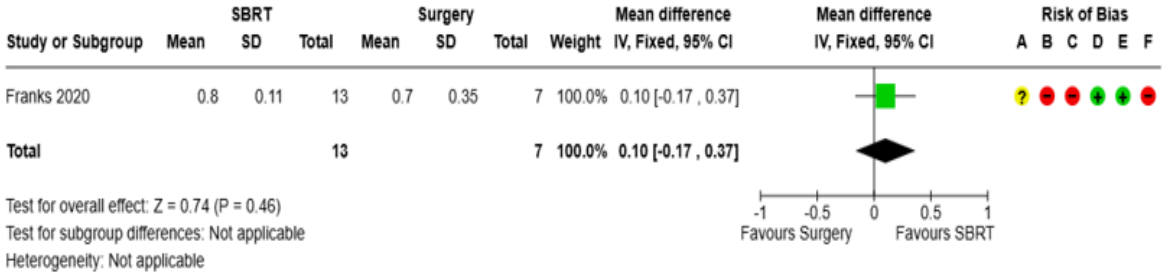



Figure 3.6 – Forest plot: 3 months Quality of Life

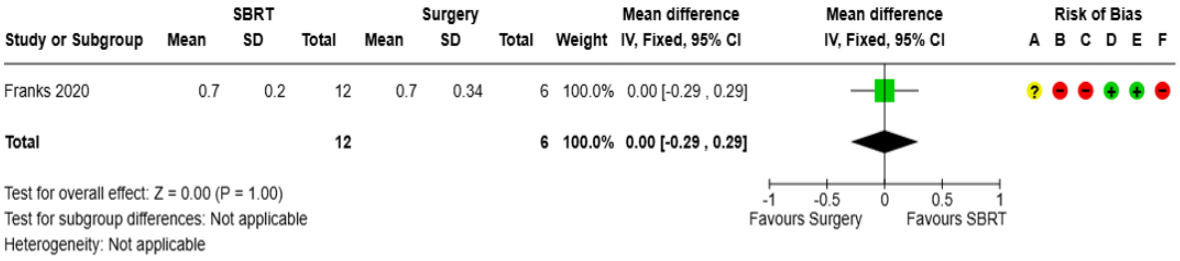



Figure 3.7 – Forest plot: 6 months Quality of Life

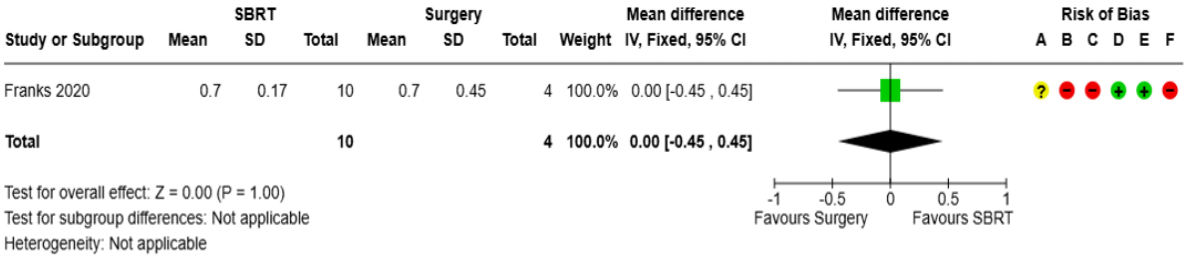


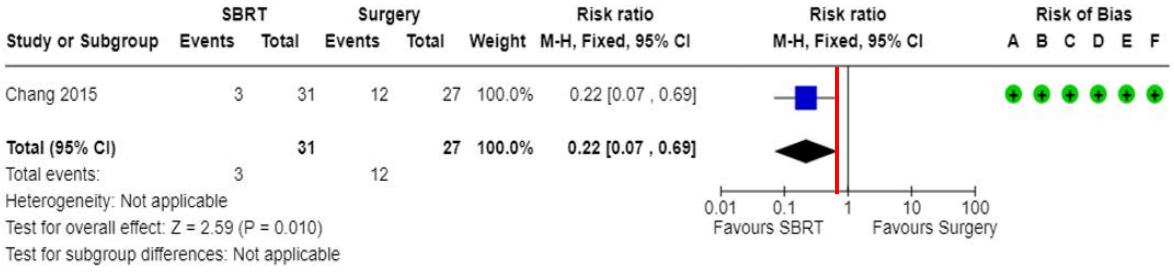
Figure 3.8 – Forest plot: Deterioration of Global Health/QoL

## Undesirable Effects

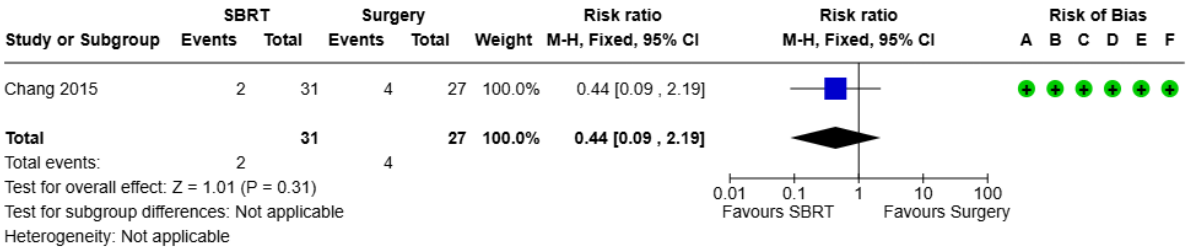
### Adverse Effects

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 3.9 - Forest Plot: Grade 3 or 4 adverse events



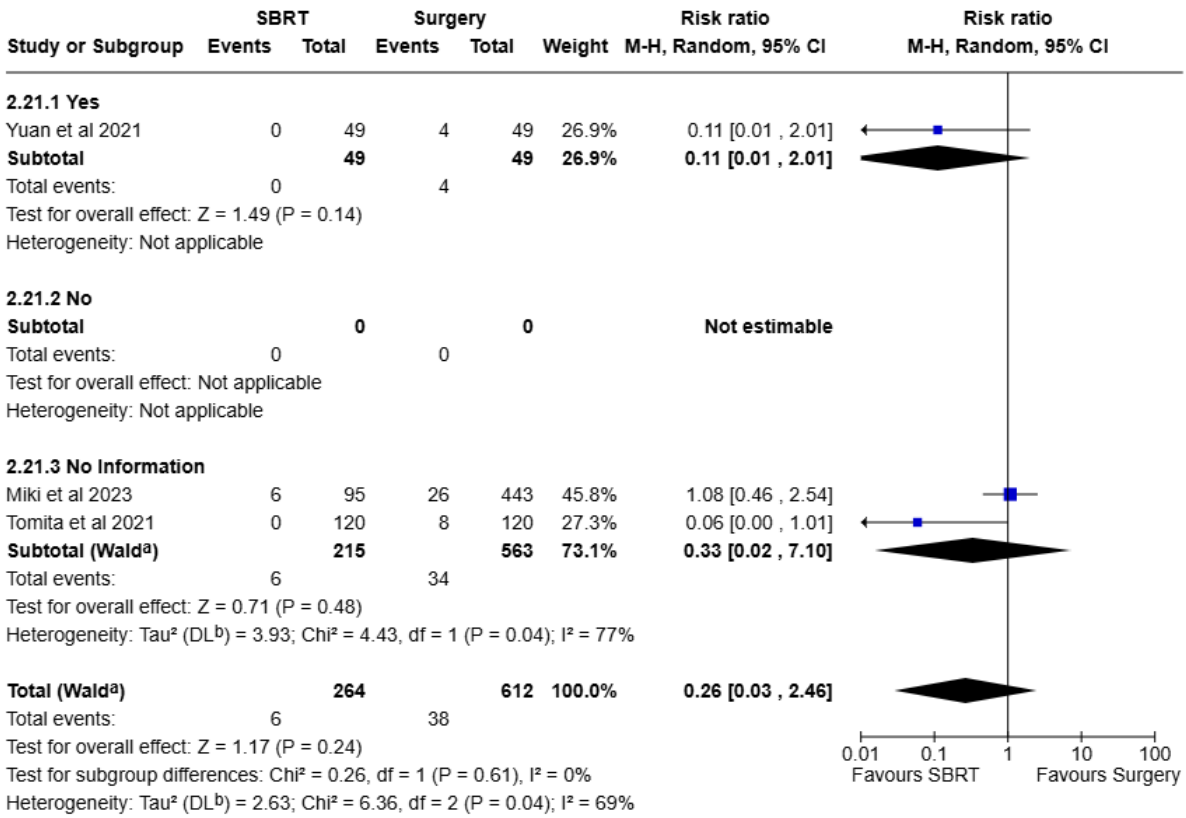

Forest Plot: Grade 3 dyspnoea




**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 from observational studies

### Grade 3 or 4 adverse events




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Summary of Findings

**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)**
**Setting:** Tertiary Care Hospital
**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,c,d,e] | 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[b,c,d,e,f] | 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[b,c,d,e,g] | 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) | ⊕⊕⊕◯ Moderate[b,c,e,g,h] | 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[b,c,d,e,g] | 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[b,c,e,f,i] | 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[b,c,e,f,i] | 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[b,c,e,f,i] | 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) | ⊕⊕⊕◯ Moderate[b,c,e,g,h] | SBRT results in large reduction in deterioration in global health/QoL. |
| 3 years recurrence free survival | 778 per 1,000 | **646 per 1,000** (271 to 968) | **HR 0.69** (0.21 to 2.28) | 58 (1 RCT) | ⊕⊕◯◯ Low[a,b,c,d,e] | The evidence suggests that SBRT does not increase 3 years recurrence free survival |
| 3 years local recurrence free survival | 1,000 per 1,000 | **970 per 1,000** (890 to 1,000) | **RR 0.97** (0.89 to 1.06) | 58 (1 RCT) | ⊕⊕◯◯ Low[a,b,c,d,e] | The evidence suggests that SBRT does not increase 3 years local recurrence free survival |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 years regional nodal recurrence free survival | 963 per 1,000 | **1000 per 1,000** (663 to 1,000) | **HR 2.89** (0.33 to 25.55) | 58 (1 RCT) | ⊕⊕◯◯ Low[a,b,c,d,e] | The evidence suggests that SBRT does not increase 3 years regional nodal recurrence free survival |
| 3 years distant metastasis free survival | 926 per 1,000 | **628 per 1,000** (75 to 1,000) | **HR 0.38** (0.03 to 4.18) | 58 (1 RCT) | ⊕⊕◯◯ Low[a,b,c,d,e] | The evidence suggests that SBRT does not increase 3 years distant metastasis free survival |

*__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. Only some concern was present in the selection of the reported result domain
b. One study only available for the outcome
c. Eligibility criteria for inclusion in the review was satisfied by the study
d. 95% CI passes through the line of no effect and OIS (optimal information size) for dichotomous variable has not been met (>2000)
e. <10 studies were included in the analysis, hence no funnel plots were made. No other reason to suspect publication bias
f. High risk of bias owing to deviations from intended interventions and missing outcome data
g. All domains of ROB were rated as low risk of bias
h. Although 95% does not cross the point of no effect, OIS has not been achieved for the dichotomous variable (>2000)
i. 95% CI passes through the line of no effect and OIS for the continuous variable has not been met (>400)

## Evidence Profile

**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)
**Setting:** Tertiary Care Hospital
**Intervention:** SBRT
**Comparison:** Surgery (Limited Resection)

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With Surgery (Limited Resection) | With SBRT | | Risk with Surgery (Limited Resection) | Risk difference with SBRT |
| **1-year overall survival** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[a] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[a,b,c,d,e] | 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[f] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁◯◯◯ Very low[b,c,d,e,f] | 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[g] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⊕⊕◯◯ Low[b,c,d,e,g] | 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[g] | not serious[b] | not serious[c] | serious[h] | none[e] | ⊕⊕⊕◯ Moderate[b,c,e,g,h] | 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[f] | not serious[b] | not serious[c] | very serious[i] | none[e] | ⊕◯◯◯ Very low[b,c,e,f,i] | 7 | 13 | - | 7 | MD **0.1 higher** (0.17 lower to 0.37 higher) |
| **3 months quality of life** | | | | | | | | | | | |
| 18 (1 RCT) | serious[f] | not serious[b] | not serious[c] | very serious[i] | none[e] | ⊕◯◯◯ Very low[b,c,e,f,i] | 6 | 12 | - | 6 | MD **0** (0.29 lower to 0.29 higher) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **6 months quality of life** | | | | | | | | | | | |
| 14 (1 RCT) | serious[f] | not serious[b] | not serious[c] | very serious[i] | none[e] | ⨁◯◯◯ Very low[b,c,e,f,i] | 4 | 10 | - | 4 | MD **0** (0.45 lower to 0.45 higher) |
| **Deterioration in global health/QoL** | | | | | | | | | | | |
| 19 (1 RCT) | not serious[g] | not serious[b] | not serious[c] | serious[h] | none[e] | ⨁⨁⨁◯ Moderate[b,c,e,g,h] | 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) |
| **3 years recurrence free survival** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[a] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[a,b,c,d,e] | 21/27 (77.8%) | 26/31 (83.9%) | **HR 0.69** (0.21 to 2.28) | 21/27 (77.8%) | **132 fewer per 1,000** (from 507 fewer to 190 more) |
| **3 years local recurrence free survival** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[a] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[a,b,c,d,e] | 27/27 (100.0%) | 30/31 (96.8%) | **RR 0.97** (0.89 to 1.06) | 27/27 (100.0%) | **30 fewer per 1,000** (from 110 fewer to 60 more) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3 years regional nodal recurrence free survival** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[a] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[a,b,c,d,e] | 26/27 (96.3%) | 27/31 (87.1%) | **HR 2.89** (0.33 to 25.55) | 26/27 (96.3%) | **37 more per 1,000** (from 300 fewer to 37 more) |
| **3 years distant metastasis free survival** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[a] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[a,b,c,d,e] | 25/27 (92.6%) | 30/31 (96.8%) | **HR 0.38** (0.03 to 4.18) | 25/27 (92.6%) | **298 fewer per 1,000** (from 851 fewer to 74 more) |
| **Grade 3 dyspnoea** | | | | | | | | | | | |
| 58 (1 RCT) | not serious[g] | not serious[b] | not serious[c] | very serious[d] | none[e] | ⨁⨁◯◯ Low[b,c,d,e,g] | 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. Only some concern was present in the selection of the reported result domain
b. One study only available for the outcome
c. Eligibility criteria for inclusion in the review was satisfied by the study
d. 95% CI passes through the line of no effect and OIS (optimal information size) for dichotomous variable has not been met (>2000)
e. <10 studies were included in the analysis, hence no funnel plots were made. No other reason to suspect publication bias
f. High risk of bias owing to deviations from intended interventions and missing outcome data
g. All domains of ROB were rated as low risk of bias
h. Although 95% does not cross the point of no effect, OIS has not been achieved for the dichotomous variable (>2000)
i. 95% CI passes through the line of no effect and OIS for the continuous variable has not been met (>400)

