Radiosurgery for brain oligometastases in lung cancer

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Abstract

Introduction

Brain metastases are a common problem in oncology patients, especially in lung cancer. The usual treatment for cerebral oligometastases is whole brain radiation therapy. Given the persistent poor prognosis of this disease, other therapeutic alternatives such as stereotactic radiosurgery have been considered. However, there is no clarity regarding the effectiveness of its addition.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified 17 systematic reviews including seven studies overall, of which four were randomized trials. All trials assessed patients with brain oligometastases, but none of them included exclusively lung cancer population. We concluded that it is not possible to clearly establish whether radiosurgery decreases neurological functionality, cognitive impairment, mortality or serious adverse effects, as the certainty of the existing evidence has been assessed as very low.

Problem

Brain oligometastases are a common problem in oncology patients. It is usually defined by a limited number of metastases (less than five), placing it as an intermediate state between localized and metastatic cancer. This stage is associated with better prognosis, since it is possible to administer local treatment in addition to the systemic treatment of the disease. Within the histological origins we can find breast, kidney and colon cancer, among others, being the most frequent lung cancer.

The usual local treatment for cerebral oligometastases is the use of corticoids or whole brain radiotherapy and it is estimated that survival could vary between two and six months [1]. Given the persistent poor prognosis of this disease, other therapeutic alternatives such as stereotactic radiosurgery has been proposed, which allows the administration of higherdoses of radiation in a localized area and may be more effective in the ablation of brain metastases. However, its indication is controversial, as it is not clear how effective can be its addition to systemic treatment or whole brain radiotherapy.

Key messages

- We are uncertain whether the addition of stereotactic radiosurgery to whole brain radiotherapy reduces the worsening of neurological function, cognitive impairment, mortality or serious adverse effects, as the certainty of the evidence has been assessed as very low.
- No studies were found that looked at quality of life.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified 17 systematic reviews [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], including seven studies overall reported in eight references [19], [20], [21], [22], [23], [24], [25], [26], of which four were randomized trials reported in five references [19], [20], [21], [22], [26]. The table and summary are based on the randomized trials, as the observational studies did not increase the level of certainty of the evidence, nor added any additional relevant information.
What types of patients were included*	All trials included patients with a diagnosis of cerebral oligometastases, regardless of their primary histology. Only two trials reported the number of patients with primary lung cancer: in one trial it was 64% [19] and in another 44% [20]. Three trials included patients with one to three brain metastases [19], [21], [22], and one trial with two to four brain metastases [20]. Three trials excluded patients with a functionality below 70 points on the Karnofsky scale [19], [20], [21].
What types of interventions were included*	All trials evaluated the addition of stereotactic radiosurgery to whole brain radiotherapy in comparison with whole brain radiotherapy alone. Regarding the doses used in the intervention, one trial reported that stereotactic radiosurgery was administered with doses between 14 to 20 Gy (average 14.6 Gy) [21]; one applied 20 Gy [22], another a 16 Gy dose [20], and one trial did not report the dose administered [19]. Only one trial specified the type of radiosurgery (Gamma knife) [22]. Regarding the comparison, three trials administered 30 Gy for the whole brain radiotherapy in 10 sessions [20], [21], [22]. One trial administered 37.5 Gy with a daily dose of 2.5 Gy [19].
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: • Mortality, assessed at 12 months follow-up. • Neurological functionality • Cognitive deterioration, assessed as improvement in the mini-mental state examination (MMSE) score at six months follow-up. • Serious (grade 3 and 4) adverse effects, assessed as late (after 90 days) or acute (less than 90 days)

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	The average follow-up of the trials was not reported. However, outcomes had a follow-up with a range between 3 to 18 months [19], [20], [21], [22].

* Information about primary studies is not extracted directly from primary studies but from identified systematic reviews, unless otherwise stated.

Summary of findings

Information on the effects of stereotactic radiosurgery on brain oligometastases in lung cancer is based on four randomized trials involving 596 patients [19], [20], [21].

Two trials evaluated mortality (358 patients) [19], [20]. One trial evaluated the outcome neurological functionality (42 patients) [21]. One trial evaluated the outcomes cognitive deterioration (154 patients) [19] and acute and late serious adverse effects (326 patients) [19]. None of the systematic reviews reported the outcome quality of life.

The summary of findings is the following:

- We are uncertain whether the addition of stereotactic radiosurgery reduces mortality as the certainty of the evidence has been assessed as very low.
- We are uncertain whether the addition of stereotactic radiosurgery reduces the deterioration of neurological functionality as the certainty of the evidence has been assessed as very low.
- We are uncertain whether the addition of stereotactic radiosurgery reduces cognitive deterioration as the certainty of the evidence has been assessed as very low.
- We are uncertain whether the addition of stereotactic radiosurgery reduces late serious adverse effects as the certainty of the evidence has been assessed as very low.
- We are uncertain whether the addition of stereotactic radiosurgery reduces acute serious adverse effects as the certainty of the evidence has been assessed as very low.
- No studies were found that looked at quality of life.

