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Overall survival of non-small cell lung cancer with spinal metastasis: a protocol for systematic review

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ABSTRACT

Our study aimed at deriving a summary survival curve in the population of non-small cell lung cancer (NSCLC) with spine metastasis. The pooled survival probabilities could provide information for a neurosurgeon to consider the extent or surgical method when handling spine metastasis in NSCLC patients. This data is currently still lacking.

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1 Review Title

Overall survival of non-small cell lung cancer with spinal metastasis: a systematic review and meta-analysis

2 Anticipated or actual start date

07 June 2021

3 Anticipated completion date

31 August 2021

4 Stage of review at time of this submission

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

5 Funding source/sponsors

pending

6 Conflicts of interest

none declared

7 Review question

1. What are the survival (time to event of death) of patients of non-small cell lung cancer (NSCLC) presented with a spinal metastasi(e)s?
2. What are the differences of the above between patients that underwent spinal surgery against those that did not?
3. What is the trend of the survival above over the recent years, i.e. the introduction of tyrosine kinase inhibitors?

8 Searches

Database to be searched
1. MEDLINE
2. EMBASE
3. Google Scholar (to complement grey literature)

One local database of the author's institute National Taiwan University Hospital is included as "Identification of new studies via other methods" within PRISMA 2020 flowchart (Page, 2021).

Reference:
Page MJ, McKenzie JE, Bossuyt PM. et al.The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 doi:10.1136/bmj.n71

9 Participants/population

Populations diagnosed with non-small cell lung cancer that presents with spinal metastasis(es).

Definitions:
1. non-small cell lung cancer: pathologically proven of any pathologies fall under the category of non-small cell lung cancer,
2. spine metastasis

Inclusion criteria
1. Dataset must have both NSCLC and spine metastasis, regardless of treatment modality

Exclusion criteria
1. Dataset that could not be isolated from non-NSCLC pathologies
2. Dataset that could not be isolated from unknown pathologies
3. Dataset that could not be isolated from those with absence of spinal metastasis

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10 Intervention(s), exposure(s)

Definition: There is no designated intervention or exposure in this study because the aim of this review is obtain the survival curve.

Inclusion criteria
1. Extractable survival curve, Kaplan-Meier curve
2. Raw data available for the survival data

Exclusion criteria
1. The above data not available/extractable
2. Number of patients at risks or the total number of events is not available.
3. Censored data not available or could not be re-estimated (data incomplete/unavailable).

11 Comparator(s)/control

no comparator is designated because this study is a single-arm data meta-analysis

12 Types of study to be included

No restriction of the types of study.
This is a single-arm study, hence all types of studies were analyzed as a whole.
However, a separation check of randomized studies vs. non-randomized studies can allow us to identify the existence of survival differences between real-world data and those included in trials. It is well known that populations included in trials can be 'perfect patients.'

13 Context

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

14 Primary outcome(s)

Survival curve of
1. surgical patients,
2. non-surgical patients, and
3. all/mixed: extracted patients, including those data inseparable into either group above

Definition of the outcomes
1. surgical patients: underwent surgery such as palliative decompression, debulking, total vertebrectomy, separation surgery, and any forms of minimal invasive (access) surgeries.
2. non-surgical patients: include any forms of non-surgical treatment such as radiotherapy, chemotherapy, or palliative care
3. all/mixed: extracted patients, including those data inseparable into either group above

Measures of effect
Summary survival curve for aggregated survival data (manage in R, package Survival)

15 Secondary outcome(s)

None designated

16 Data extraction (selection and coding)

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A pre-piloted form will be designed by Chai CL

Jeon JP and Chai CL work independently on concluding the search strategy and study selection according to the aforementioned inclusion and exclusion criteria.

Chai CL work independently on the extraction of data from included studies using a pre-piloted form. Jeon JP oversees the accuracy. WhereTsuang FY will resolve disagreements.

Extraction of the survival data:
1. Use individual patient data if available
2. Extract the published figure (image) of survival curve with Webplotdigitizer, Rohatgi (2020)
3. Convert to IPD via package IPDfromKM in R, Liu 2021
4. Obtain survival function or Kaplan-Meier curve data, with number of patients at risk (best effort to calculate if possible)

All excluded and failure of extraction studies are reported with reasons documented (in data supplements).