## 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.<br><br>**Strength**: Conditional<br>**Certainty of evidence** – Low | |

**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

## 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:

- T stage
- Nodal involvement
- Histology
- PDL1
- Smoking status
- Type of EGFR mutation

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

6. Overall survival (6 studies)
7. Adverse effects (7 studies)
8. Quality of life (3 studies)
9. Disease free survival (9 studies)
10. Response Rate (No studies)
11. Cost (No studies)

### 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

**Outcomes**

The following critical and important outcomes were evaluated:

6. Overall survival (Critical outcome)
7. Adverse effects (Critical outcome)
8. Quality of life (Critical outcome)
9. Disease free survival (Important outcome)
10. Response rate (Important outcome)
11. Cost (Important outcome)

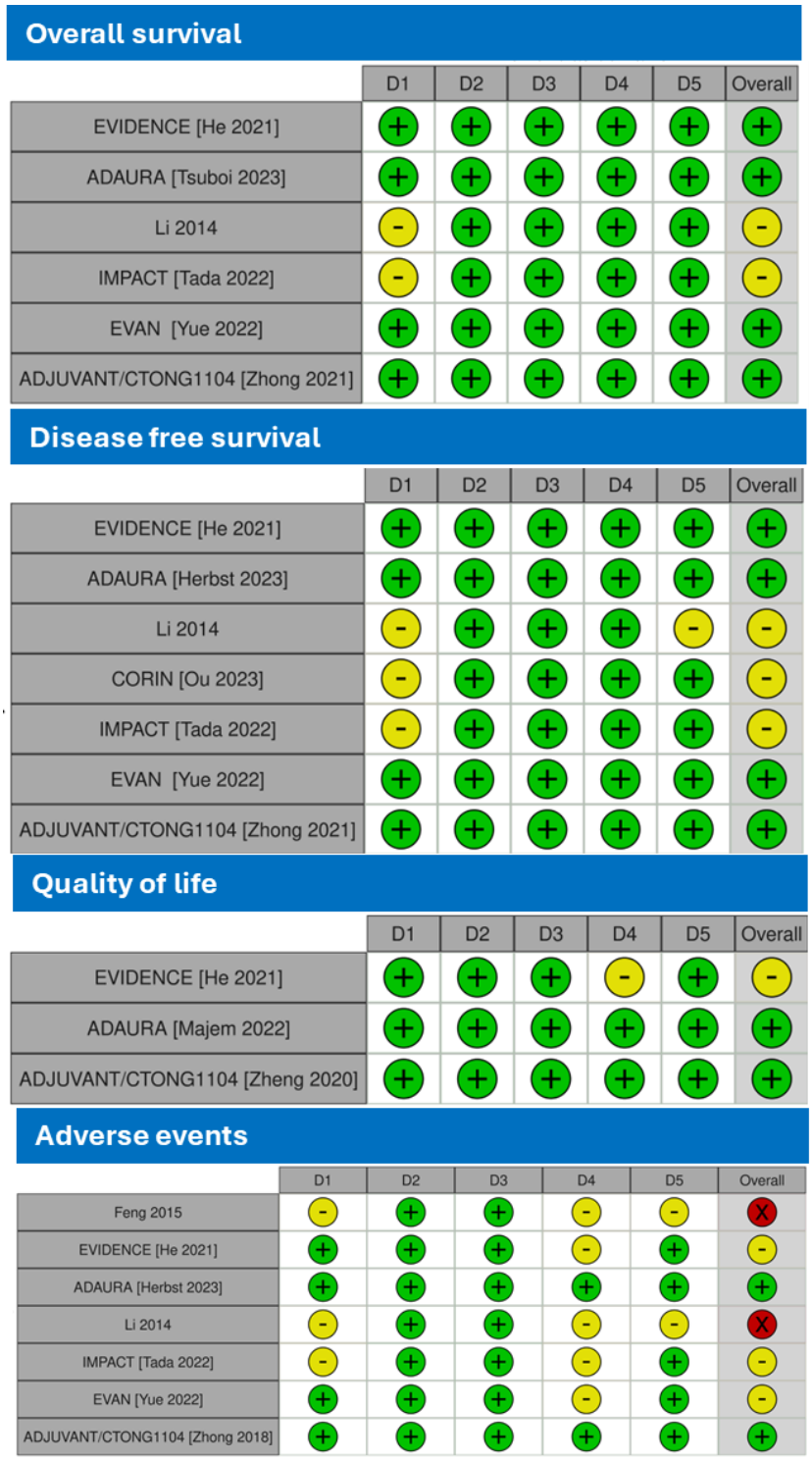
## Critical Outcome reviewed and their MCID provided by GDG

| 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 |

## PICO

| Framework | Inclusion criteria |
|---|---|
| Population | Patients diagnosed with early-stage non-small cell lung cancer (NSCLC) with an EGFR mutation<br>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<br>Subgroups: Adjuvant TKI therapy e.g. Gefitinib/Erlotinib/Afatinib/Osimertinib |
| Comparator | Chemotherapy alone or observation<br>Subgroups: 1. chemotherapy vs observation |
| Outcome | Overall survival (Critical outcome)<br>Adverse effects (Critical outcome)<br>Quality of life (Critical outcome)<br>Disease free survival (Important outcome)<br>Response rate (Important outcome)<br>Cost (Important outcome) |

## 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 |

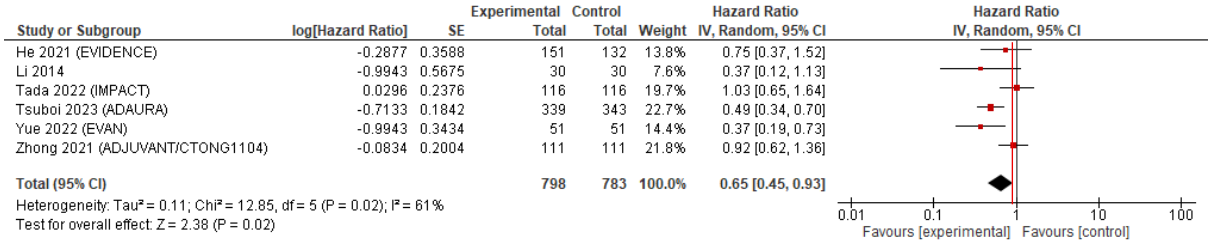
| | |
|---|---|
| + | Low risk |
| - | Some concerns |
| X | High risk |

## Desirable Effects

### Overall Survival

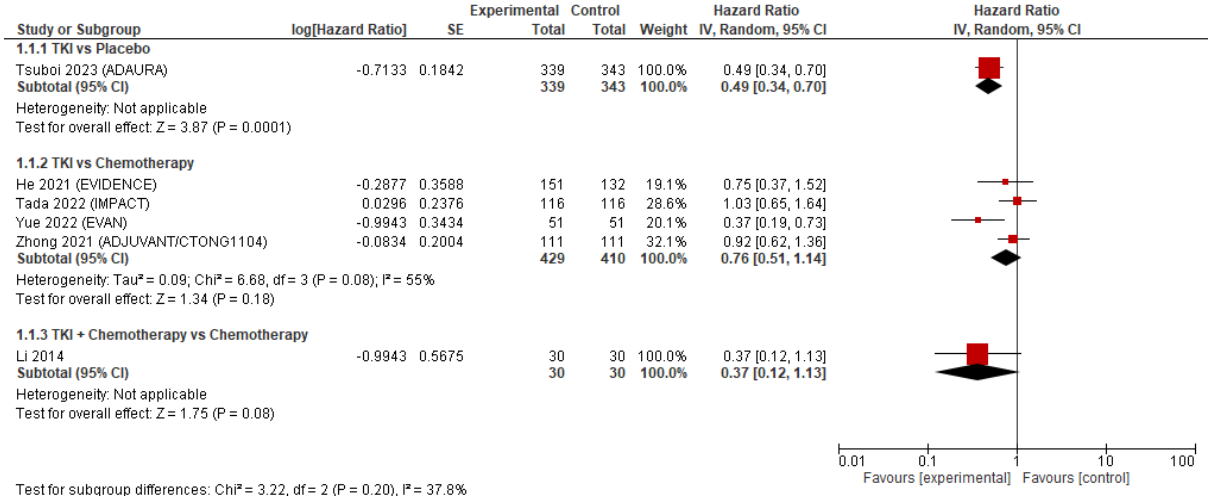
The evidence from six trials (total ≈1,581 patients; 798 experimental vs 783 control) shows that TKI ± chemotherapy reduced the hazard of death by about 35% versus chemotherapy/observation (HR 0.65, 95% CI 0.45–0.93; Z=2.38, p=0.02) in patients with early-stage non-small cell lung cancer (NSCLC) indicating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

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



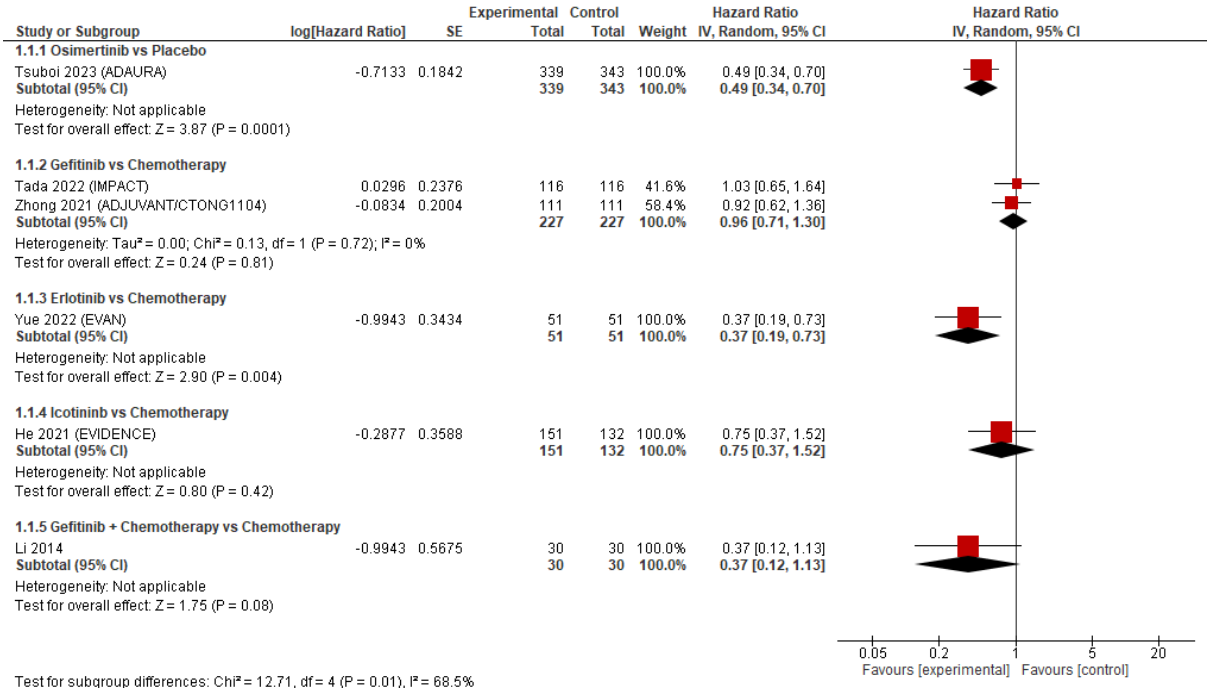

Red line denoted MCID of 5% (absolute survival gain)

### Subgroup analysis of overall survival outcome based on type of comparators

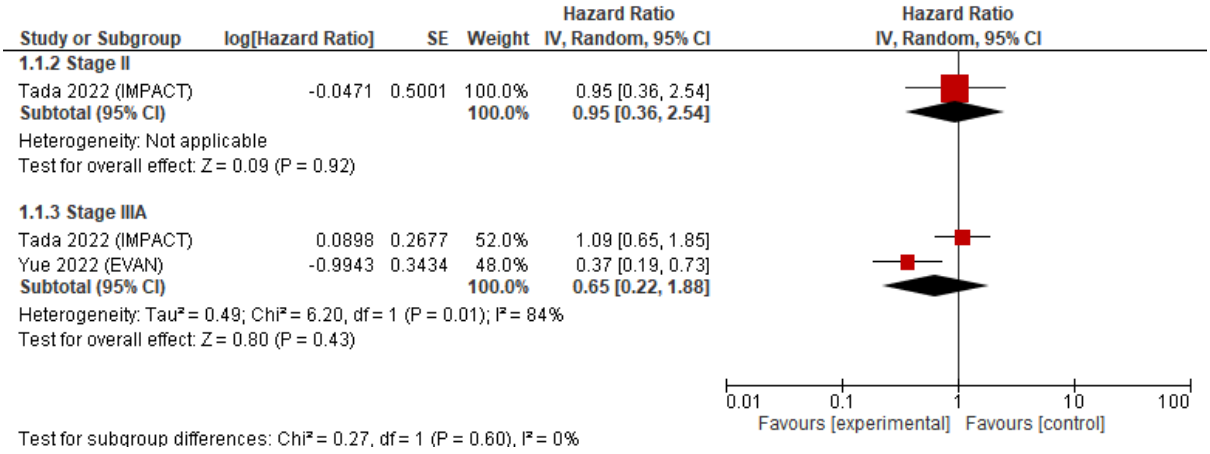



The test for subgroup differences is non-significant (p=0.20), meaning there is no reliable evidence that the effect truly differs across subgroups

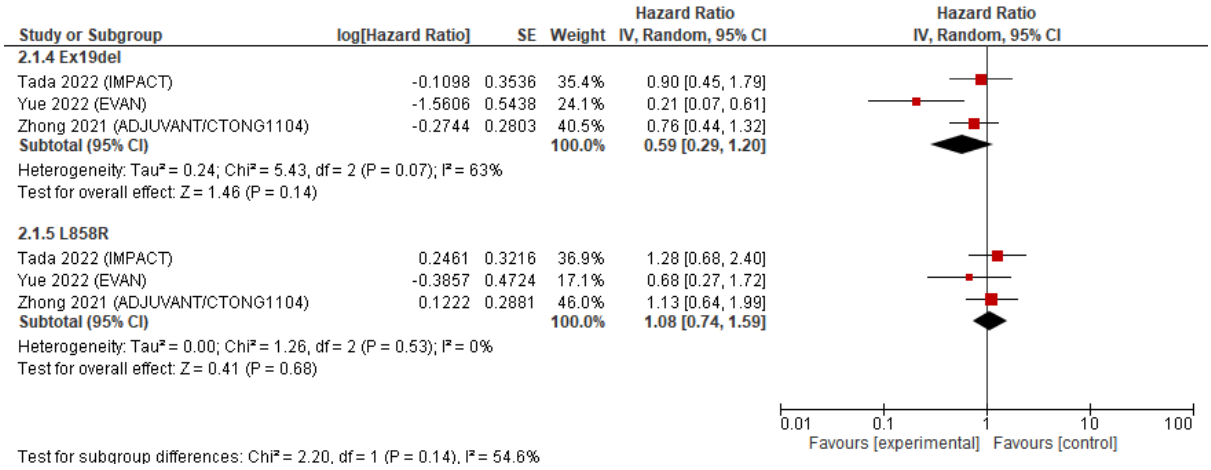
## Subgroup analysis of overall survival outcome based on TKIs and comparators