Radiosurgery for brain oligometastases in lung cancer					
Patients	Brain oligometastases in lung cancer				
Intervention	Addition of stereotactic radiosurgery to whole brain radiotherapy				
Comparison	Whole brain radiotherapy				
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT radiosurgery	**WITH radiosurgery**		
	Difference: patients per 1000			
Mortality	762 per 1000	762 per 1000	HR 0.82 (0.65 a 1.02)	⊕◯◯◯[1,2,3] Very low
	Difference: 70 less (Margin of error: 155 less to 7 more)			
Deterioration of neurological functionality	48 per 1000	95 per 1000	RR 2.00 (0.2 a 20.41)	⊕◯◯◯[1,2,3] Very low
	Difference: 47 more (Margin of error: 38 less to 924 more)			
Improvement in cognitive function	320 per 1000	253 per 1000	RR 0.79 (0.48 a 1.31)	⊕◯◯◯[1,2,3] Very low
	Difference: 67 less (Margin of error: 166 less to 99 more)			
Acute serious adverse effects **	18 per 1000	38 per 1000	RR 2.08 (0.97 a 12.34)	⊕◯◯◯[1,2,3] Very low
	Difference: 1 more (Margin of error: 0 less to 10 more)			
Late serious adverse effects **	0 per 1000	1 per1000	HR 9.34 (0.51 a 172.01)	⊕◯◯◯[1,2,3] Very low
	Difference: 20 more (Margin of error: 8 less to 129 more)			
Quality of life	The outcome quality of life was not measured or reported by systematic reviews.			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
HR: Hazard ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT radiosurgery** is based on the risk in the control group of the trials. The risk **WITH radiosurgery** (and its margin of error) is calculated from relative effect (and its margin of error).
** Acute or late serious (grade 3 and 4) adverse events were classified according to whether they occurred before or after 90 days of brain radiosurgery or radiotherapy.

[1] The certainty of evidence was downgraded one level for the serious risk of bias, due to the studies being unblinded.
[2] The certainty of evidence was downgraded one level due to indirect evidence, because the results come from trials that included multiple primary histologies, not only lung cancer.
[3] The certainty of evidence was downgraded one level for imprecision, since each end of the confidence interval leads to a different decision. In the case of the outcome deterioration of neurological functionality it was decided to decrease an additional level, due to the fact that more imprecision was observed, and each end of the confidence interval carries a very different decision.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

This evidence applies to patients with lung cancer and brain oligometastases (less than five metastases), regardless of the histology of the cancer.

This evidence does not apply to patients with a performance score of less than 70 points on the Karnofsky scale.

About the outcomes included in this summary

The outcomes included in the summary of findings table are those considered critical for decision-making, according to the opinion of the authors of this summary, and in general coincide with those reported by the systematic reviews identified.

The outcome "quality of life" is considered relevant for decision-making, however, this was not measured by systematic reviews.

Balance between benefits and risks, and certainty of the evidence

The results of this summary indicate that the addition of radiosurgery may decrease the risk of mortality, but this would be associated with greater adverse effects, impaired neurological and cognitive function. However, for all outcomes, the certainty of the evidence has been assessed as very low.

Considering the evidence, it is not possible to perform an adequate analysis of the balance between benefits and harm, due to the existing uncertainty.

Resource considerations

The systematic reviews did not evaluate the economic impact of the intervention, but it is considered that the addition of radiosurgery has higher associated costs compared to the administration of whole brain radiotherapy alone.

Due to the very low certainty of the evidence, it is not possible to make an adequate balance between costs and benefits.

What would patients and their doctors think about this intervention

Facing the available evidence, both patients and therapists should be against the addition of radiosurgery. However, some patients may prefer its use, since it is a targeted, non-invasive procedure and the disease has an uncertain prognosis.

Because of this, it is important to inform patients about the limitations and conclusions of the existing evidence.

Differences between this summary and other sources

Our conclusions are consistent with those reported by the systematic reviews that included all identified trials [11], [13], since no differences between the interventions are reported.

However, many of the reviews conclude that a specific subgroup of patients (single metastasis) [6], [7], [11], [13], [15], [18] would benefit from the intervention as it would improve their survival and one review [18] concludes that the addition of radiosurgery could be used as a salvage in patients with poor prognostic factors.

These differences might be explained due to the fact that this summary of evidence does not contemplate a specific analysis for patients with single metastasis. In addition, only two reviews [11], [13] performed a GRADE assessment of the evidence.

The Clinical practice guideline on the optimal radiotherapeutic management of brain metastases [27] concludes that radiosurgery should be offered to patients with single brain metastases who are not candidates for surgery.

Could this evidence change in the future?

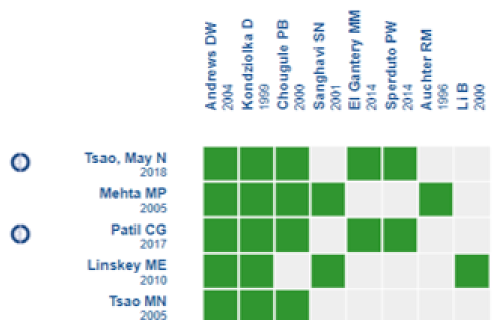
It is very likely that the information provided in this summary will change in the future, because the certainty of the available evidence is very low.

An ongoing systematic review [28] was identified in PROSPERO.

No ongoing trials were identified in the World Health Organization's International Clinical Trials Registry Platform.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version** [Addition of radiosurgery to whole brain radiotherapy or systemic therapy for the treatment of brain oligometastases.]

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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