Coding: as per defined outcome. Whereas data inseparable to surgical vs. non-surgical group, (and individual data not available despite contacting the corresponding author) will be placed in "3. all group"

Survival data are converted accordingly under the framework proposed by Tierney et al (2007)

Reference:
1. Tierney JF, Stewart LA, Ghersi D. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16
2. Ankit Rohatgi. WebPlotDigitizer. Available at https://automeris.io/WebPlotDigitizer, Version: 4.4 Accessed 27 May 2021
3. Liu N, Zhou YH, Lee JJ. IPDfromKM: Reconstruct Individual Patient Data from Published Kaplan-Meier Survival Curves https://doi.org/10.21203/rs.3.rs-117525/v1 Accessed 28 May 2021

17 Strategy for qualitative synthesis

GRADE for the certainty of evidence

Risk of bias (limitation) assessment
Dr. Tsuang and Dr. Chai work independently on risk of bias (limitations) assessment for individual outcomes and body of evidence according to GRADE guidelines: 4 (see reference).

Outcomes listed below is specified to be assessed using GRADE for quality of evidence and presented in the summary of findings (Guyatt, 2011).

2. Median overall survival of all patients, surgical patients, and non-surgical patients

The funnel plot will be performed to assess publication bias if feasible.
All disagreement and accuracy will be resolved by discussion between Jeon and Chai

References:
Gordon H. Guyatt et al. GRADE guidelines: 1. Introductiond GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology 64 (2011) 383e394 doi: 10.1016/j.jclinepi.2010.04.026
Gordon H. Guyatt et al. GRADE guidelines: 4. Rating the quality of evidencedstudy limitations (risk of bias). Journal of Clinical Epidemiology 64 (2011) 407e415 doi: 10.1016/j.jclinepi.2010.07.017

18 Strategy for quantitative synthesis

Derive a summary survival curve for from individual survival data in R, package Survival. Log Rank's test to compare the curves for statistical reason. Beware that both surgical and non-surgical populations are two different populations.

1. Survival curve of all patients (represents all included studies)

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2. Surgical patients, and
3. Non-surgical patients

If data is not suitable for pooling, a narrative synthesis will be performed.

Meta-analysis of trials and observational studies are separately performed and not subject to pooling.

A standard of 95% confidence interval will be used in the meta-analysis.

P value <0.05: significant; P value for interaction <0.1: significant

We will assess heterogeneity using the χ^2 test and the I^2 statistic (I^2 less than 40%: unimportant; 30-60%: moderate; 50-90%: substantial, 75-100%: considerable (Higgins, 2008).

Reference:
1. Liu N, Zhou YH, Lee JJ. IPDfromKM: Reconstruct Individual Patient Data from Published Kaplan-Meier Survival Curves https://doi.org/10.21203/rs.3.rs-117525/v1 Accessed 28 May 2021

19 Analysis of subgroups or subsets or moderators

A moderator analysis will be performed using a frailty model in R to explore study-level factors potentially associated with survival. Each study is regarded as a cluster.

Note that moderators are analyzed separately within the surgical and non-surgical patients respectively. It is because the two groups are believed to have similar baseline that permits direct comparison.

Predefined moderators:
1. Last follow-up date of the study
2. Mean age of the study
3. Proportion of positivity of EGFR mutation
4. Proportion of patients receiving tyrosine kinase inhibitors (TKIs) (cancer immunotherapy)
5. Proportion of patients with synchronous spine metastasis

Definitions
synchronous metastasis: the metastasis is diagnosed within 6 months of the primary cancer.
metachronous metastasis: the metastasis is diagnosed more than 6 months after the diagnosis of the first primary cancer

Arrange median survival time with catepillar plots to check the trend of survival over the years.

20 Type and method of review

Single-arm meta-analysis of survival studies, oncology, spinal metastasis, non-small cell lung cancer

21 Dissemination plans

We will publish the review on completion

22 Current review status

Review Started

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