## Subgroup analysis of overall survival outcome based on staging of NSCLC (TKI vs Chemotherapy)

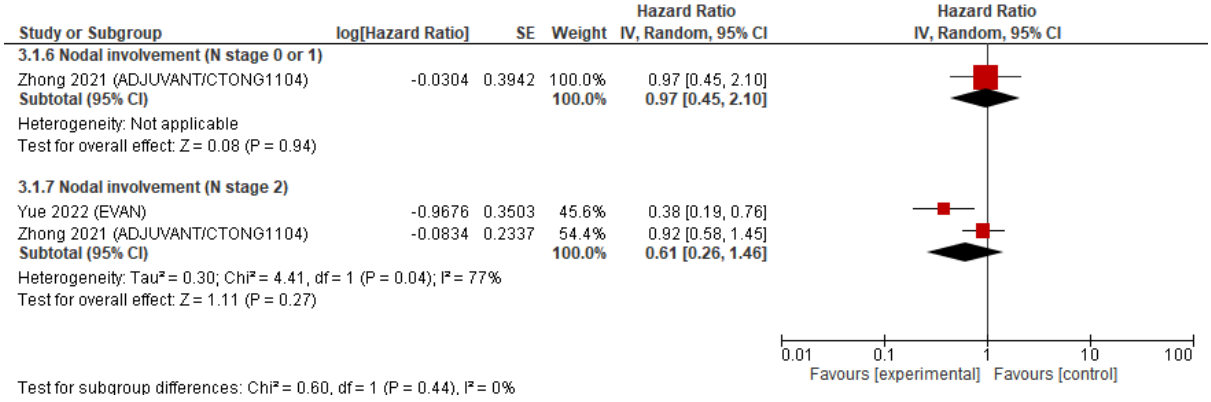


## Subgroup analysis of overall survival outcome based on type of EGFR mutation (TKI vs Chemotherapy)




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

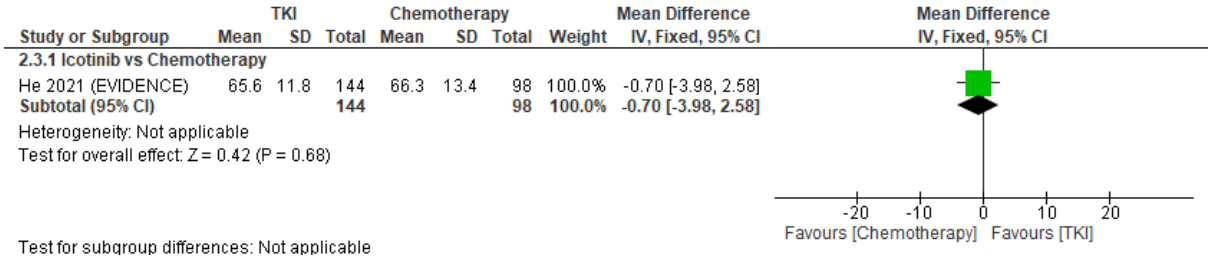
## Subgroup analysis of overall survival outcome based on nodal involvement (TKI vs Chemotherapy)



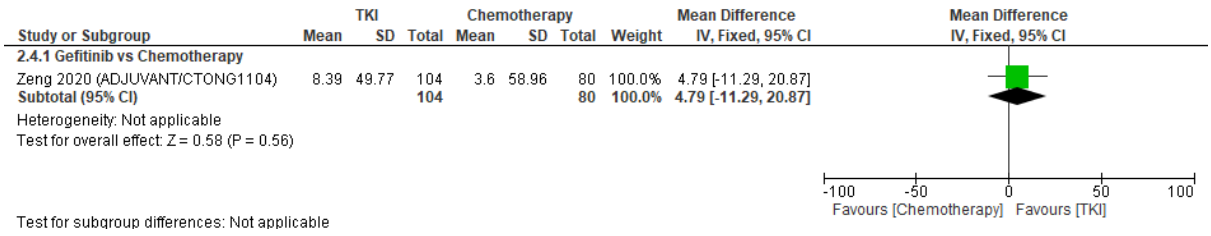

The test for subgroup differences is non-significant (p=0.44), meaning there is no reliable evidence that the effect truly differs across subgroups

**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

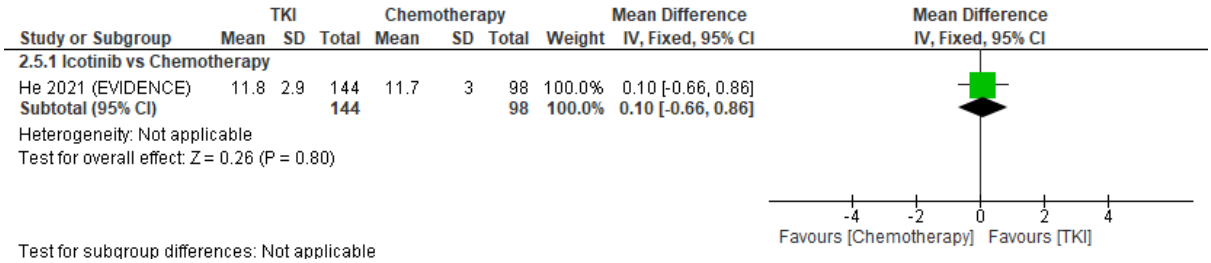



QoL (FACT-L) changes in QoL score at 141 weeks from baseline based on type of TKI and comparator

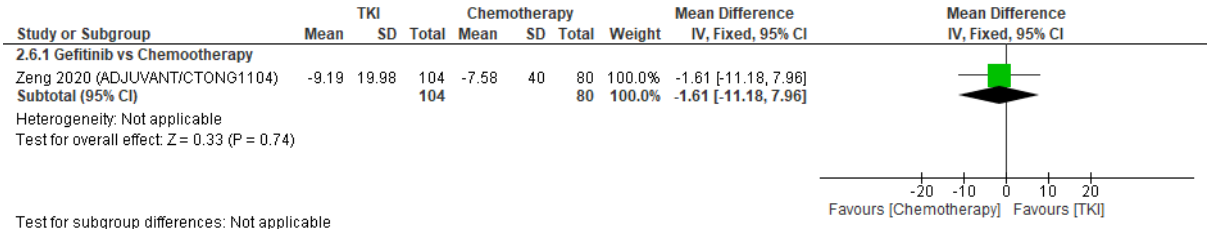



He et al presented the mean QoL score at the end of the 36-week follow-up period, while Zeng et al presented mean changes in QoL score at 141 weeks from baseline.

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



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

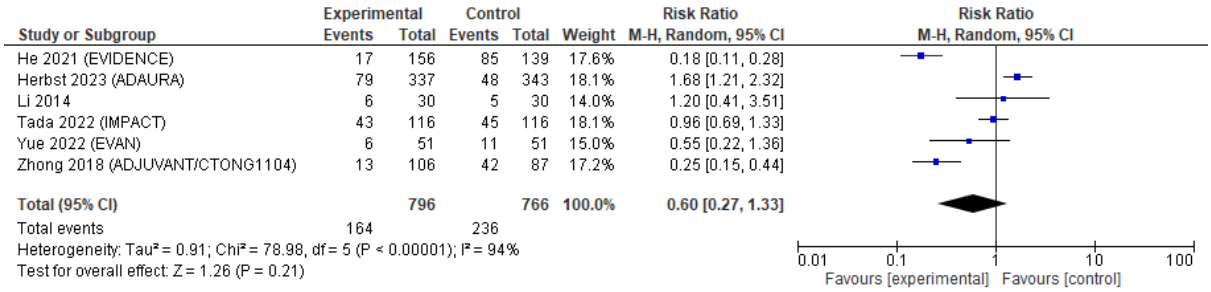



He et al presented the mean QoL score at the end of the 36-week follow-up period, while Zeng et al presented mean changes in QoL score at 141 weeks from baseline.

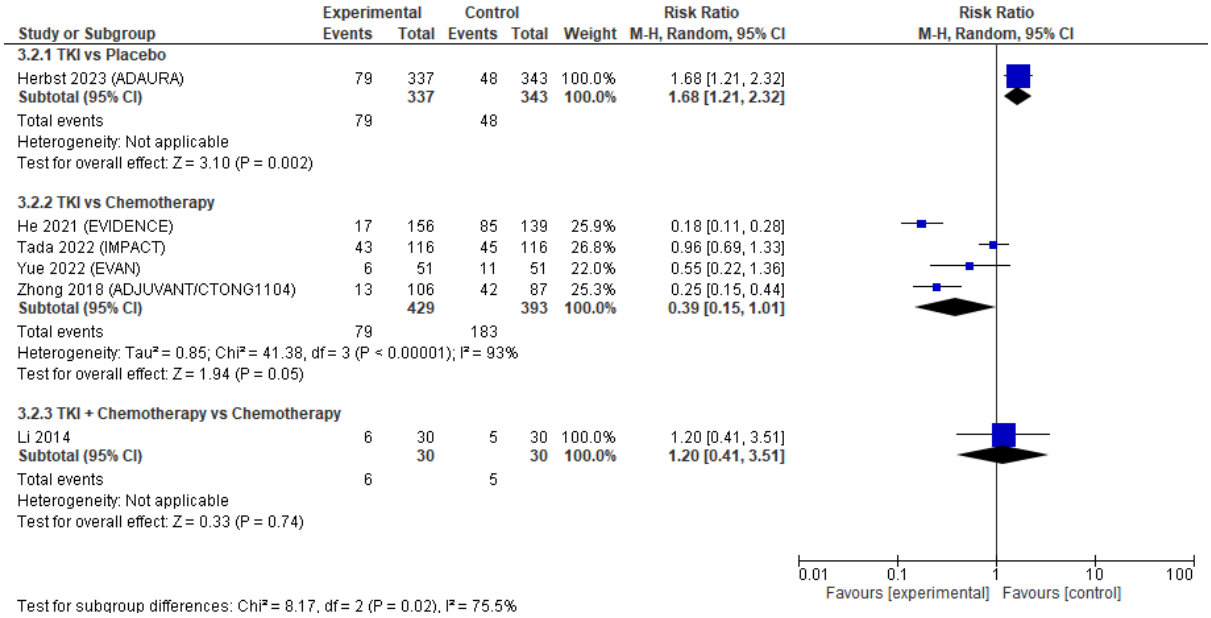
## Undesirable Effects

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, diarrhea, 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).

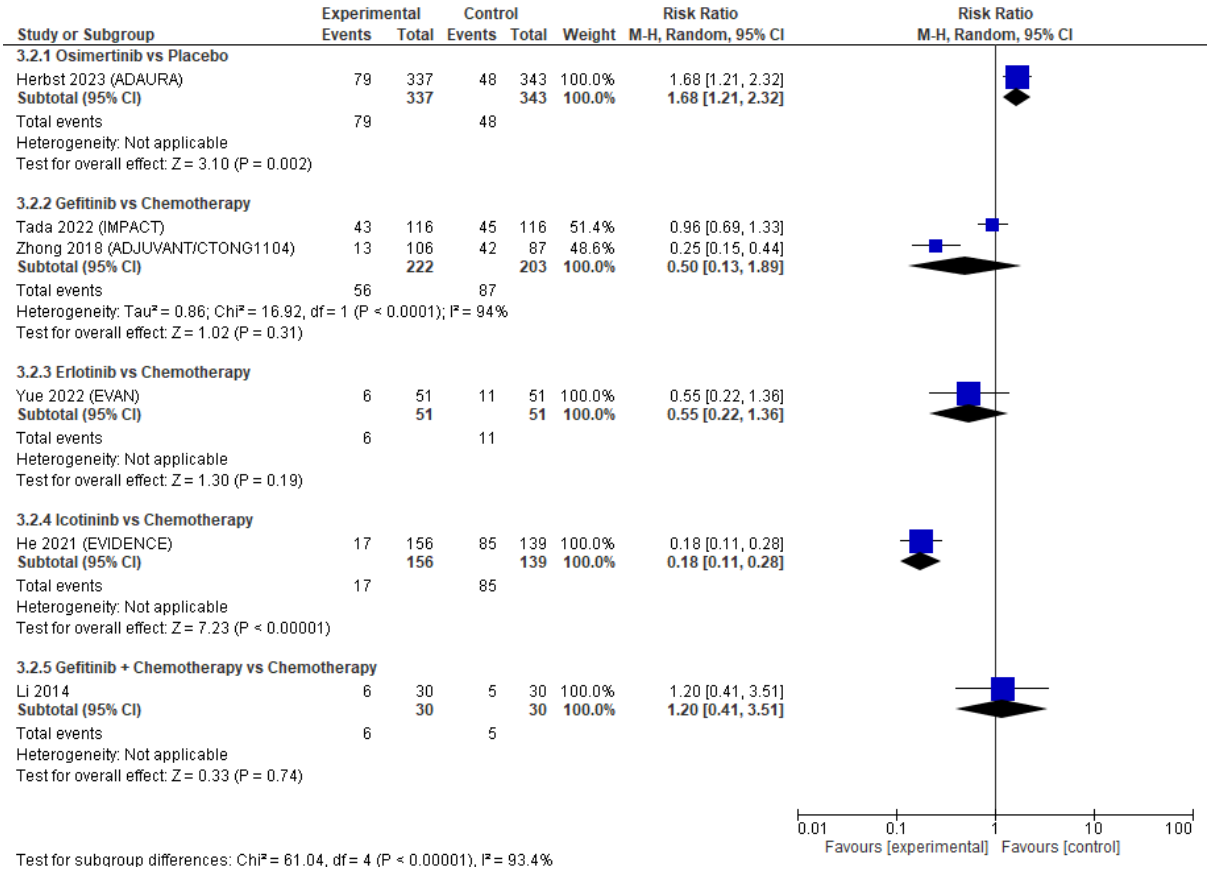
### Outcome: Adverse events Grade 3 or more (TKI ± Chemotherapy vs. Chemotherapy or Observation)




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



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



**Summary of findings: Summary of findings: Overall survival outcome**

**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) | ⨁⨁◯◯ Low | 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[a] | TKI ± Chemotherapy may result in little to no difference in hRQoL (FACT-L) changes in score at 141 weeks from baseline. |

**Summary of findings: Summary of findings: Overall survival outcome**

**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** | | | | |
| 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 | 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 | 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 | The evidence is very uncertain about the effect of TKI ± Chemotherapy on adverse events of Grade 3 or more. |

-

**Summary of findings: Summary of findings: Overall survival outcome**

**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** | | | | |

*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

-

**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 | not serious | serious[a] | not serious | serious[b] | none | 144 | 98 | - | MD 0.7 lower (3.98 lower to 2.58 higher) | ⊕⊕◯◯ Low[a,b] |
| **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[a] | not serious | serious[b] | none | 104 | 80 | - | MD 4.79 higher (11.29 lower to 20.87 higher) | ⊕⊕◯◯ Low[a,b] |

| 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) | |
| **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[a] | not serious | serious[b] | none | 144 | 98 | - | MD 0.1 higher (0.66 lower to 0.86 higher) | ⊕⊕◯◯ Low[a,b] |
| **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[a] | not serious | serious[b] | none | 104 | 80 | - | MD 1.61 lower (11.18 lower to 7.96 higher) | ⊕⊕◯◯ Low[a,b] |
| **Adverse events of Grade 3 or more** | | | | | | | | | | | |
| 6 | randomised trials | not serious | serious[c] | not serious | serious[d] | 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. Only one study in this group
b. Wide confidence interval crossing the line of no effect.
c. High heterogeneity and non-overlapping confidence intervals among individual studies
d. Wide confidence interval crossing the line of no effect.
e. Possibility of publication bias based on Egger's regression test (see below)

**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 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.<br><br>**Strength**: Strong<br>**Certainty of evidence** – High for efficacy and very low for side effects | |

**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?**

## 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:

- Type of mutation
- Metastatic sites
- Gender
- Smoking status

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

12. Overall survival (6 studies)
13. Adverse effects (5 studies)
14. Progression free survival (6 studies)
15. Response Rate (4 studies)
16. Quality of life (4 studies)
17. Cost (4 studies)

### Intervention

2nd & 3rd generation TKI (Subgroup: Afatanib/Dacomitinib/ Osimertinib)

**Comparator**

1st generation TKI 1. Geftinib/Erlotinib 2. Geftinib/Erlotinib with chemotherapy 3. Geftinib/Erlotinib with antiangiogenic agents (Bevacizumab/ Ramucirumab)

**Outcome**

The following critical and important outcomes were evaluated:

12. Overall survival (Critical outcome)
13. Adverse effects (Critical outcome)
14. Progression free Survival (Important outcome)
15. Response Rate (Important outcome)
16. Quality of life (Important outcome)
17. Cost (Important outcome)

## Critical Outcome reviewed and their MCID provided by GDG

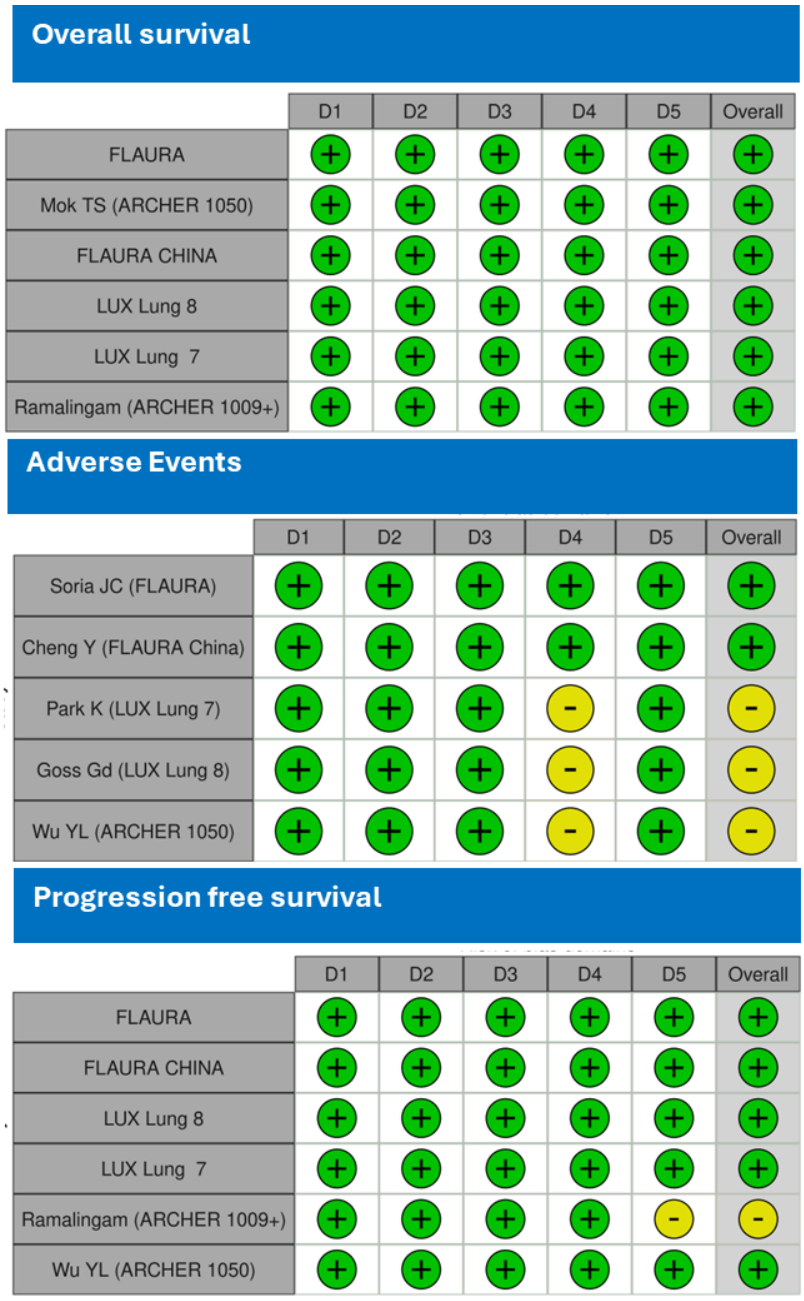
| Sr. No | Critical outcome reviewed | What does it measure | MCID decided by GDG |
|---|---|---|---|
| 1 | Overall Survival | OS (Proportion of people who have survived at a particular time point) | 5% at 2 years |
| | | OS (Proportion increase in median survival) | 6 months |
| 2 | Adverse events | Proportion difference in grade 3 or higher AEs | 10% |

## Review 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?

| Framework | Inclusion criteria |
|---|---|
| Population | Patients with advanced NSCLC harbouring 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)<br>Adverse effects (Critical Outcome)<br>Progression free survival (Important outcome)<br>Response rate (Important outcome) |

| | |
|---|---|
| | Quality of life (Important outcome)<br>Cost (Important outcome) |

## 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 |

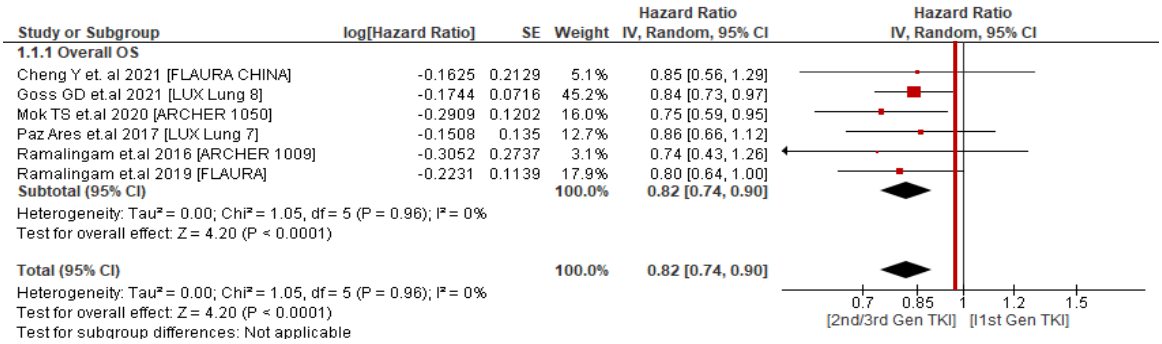
| | |
|---|---|
| + | Low risk |
| - | Some concerns |
| X | High risk |

## Desirable Effects

### Overall Survival

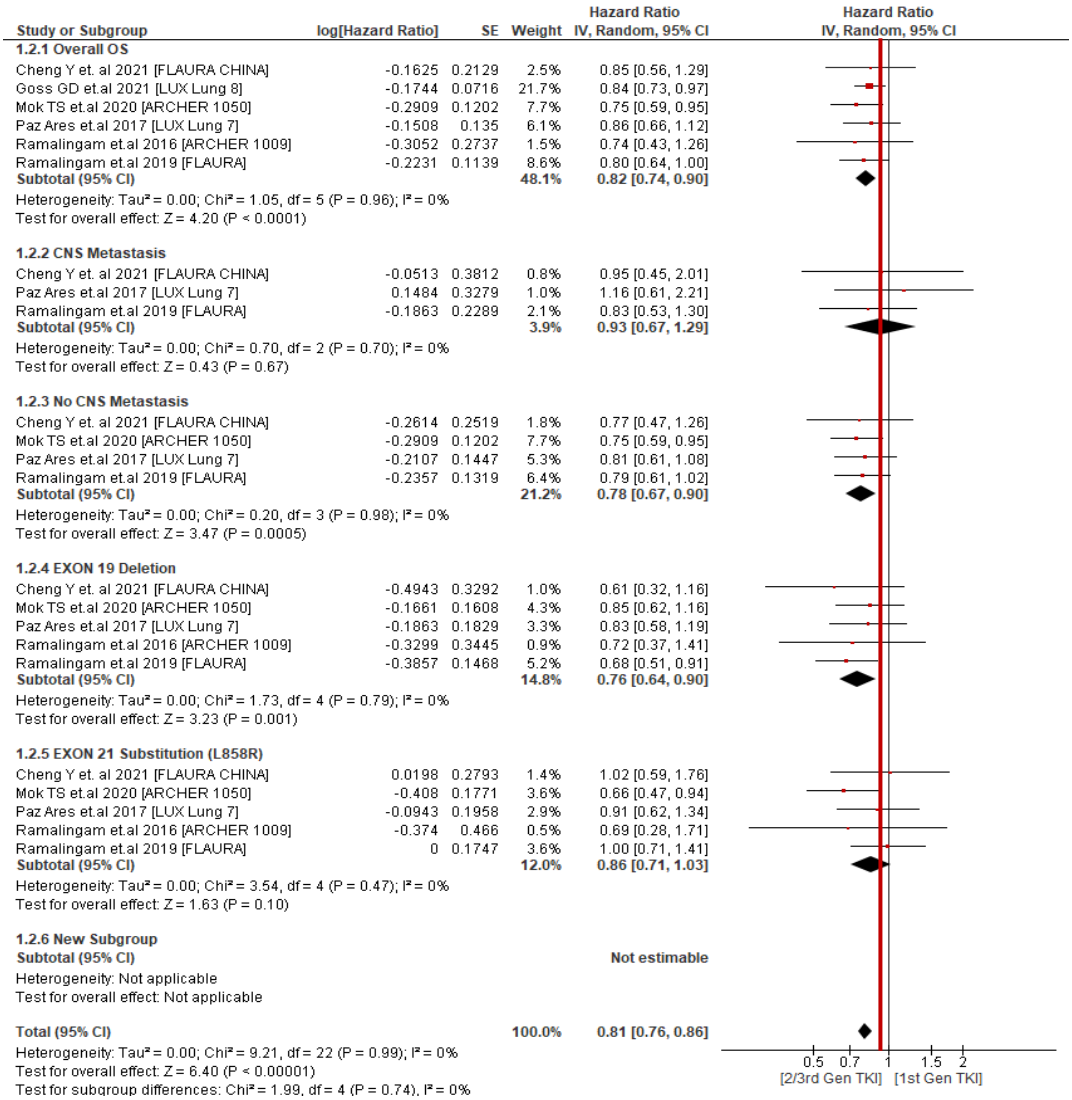
A pooled analysis of 6 randomized controlled trials shows a statistically significant and clinically meaningful improvement in overall survival with second- and third-generation EGFR TKIs compared with first-generation TKIs (with or without chemotherapy/anti-angiogenic agents): HR 0.82 (95% CI 0.74–0.90; 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.

### Overall survival (OS) using HR




MCID line is in red

**Subgroup analysis;** CNS metastasis & type of mutation

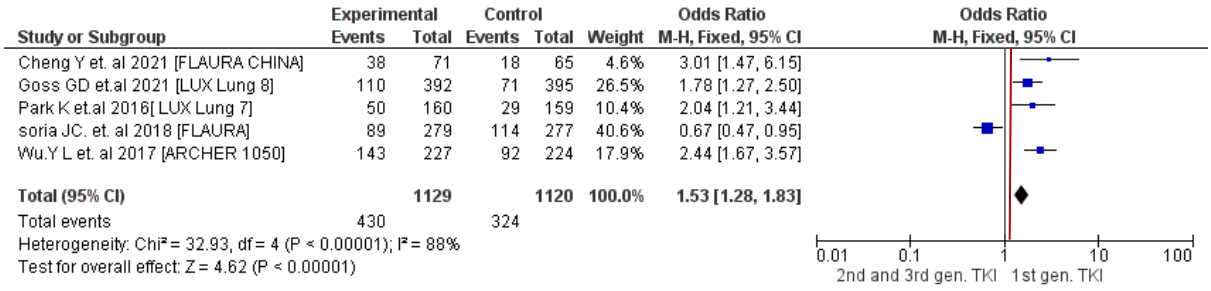



MCID line is in red

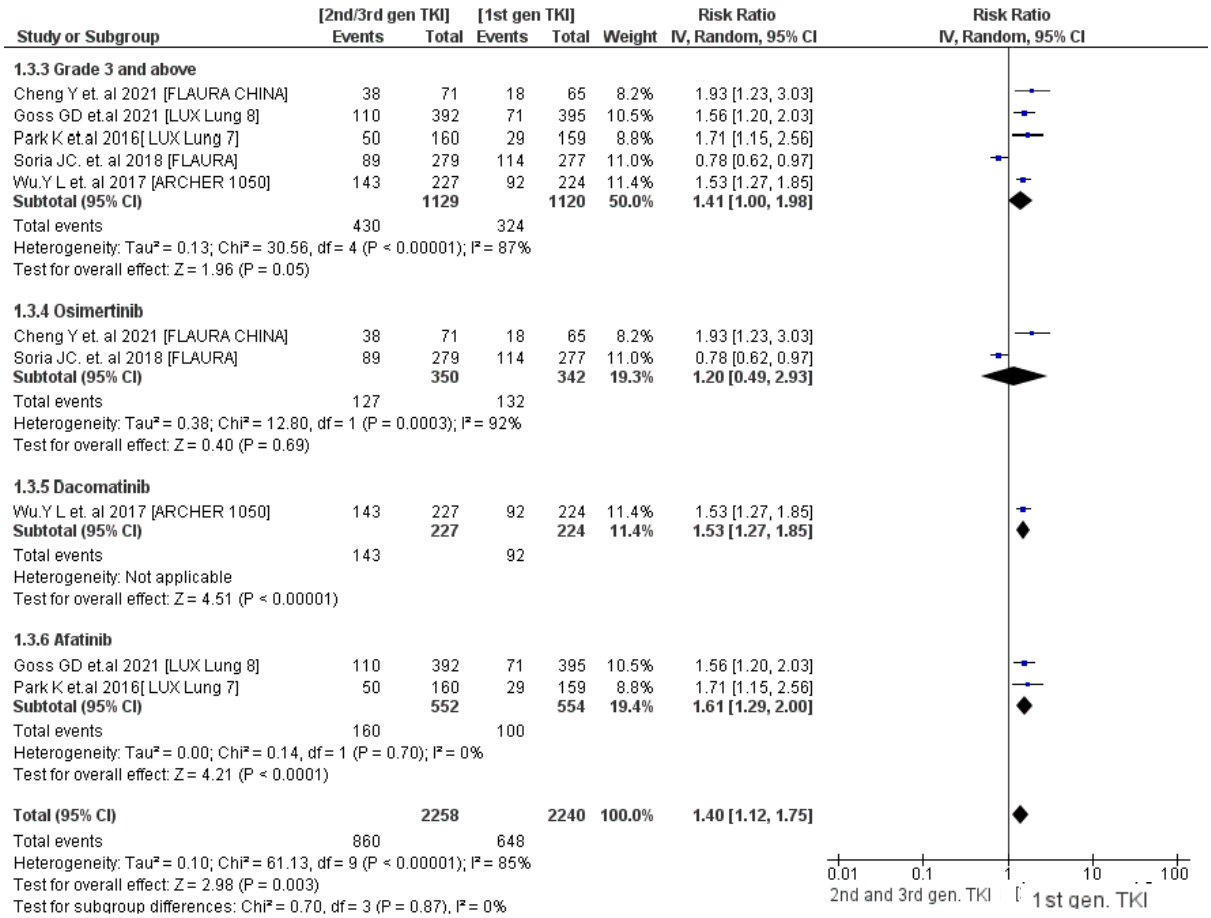
## Undesirable Effects

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).

### Grade 3 and above adverse events




### Subgroup analysis based on type of TKIs



## Summary of findings:

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

**Patient or population:** NSCLC with EGFR mutation

**Setting:** Indian

**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%)<br>FU 26 to 48 months | - | **HR 0.82**<br>(0.74 to 0.90) | 2359<br>(6 RCTs) | ⨁⨁⨁⨁<br>High | |
| Adverse events grade 3 or more | 289 per 1,000 | **384 per 1,000**<br>(343 to 427) | **OR 1.53**<br>(1.28 to 1.83) | 2249<br>(5 RCTs) | ⨁⨁◯◯<br>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.

***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

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

**Patient or population: NSCLC with EGFR mutation**

**Setting: Indian**

**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. As per SOP guidance, when less than two-third of the contributing weight comes from low-risk studies, a downgrade by one level is warranted.

b. Significant inconsistency among the trials ($i^2$ is 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<br><br>**Strength:** Conditional<br>**Certainty of evidence** – High for efficacy & Low for side effects | |

**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?**

## 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:

- Histology
- PD-L1 status
- Age
- Smoking status

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

18. Overall survival (22 studies)
19. Adverse effects (23 studies)
20. Progression free survival (22 studies)
21. Response Rate (23 studies)
22. Quality of life (11 studies)
23. Cost (No studies)

### Intervention

Immunotherapy with/without chemotherapy (platinum-based doublet chemotherapy)

### Comparator

Chemotherapy alone (Platinum-based doublet chemotherapy)

### Outcome

The following critical and important outcomes were evaluated:

1. Overall survival (Critical Outcome)
2. Adverse effects (Critical Outcome)
3. Progression free survival (Important Outcome)
4. Response Rate (Important Outcome)

5. Quality of life (Important Outcome)
6. 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% |

# PICO

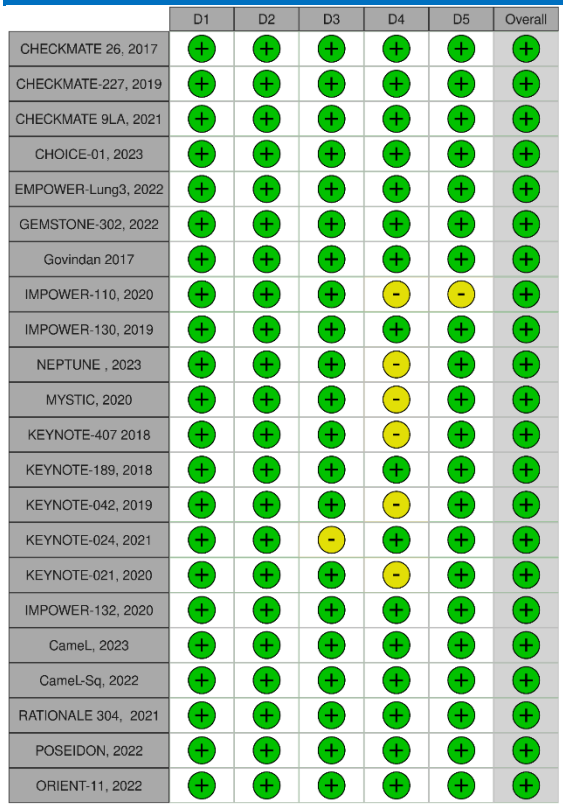
| Framework | Inclusion criteria |
|---|---|
| Population | Patients with advanced NSCLC and no oncogenic driver alteration<br><br>Subgroups: Histology, PD-L1 status, Age, Smoking status |
| Intervention | Immunotherapy with/without chemotherapy (platinum-based doublet chemotherapy)<br>Subgroups:<br>1. Combination immunochemotherapy vs. Mono-immunotherapy<br>2. Immunotherapy drugs (Pembrolizumab, Atezolizumab, Nivolumab, and Durvalumab)<br>3. Dual Immunotherapy combinations (a. Nivolumab and Ipilimumab b. Durvalumab and Tremelimumab |
| Comparator | Chemotherapy alone (Platinum-based doublet chemotherapy) |
| Outcome | Overall survival (Critical outcome)<br>Adverse effects (Critical outcome)<br>Progression-free survival (Important outcome)<br>Response rate (Important outcome)<br>Quality of life (Important outcome)<br>Cost (Important outcome) |

## 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** |
| X | **High risk** |

# Desirable Effects

## Overall Survival

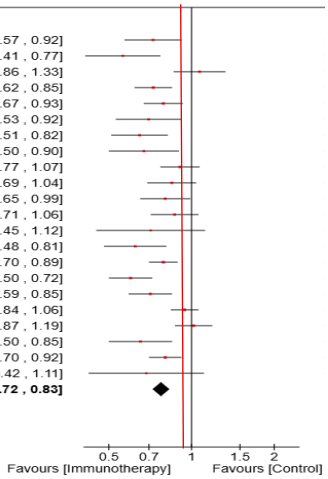
The pooled evidence from 23 randomized controlled trials shows that immunotherapy (alone or combined with chemotherapy) significantly improves overall survival in patients with advanced NSCLC without oncogenic driver alterations, producing a 23% relative reduction in the hazard of death compared with 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.

Forest plot: Overall survival (OS) using HR

| Study or Subgroup | log[HR] | SE | Immunotherapy Total | Chemotherapy/Control Total | Weight | Hazard ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Primary Analysis** | | | | | | |
| CameL 2023 | -0.3228 | 0.1221 | 205 | 207 | 4.1% | 0.72 [0.57 , 0.92] |
| CameL-Sq 2022 | -0.5765 | 0.1608 | 193 | 196 | 3.1% | 0.56 [0.41 , 0.77] |
| CHECKMATE 26 2017 | 0.0672 | 0.1112 | 271 | 270 | 4.5% | 1.07 [0.86 , 1.33] |
| CHECKMATE 9 LA 2021 | -0.3203 | 0.0805 | 361 | 358 | 5.7% | 0.73 [0.62 , 0.85] |
| CHECKMATE-227 2019 | -0.2365 | 0.0837 | 1056 | 583 | 5.5% | 0.79 [0.67 , 0.93] |
| CHOICE-01 2023 | -0.3591 | 0.1407 | 309 | 156 | 3.6% | 0.70 [0.53 , 0.92] |
| EMPOWER-Lung3 2022 | -0.4359 | 0.1211 | 312 | 154 | 4.2% | 0.65 [0.51 , 0.82] |
| GEMSTONE 2022 | -0.3993 | 0.1499 | 320 | 159 | 3.3% | 0.67 [0.50 , 0.90] |
| Govindan 2017 | -0.0969 | 0.0839 | 388 | 361 | 5.5% | 0.91 [0.77 , 1.07] |
| IMPOWER 110 2020 | -0.1659 | 0.1047 | 277 | 277 | 4.7% | 0.85 [0.69 , 1.04] |
| IMPOWER-130 2019 | -0.2204 | 0.1073 | 483 | 240 | 4.7% | 0.80 [0.65 , 0.99] |
| IMPOWER-132 2020 | -0.1421 | 0.1022 | 292 | 286 | 4.8% | 0.87 [0.71 , 1.06] |
| KEYNOTE-021 2020 | -0.3426 | 0.2326 | 60 | 63 | 1.8% | 0.71 [0.45 , 1.12] |
| KEYNOTE-024 2021 | -0.4723 | 0.1335 | 154 | 151 | 3.8% | 0.62 [0.48 , 0.81] |
| KEYNOTE-042 2019 | -0.2366 | 0.0613 | 637 | 637 | 6.4% | 0.79 [0.70 , 0.89] |
| KEYNOTE-189 2018 | -0.5108 | 0.093 | 410 | 206 | 5.2% | 0.60 [0.50 , 0.72] |
| KEYNOTE-407 2018 | -0.3451 | 0.0931 | 278 | 281 | 5.2% | 0.71 [0.59 , 0.85] |
| MYSTIC 2020 | -0.058 | 0.0593 | 746 | 372 | 6.5% | 0.94 [0.84 , 1.06] |
| NEPTUNE 2023 | 0.0173 | 0.0799 | 410 | 413 | 5.7% | 1.02 [0.87 , 1.19] |
| ORIENT-11 2022 | -0.4278 | 0.1354 | 266 | 131 | 3.7% | 0.65 [0.50 , 0.85] |
| POSIDON 2022 | -0.22 | 0.0697 | 675 | 337 | 6.1% | 0.80 [0.70 , 0.92] |
| RATIONALE 304 2021 | -0.3792 | 0.2467 | 223 | 111 | 1.7% | 0.68 [0.42 , 1.11] |
| **Subtotal (Wald[a])** | | | **8326** | **5949** | **100.0%** | **0.77 [0.72 , 0.83]** |

Test for overall effect: Z = 7.13 (P < 0.00001)
Heterogeneity: Tau² (DL[b], 95% CI) = 0.02 [0.01 , 0.05]; Chi² = 56.94, df = 21 (P < 0.0001); I² = 63%

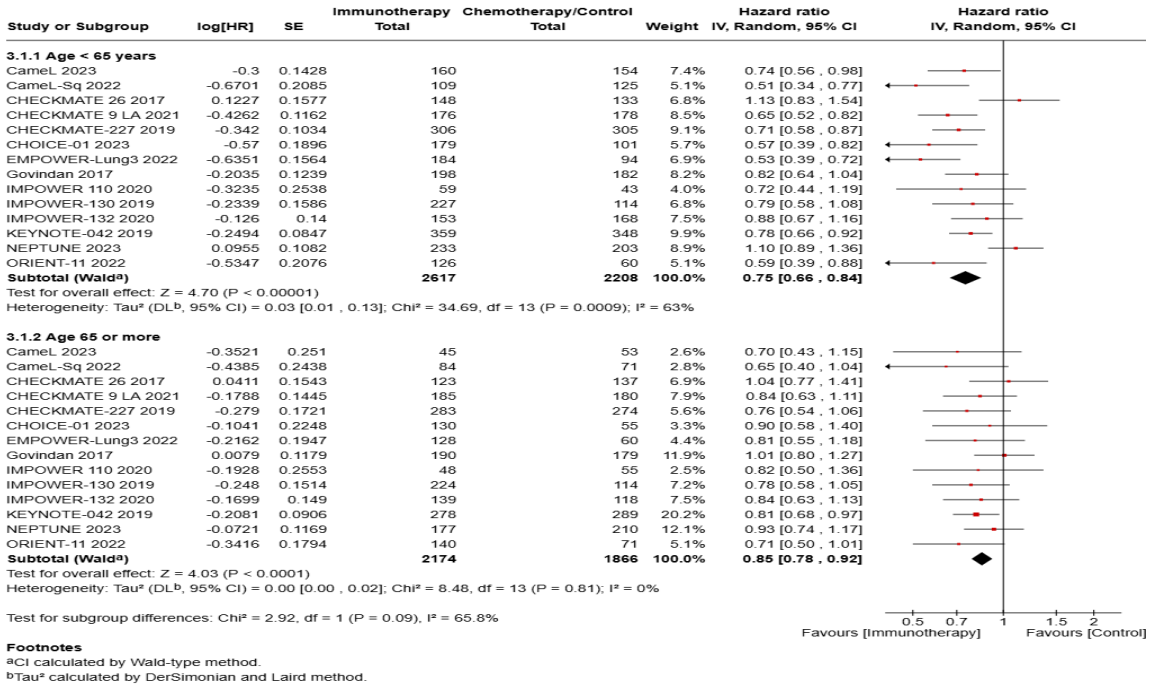
Test for subgroup differences: Not applicable




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

Red line indicated MCID provided by GDG (5%)

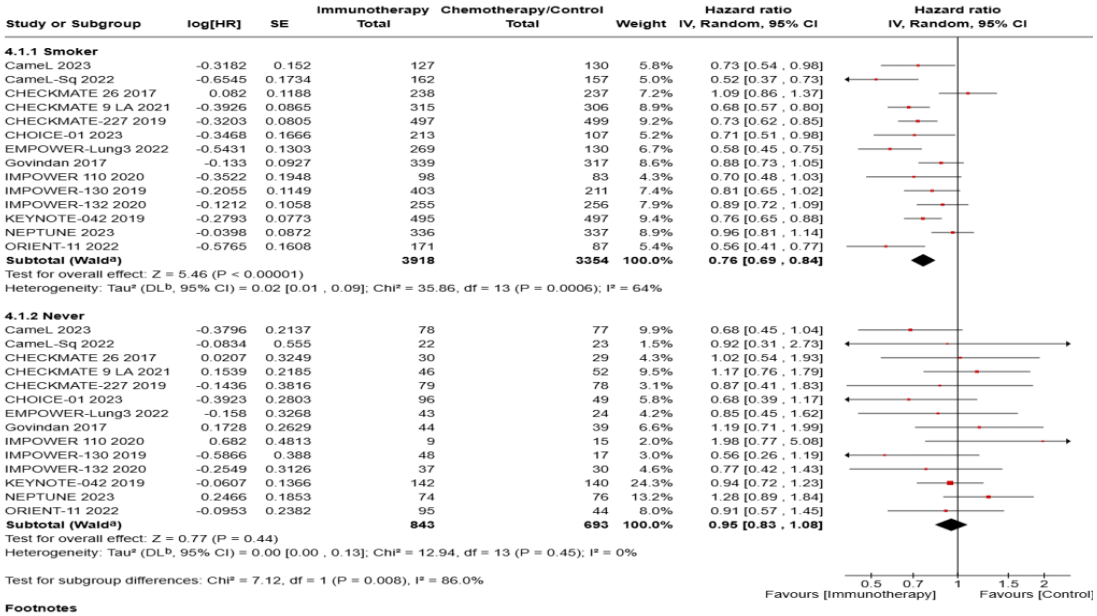
## Overall survival (hazard ratio) Subgroup for age (<65 years *vs.* > 65 years)




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

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

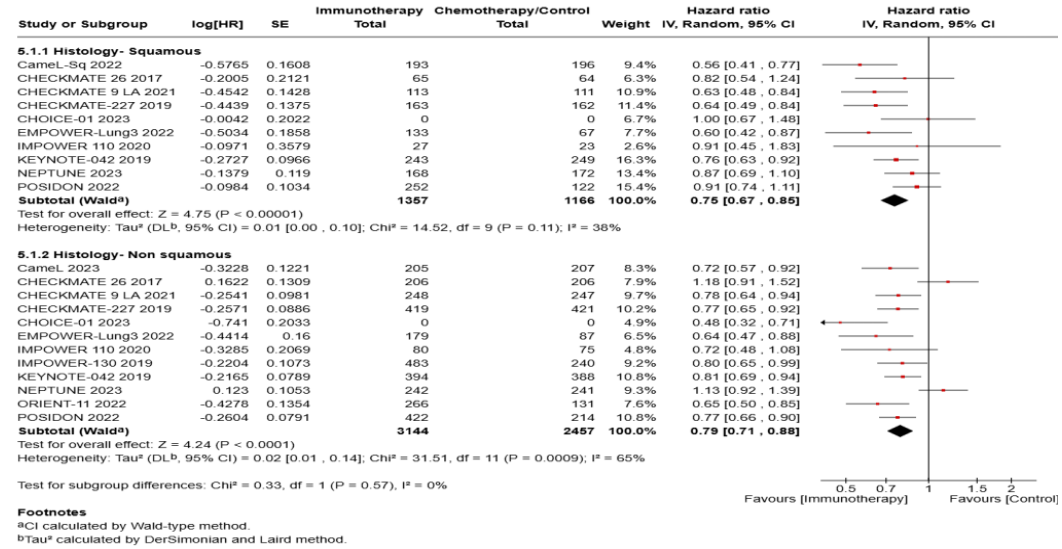
## Overall survival (hazard ratio) Subgroup for Smoking status




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

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).

## Overall survival (hazard ratio) Subgroup for Histology

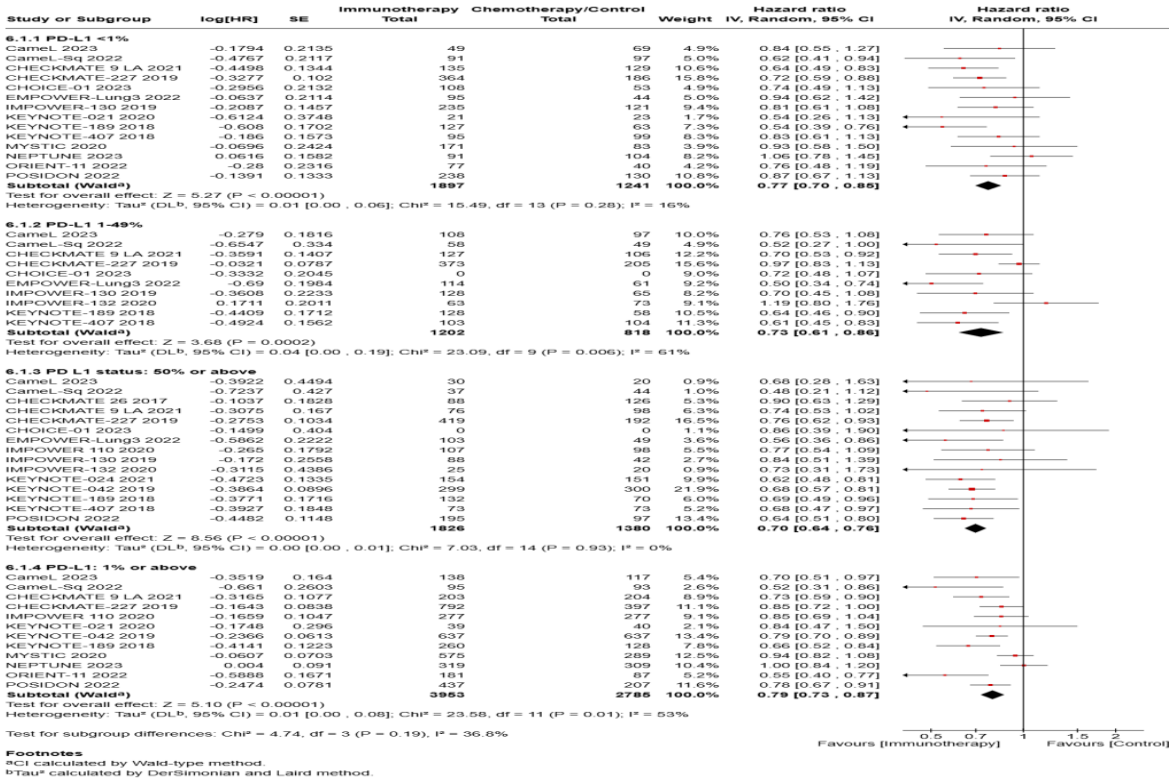


| Study or Subgroup | log[HR] | SE | Immunotherapy Total | Chemotherapy/Control Total | Weight | Hazard ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.1.1 Histology- Squamous** | | | | | | |
| CameL-Sq 2022 | -0.5765 | 0.1608 | 193 | 196 | 9.4% | 0.56 [0.41 , 0.77] |
| CHECKMATE 26 2017 | -0.2005 | 0.2121 | 65 | 64 | 6.3% | 0.82 [0.54 , 1.24] |
| CHECKMATE 9 LA 2021 | -0.4542 | 0.1428 | 113 | 111 | 10.9% | 0.63 [0.48 , 0.84] |
| CHECKMATE-227 2019 | -0.4439 | 0.1375 | 163 | 162 | 11.4% | 0.64 [0.49 , 0.84] |
| CHOICE-01 2023 | -0.0042 | 0.2022 | 0 | 0 | 6.7% | 1.00 [0.67 , 1.48] |
| EMPOWER-Lung3 2022 | -0.5034 | 0.1858 | 133 | 67 | 7.7% | 0.60 [0.42 , 0.87] |
| IMPOWER 110 2020 | -0.0971 | 0.3579 | 27 | 23 | 2.6% | 0.91 [0.45 , 1.83] |
| KEYNOTE-042 2019 | -0.2727 | 0.0966 | 243 | 249 | 16.3% | 0.76 [0.63 , 0.92] |
| NEPTUNE 2023 | -0.1379 | 0.119 | 168 | 172 | 13.4% | 0.87 [0.69 , 1.10] |
| POSIDON 2022 | -0.0984 | 0.1034 | 252 | 122 | 15.4% | 0.91 [0.74 , 1.11] |
| **Subtotal (Wald[a])** | | | **1357** | **1166** | **100.0%** | **0.75 [0.67 , 0.85]** |
| Test for overall effect: Z = 4.75 (P < 0.00001) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.01 [0.00 , 0.10]; Chi² = 14.52, df = 9 (P = 0.11); I² = 38% | | | | | | |
| **5.1.2 Histology- Non squamous** | | | | | | |
| CameL 2023 | -0.3228 | 0.1221 | 205 | 207 | 8.3% | 0.72 [0.57 , 0.92] |
| CHECKMATE 26 2017 | 0.1622 | 0.1309 | 206 | 206 | 7.9% | 1.18 [0.91 , 1.52] |
| CHECKMATE 9 LA 2021 | -0.2541 | 0.0981 | 248 | 247 | 9.7% | 0.78 [0.64 , 0.94] |
| CHECKMATE-227 2019 | -0.2571 | 0.0886 | 419 | 421 | 10.2% | 0.77 [0.65 , 0.92] |
| CHOICE-01 2023 | -0.741 | 0.2033 | 0 | 0 | 4.9% | 0.48 [0.32 , 0.71] |
| EMPOWER-Lung3 2022 | -0.4414 | 0.16 | 179 | 87 | 6.5% | 0.64 [0.47 , 0.88] |
| IMPOWER 110 2020 | -0.3285 | 0.2069 | 80 | 75 | 4.8% | 0.72 [0.48 , 1.08] |
| IMPOWER-130 2019 | -0.2204 | 0.1073 | 483 | 240 | 9.2% | 0.80 [0.65 , 0.99] |
| KEYNOTE-042 2019 | -0.2165 | 0.0789 | 394 | 388 | 10.8% | 0.81 [0.69 , 0.94] |
| NEPTUNE 2023 | 0.123 | 0.1053 | 242 | 241 | 9.3% | 1.13 [0.92 , 1.39] |
| ORIENT-11 2022 | -0.4278 | 0.1354 | 266 | 131 | 7.6% | 0.65 [0.50 , 0.85] |
| POSIDON 2022 | -0.2604 | 0.0791 | 422 | 214 | 10.8% | 0.77 [0.66 , 0.90] |
| **Subtotal (Wald[a])** | | | **3144** | **2457** | **100.0%** | **0.79 [0.71 , 0.88]** |
| Test for overall effect: Z = 4.24 (P < 0.0001) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.02 [0.01 , 0.14]; Chi² = 31.51, df = 11 (P = 0.0009); I² = 65% | | | | | | |
| 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.

## Overall survival (hazard ratio) Subgroup for PD-L1 status



| Study or Subgroup | log[HR] | SE | Immunotherapy Total | Chemotherapy/Control Total | Weight | Hazard ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **6.1.1 PD-L1 <1%** | | | | | | |
| CameL 2023 | -0.1794 | 0.2135 | 49 | 69 | 4.9% | 0.84 [0.55 , 1.27] |
| CameL-Sq 2022 | -0.4767 | 0.2117 | 91 | 97 | 5.0% | 0.62 [0.41 , 0.94] |
| CHECKMATE 9 LA 2021 | -0.4498 | 0.1344 | 135 | 129 | 10.6% | 0.64 [0.49 , 0.83] |
| CHECKMATE-227 2019 | -0.3277 | 0.102 | 364 | 186 | 15.8% | 0.72 [0.59 , 0.88] |
| CHOICE-01 2023 | -0.2956 | 0.2132 | 108 | 53 | 4.9% | 0.74 [0.49 , 1.13] |
| EMPOWER-Lung3 2022 | -0.0637 | 0.2114 | 95 | 44 | 5.0% | 0.94 [0.62 , 1.42] |
| IMPOWER-130 2019 | -0.2087 | 0.1457 | 235 | 121 | 9.4% | 0.81 [0.61 , 1.08] |
| KEYNOTE-021 2020 | -0.6124 | 0.3748 | 21 | 23 | 1.7% | 0.54 [0.26 , 1.13] |
| KEYNOTE-189 2018 | -0.608 | 0.1702 | 127 | 63 | 7.3% | 0.54 [0.39 , 0.76] |
| KEYNOTE-407 2018 | -0.186 | 0.1573 | 95 | 99 | 8.3% | 0.83 [0.61 , 1.13] |
| MYSTIC 2020 | -0.0596 | 0.2424 | 171 | 83 | 3.9% | 0.93 [0.58 , 1.50] |
| NEPTUNE 2023 | 0.0616 | 0.1582 | 91 | 104 | 8.2% | 1.06 [0.78 , 1.45] |
| ORIENT-11 2022 | -0.28 | 0.2316 | 77 | 40 | 4.2% | 0.76 [0.48 , 1.19] |
| POSIDON 2022 | -0.1391 | 0.1333 | 238 | 130 | 10.8% | 0.87 [0.67 , 1.13] |
| **Subtotal (Wald[a])** | | | **1897** | **1241** | **100.0%** | **0.77 [0.70 , 0.88]** |
| Test for overall effect: Z = 5.27 (P < 0.00001) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.01 [0.00 , 0.06]; Chi² = 15.49, df = 13 (P = 0.28); I² = 16% | | | | | | |
| **6.1.2 PD-L1 1-49%** | | | | | | |
| CameL 2023 | -0.279 | 0.1816 | 108 | 97 | 10.0% | 0.76 [0.53 , 1.08] |
| CameL-Sq 2022 | -0.6547 | 0.334 | 58 | 49 | 4.9% | 0.52 [0.27 , 1.00] |
| CHECKMATE 9 LA 2021 | -0.3591 | 0.1407 | 127 | 106 | 12.2% | 0.70 [0.53 , 0.92] |
| CHECKMATE-227 2019 | -0.0321 | 0.0787 | 373 | 205 | 15.6% | 0.97 [0.83 , 1.13] |
| CHOICE-01 2023 | -0.3332 | 0.2045 | 0 | 0 | 9.0% | 0.72 [0.48 , 1.07] |
| EMPOWER-Lung3 2022 | -0.69 | 0.1984 | 114 | 61 | 9.2% | 0.50 [0.34 , 0.74] |
| IMPOWER-130 2019 | -0.3608 | 0.2233 | 128 | 65 | 8.2% | 0.70 [0.45 , 1.08] |
| IMPOWER-132 2020 | 0.1711 | 0.2011 | 63 | 73 | 9.1% | 1.19 [0.80 , 1.76] |
| KEYNOTE-189 2018 | -0.4409 | 0.1712 | 128 | 58 | 10.5% | 0.64 [0.46 , 0.90] |
| KEYNOTE-407 2018 | -0.4924 | 0.1562 | 103 | 104 | 11.3% | 0.61 [0.45 , 0.83] |
| **Subtotal (Wald[a])** | | | **1202** | **818** | **100.0%** | **0.73 [0.61 , 0.86]** |
| Test for overall effect: Z = 3.68 (P = 0.0002) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.04 [0.00 , 0.19]; Chi² = 23.09, df = 9 (P = 0.006); I² = 61% | | | | | | |
| **6.1.3 PD-L1 status: 50% or above** | | | | | | |
| CameL 2023 | -0.3922 | 0.4494 | 30 | 20 | 0.9% | 0.68 [0.28 , 1.63] |
| CameL-Sq 2022 | -0.7237 | 0.427 | 37 | 44 | 1.0% | 0.48 [0.21 , 1.12] |
| CHECKMATE 26 2017 | -0.1037 | 0.1828 | 88 | 126 | 5.3% | 0.90 [0.63 , 1.29] |
| CHECKMATE 9 LA 2021 | -0.3075 | 0.167 | 76 | 98 | 6.3% | 0.74 [0.53 , 1.02] |
| CHECKMATE-227 2019 | -0.2753 | 0.1034 | 419 | 192 | 16.5% | 0.76 [0.62 , 0.93] |
| CHOICE-01 2023 | -0.1499 | 0.404 | 0 | 0 | 1.1% | 0.86 [0.39 , 1.90] |
| EMPOWER-Lung3 2022 | -0.5862 | 0.2222 | 103 | 49 | 3.6% | 0.56 [0.36 , 0.86] |
| IMPOWER 110 2020 | -0.265 | 0.1792 | 107 | 98 | 5.5% | 0.77 [0.54 , 1.09] |
| IMPOWER-130 2019 | -0.172 | 0.2558 | 88 | 42 | 2.7% | 0.84 [0.51 , 1.39] |
| IMPOWER-132 2020 | -0.3115 | 0.4386 | 25 | 20 | 0.9% | 0.73 [0.31 , 1.73] |
| KEYNOTE-024 2021 | -0.4723 | 0.1335 | 154 | 151 | 9.9% | 0.62 [0.48 , 0.81] |
| KEYNOTE-042 2019 | -0.3864 | 0.0896 | 299 | 300 | 21.9% | 0.68 [0.57 , 0.81] |
| KEYNOTE-189 2018 | -0.3771 | 0.1716 | 132 | 70 | 6.0% | 0.69 [0.49 , 0.96] |
| KEYNOTE-407 2018 | -0.3927 | 0.1848 | 73 | 73 | 5.2% | 0.68 [0.47 , 0.97] |
| POSIDON 2022 | -0.4482 | 0.1148 | 195 | 97 | 13.4% | 0.64 [0.51 , 0.80] |
| **Subtotal (Wald[a])** | | | **1826** | **1380** | **100.0%** | **0.70 [0.64 , 0.76]** |
| Test for overall effect: Z = 8.56 (P < 0.00001) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.00 [0.00 , 0.01]; Chi² = 7.03, df = 14 (P = 0.93); I² = 0% | | | | | | |
| **6.1.4 PD-L1: 1% or above** | | | | | | |
| CameL 2023 | -0.3519 | 0.164 | 138 | 117 | 5.4% | 0.70 [0.51 , 0.97] |
| CameL-Sq 2022 | -0.661 | 0.2603 | 95 | 93 | 2.6% | 0.52 [0.31 , 0.86] |
| CHECKMATE 9 LA 2021 | -0.3165 | 0.1077 | 203 | 204 | 8.9% | 0.73 [0.59 , 0.90] |
| CHECKMATE-227 2019 | -0.1643 | 0.0838 | 792 | 397 | 11.1% | 0.85 [0.72 , 1.00] |
| IMPOWER 110 2020 | -0.1659 | 0.1047 | 277 | 277 | 9.1% | 0.85 [0.69 , 1.04] |
| KEYNOTE-021 2020 | -0.1748 | 0.296 | 39 | 40 | 2.1% | 0.84 [0.47 , 1.50] |
| KEYNOTE-042 2019 | -0.2366 | 0.0613 | 637 | 637 | 13.4% | 0.79 [0.70 , 0.89] |
| KEYNOTE-189 2018 | -0.4141 | 0.1223 | 260 | 128 | 7.8% | 0.66 [0.52 , 0.84] |
| MYSTIC 2020 | -0.0607 | 0.0703 | 575 | 289 | 12.5% | 0.94 [0.82 , 1.08] |
| NEPTUNE 2023 | 0.004 | 0.091 | 319 | 309 | 10.4% | 1.00 [0.84 , 1.20] |
| ORIENT-11 2022 | -0.5888 | 0.1671 | 181 | 87 | 5.2% | 0.55 [0.40 , 0.77] |
| POSIDON 2022 | -0.2474 | 0.0781 | 437 | 207 | 11.6% | 0.78 [0.67 , 0.91] |
| **Subtotal (Wald[a])** | | | **3953** | **2785** | **100.0%** | **0.79 [0.73 , 0.87]** |
| Test for overall effect: Z = 5.10 (P < 0.00001) | | | | | | |
| Heterogeneity: Tau² (DL[b], 95% CI) = 0.01 [0.00 , 0.08]; Chi² = 23.58, df = 11 (P = 0.01); I² = 53% | | | | | | |
| Test for subgroup differences: Chi² = 4.74, df = 3 (P = 0.19), I² = 36.8% | | | | | | |

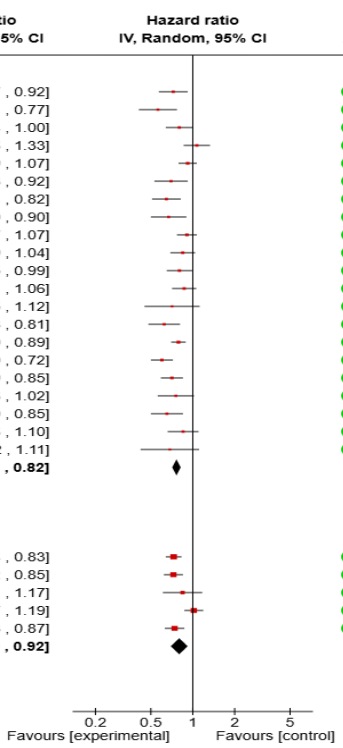


**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

## 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 | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|
| **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% | | | | | | | |



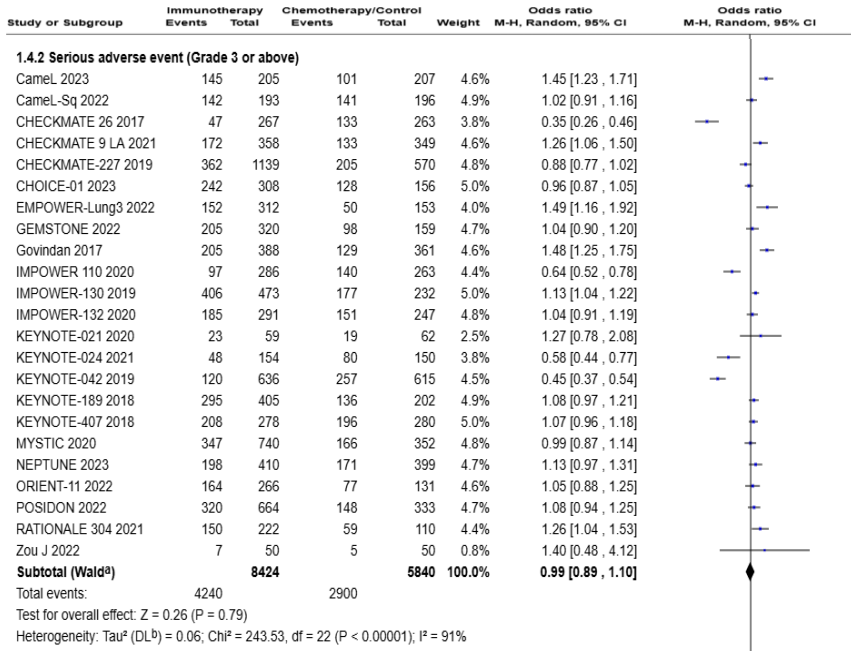

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**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.

### Forest plot: Adverse events (Grade ≥3)

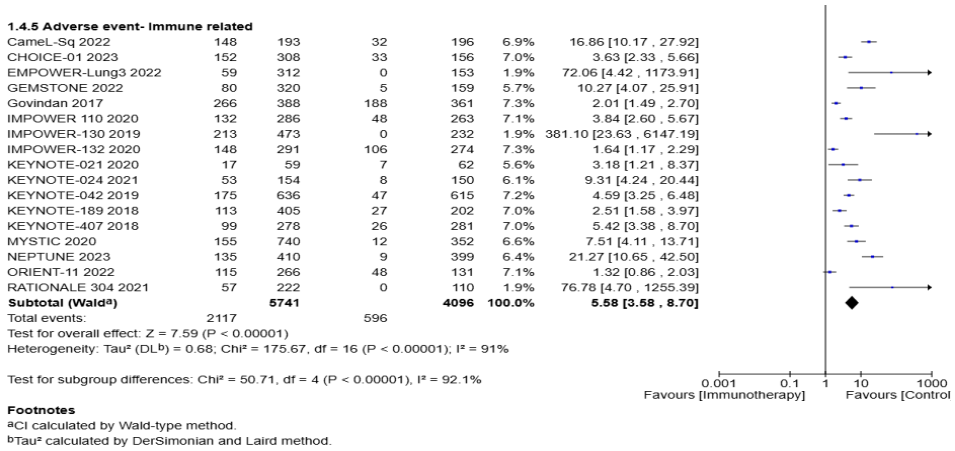


| Study or Subgroup | Immunotherapy Events | Total | Chemotherapy/Control Events | Total | Weight | Odds ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.2 Serious adverse event (Grade 3 or above)** | | | | | | |
| CameL 2023 | 145 | 205 | 101 | 207 | 4.6% | 1.45 [1.23 , 1.71] |
| CameL-Sq 2022 | 142 | 193 | 141 | 196 | 4.9% | 1.02 [0.91 , 1.16] |
| CHECKMATE 26 2017 | 47 | 267 | 133 | 263 | 3.8% | 0.35 [0.26 , 0.46] |
| CHECKMATE 9 LA 2021 | 172 | 358 | 133 | 349 | 4.6% | 1.26 [1.06 , 1.50] |
| CHECKMATE-227 2019 | 362 | 1139 | 205 | 570 | 4.8% | 0.88 [0.77 , 1.02] |
| CHOICE-01 2023 | 242 | 308 | 128 | 156 | 5.0% | 0.96 [0.87 , 1.05] |
| EMPOWER-Lung3 2022 | 152 | 312 | 50 | 153 | 4.0% | 1.49 [1.16 , 1.92] |
| GEMSTONE 2022 | 205 | 320 | 98 | 159 | 4.7% | 1.04 [0.90 , 1.20] |
| Govindan 2017 | 205 | 388 | 129 | 361 | 4.6% | 1.48 [1.25 , 1.75] |
| IMPOWER 110 2020 | 97 | 286 | 140 | 263 | 4.4% | 0.64 [0.52 , 0.78] |
| IMPOWER-130 2019 | 406 | 473 | 177 | 232 | 5.0% | 1.13 [1.04 , 1.22] |
| IMPOWER-132 2020 | 185 | 291 | 151 | 247 | 4.8% | 1.04 [0.91 , 1.19] |
| KEYNOTE-021 2020 | 23 | 59 | 19 | 62 | 2.5% | 1.27 [0.78 , 2.08] |
| KEYNOTE-024 2021 | 48 | 154 | 80 | 150 | 3.8% | 0.58 [0.44 , 0.77] |
| KEYNOTE-042 2019 | 120 | 636 | 257 | 615 | 4.5% | 0.45 [0.37 , 0.54] |
| KEYNOTE-189 2018 | 295 | 405 | 136 | 202 | 4.9% | 1.08 [0.97 , 1.21] |
| KEYNOTE-407 2018 | 208 | 278 | 196 | 280 | 5.0% | 1.07 [0.96 , 1.18] |
| MYSTIC 2020 | 347 | 740 | 166 | 352 | 4.8% | 0.99 [0.87 , 1.14] |
| NEPTUNE 2023 | 198 | 410 | 171 | 399 | 4.7% | 1.13 [0.97 , 1.31] |
| ORIENT-11 2022 | 164 | 266 | 77 | 131 | 4.6% | 1.05 [0.88 , 1.25] |
| POSIDON 2022 | 320 | 664 | 148 | 333 | 4.7% | 1.08 [0.94 , 1.25] |
| RATIONALE 304 2021 | 150 | 222 | 59 | 110 | 4.4% | 1.26 [1.04 , 1.53] |
| Zou J 2022 | 7 | 50 | 5 | 50 | 0.8% | 1.40 [0.48 , 4.12] |
| **Subtotal (Wald[a])** | | **8424** | | **5840** | **100.0%** | **0.99 [0.89 , 1.10]** |
| Total events: | 4240 | | 2900 | | | |

Test for overall effect: Z = 0.26 (P = 0.79)

Heterogeneity: Tau² (DL[b]) = 0.06; Chi² = 243.53, df = 22 (P < 0.00001); I² = 91%

### Forest plot: Adverse events (immune related)



| | | | | | | |
|---|---|---|---|---|---|---|
| **1.4.5 Adverse event- Immune related** | | | | | | |
| CameL-Sq 2022 | 148 | 193 | 32 | 196 | 6.9% | 16.86 [10.17 , 27.92] |
| CHOICE-01 2023 | 152 | 308 | 33 | 156 | 7.0% | 3.63 [2.33 , 5.66] |
| EMPOWER-Lung3 2022 | 59 | 312 | 0 | 153 | 1.9% | 72.06 [4.42 , 1173.91] |
| GEMSTONE 2022 | 80 | 320 | 5 | 159 | 5.7% | 10.27 [4.07 , 25.91] |
| Govindan 2017 | 266 | 388 | 188 | 361 | 7.3% | 2.01 [1.49 , 2.70] |
| IMPOWER 110 2020 | 132 | 286 | 48 | 263 | 7.1% | 3.84 [2.60 , 5.67] |
| IMPOWER-130 2019 | 213 | 473 | 0 | 232 | 1.9% | 381.10 [23.63 , 6147.19] |
| IMPOWER-132 2020 | 148 | 291 | 106 | 274 | 7.3% | 1.64 [1.17 , 2.29] |
| KEYNOTE-021 2020 | 17 | 59 | 7 | 62 | 5.6% | 3.18 [1.21 , 8.37] |
| KEYNOTE-024 2021 | 53 | 154 | 8 | 150 | 6.1% | 9.31 [4.24 , 20.44] |
| KEYNOTE-042 2019 | 175 | 636 | 47 | 615 | 7.2% | 4.59 [3.25 , 6.48] |
| KEYNOTE-189 2018 | 113 | 405 | 27 | 202 | 7.0% | 2.51 [1.58 , 3.97] |
| KEYNOTE-407 2018 | 99 | 278 | 26 | 281 | 7.0% | 5.42 [3.38 , 8.70] |
| MYSTIC 2020 | 155 | 740 | 12 | 352 | 6.6% | 7.51 [4.11 , 13.71] |
| NEPTUNE 2023 | 135 | 410 | 9 | 399 | 6.4% | 21.27 [10.65 , 42.50] |
| ORIENT-11 2022 | 115 | 266 | 48 | 131 | 7.1% | 1.32 [0.86 , 2.03] |
| RATIONALE 304 2021 | 57 | 222 | 0 | 110 | 1.9% | 76.78 [4.70 , 1255.39] |
| **Subtotal (Wald[a])** | | **5741** | | **4096** | **100.0%** | **5.58 [3.58 , 8.70]** |
| Total events: | 2117 | | 596 | | | |

Test for overall effect: Z = 7.59 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.68; Chi² = 175.67, df = 16 (P < 0.00001); I² = 91%

Test for subgroup differences: Chi² = 50.71, df = 4 (P < 0.00001), I² = 92.1%

0.001 0.1 1 10 1000

Favours [Immunotherapy] Favours [Control

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Summary of findings:

**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 | |
| Overall survival-Smokers (OS-Smokers) assessed with: Hazard Ratio | | - | **HR 0.76** (0.69 to 0.84) | 7272 (14 RCTs) | ⊕⊕◯◯ Low | |
| Overall survival-Non-smokers assessed with: Hazard ratio | | - | **HR 0.95** (0.83 to 1.04) | 1536 (14 RCTs) | ⊕⊕◯◯ Low | |
| 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 | |

| | | | | | |
|---|---|---|---|---|---|
| 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 |

**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.

***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

**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
**Setting:** Indian
**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) | - | ⨁⨁◯◯ 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[c,a] | CRITICAL |

**CI:** confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

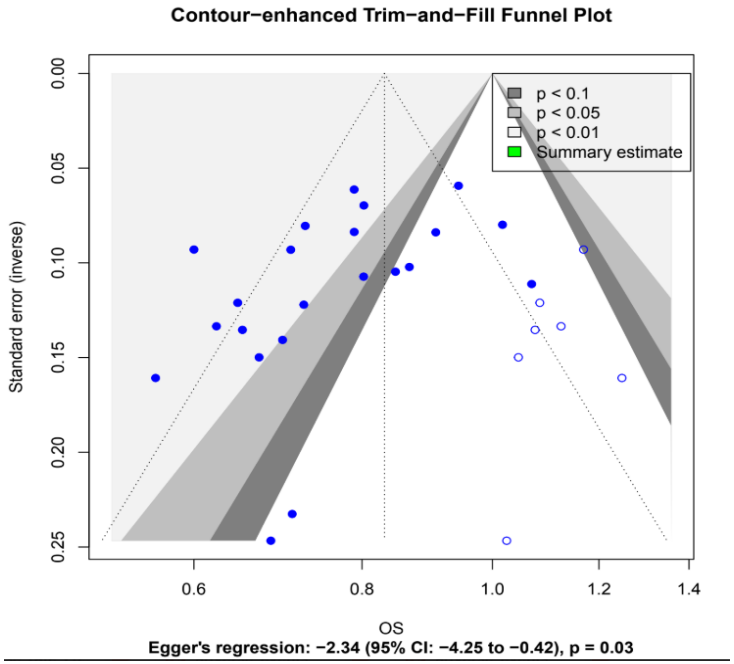
*Explanations*

a. Heterogeneity among the included studies. $I^2$ 63%, downgraded by one level

b. Publication bias strongly suspected, downgraded by one level

c. Effect estimate crosses the line of no effect

*Publication bias:  overall survival



## 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.<br><br>**Strength**: Conditional<br>**Certainty of evidence** – Low | |

**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?**

## 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)

### Intervention

Neoadjuvant chemotherapy with/without immunotherapy followed by surgery

Subgroups:

1. Neoadjuvant chemotherapy only followed by surgery
2. 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

The following critical and important outcomes were evaluated:

1. Overall survival (Critical outcome)
2. Adverse effects (Critical outcome)
3. Quality of life (Critical outcome)
4. Disease-free survival (Important outcome)
5. Response rate (Important outcome)
6. Surgical outcomes (intraoperative and postoperative complications) (Important outcome)

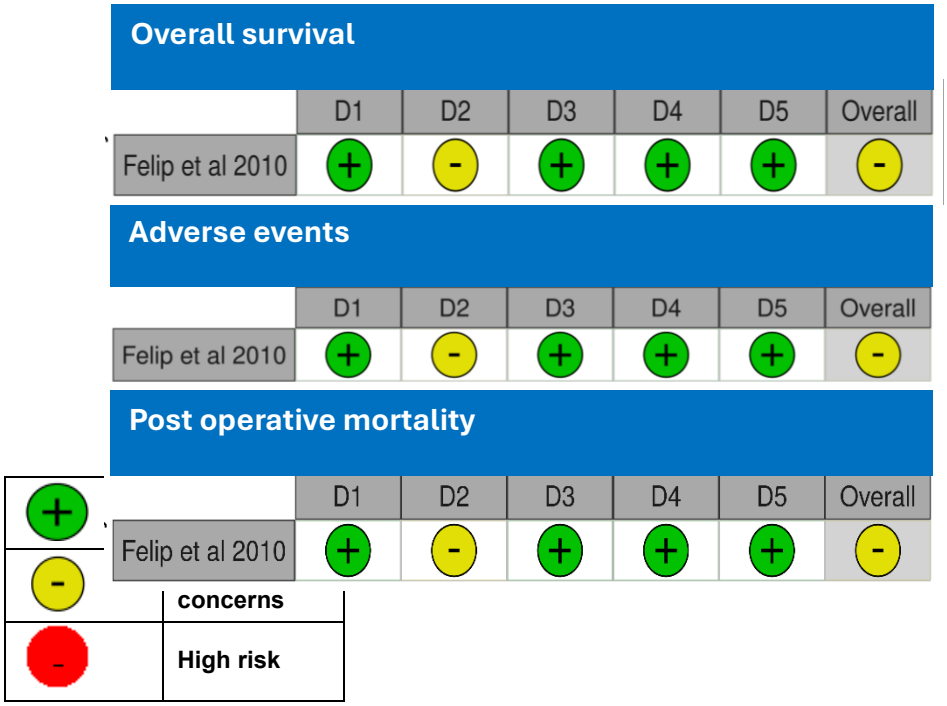
## Critical Outcome reviewed and their MCID provided by GDG

| | Critical outcome | MCID |
|---|---|---|
| | | |
| **Overall survival** | OS (Proportion of people who have survived at a particular time point) | 5% at 2 years<br>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<br>10% difference in any grade AEs |

| Framework | Description |
|---|---|
| Population | Patients with operable non-small cell lung cancer<br>Subgroups: 1. T stage 2. Nodal involvement 3. Histology 4. PDL1<br>6. Smoking status |
| Intervention | Neoadjuvant chemotherapy with/without immunotherapy followed by surgery<br>Subgroups:<br>Neoadjuvant chemotherapy only followed by surgery<br>Neoadjuvant chemotherapy with immunotherapy followed by surgery |
| Comparator | Upfront surgery followed by adjuvant chemotherapy with/without immunotherapy<br>Subgroups:<br>1. Upfront surgery followed by chemotherapy only<br>2. Upfront surgery followed by chemotherapy and immunotherapy<br>3. Upfront surgery followed by immunotherapy only |

| | |
|---|---|
| Outcome | Overall survival (Critical outcome)<br>Adverse effects (Critical outcome)<br>Quality of life (Critical outcome)<br>Disease-free survival (Important outcome)<br>Response rate (Important outcome)<br>Surgical outcomes (intraoperative and postoperative complications) (Important outcome) |

## Risk of Bias Assessment



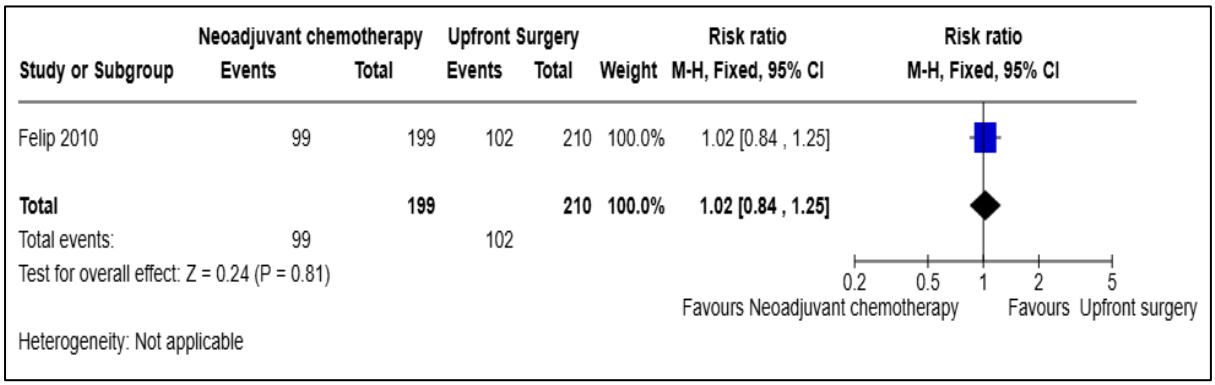

| | |
|---|---|
| **D1** | **Randomisation process** |
| **D2** | **Deviations from the intended interventions** |
| **D3** | **Missing outcome data** |
| **D4** | **Measurement of the outcome** |
| **D5** | **Selection of the reported result** |

## 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.

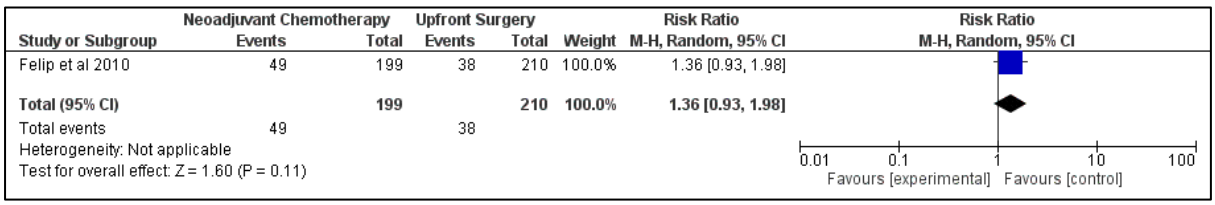
Forest plot: Overall Survival




## 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.

Forest Plot: Adverse events of grade 3 or higher



## Summary of Findings

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

**Patient or population:** Operable Non-Small Cell Lung Cancer
**Setting:** Tertiary Care Hospital
**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 |
| **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

## Evidence Profile

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

**Patient or population:** Operable Non-Small Cell Lung Cancer
**Setting:** Tertiary Care Hospital
**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**

j. downgraded by one level as there were some concerns in risk of bias because none of the studies contributing to the effect estimate were at low risk of bias.
k. Downgraded by one level as there is only one study
**l.** downgraded by one level for imprecision because the confidence interval includes both the possibility of meaningful benefit and harm.

## 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.<br><br>**Strength:** Conditional<br>**Certainty of evidence:** Very low | |

**In patients with NSCLC, how effective is immunotherapy (immune checkpoint inhibitors) delivered as individualized dosing regimen (low dose) compared to standard full dose immunotherapy?**

## 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

**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

## 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:

- Overall survival (2 studies)
- Side effects (1 study)
- Quality of life (No studies)
- Progression free survival (2 studies)
- Response rate (2 studies)
- Cost (2 studies)

### Intervention

Individualized dosing regimen

**Subgroups:** Weight based dose calculation/ reduced dose / reduced frequency dosing schedule/reduced dose and reduced frequency/Weight based and reduced dose

### Comparator

### Outcome

The following critical and important outcomes were evaluated:

- 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 |

## PICO Question

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

## 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

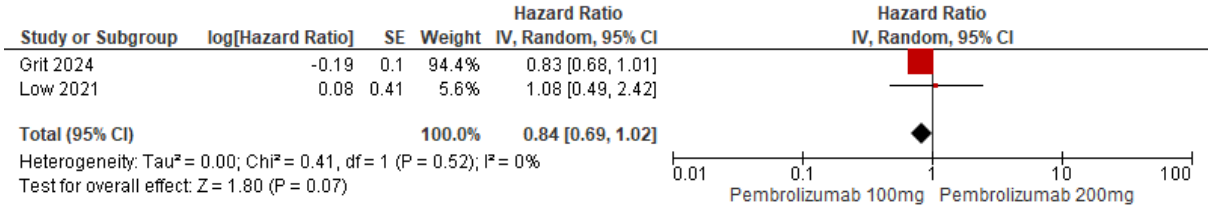
### Overall Survival

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.

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



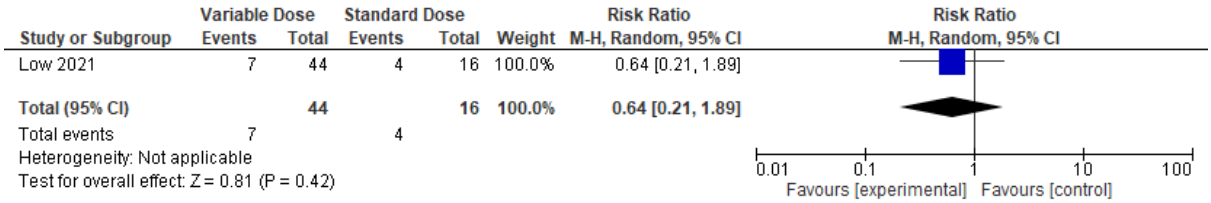

### Quality of Life

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.

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



**Summary of findings:**

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

**Patient or population: patients with NSCLC**

**Setting: Indian**

**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 |
| 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 |

## 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**

**Setting: Indian**

**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 | not serious | none | 26% | 40% | **HR 0.84** (0.69 to 1.02) | **55 fewer per 1,000** (from 112 fewer to 6 more) | ⊕◯◯◯ very low | |
| **Grade 3 or more adverse events** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | non-randomised studies | not serious | not serious | serious | not serious | none | 7/44 (15.9%) | 4/16 (25.0%) | **RR 0.64** (0.21 to 1.89) | **90 fewer per 1,000** (from 198 fewer to 222 more) | ⊕◯◯◯ very low | |

## 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.<br><br>Strength: Conditional<br>Certainty of evidence: Very low | |