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Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer (Review)

Fuentes R, Bonfill Cosp X, Expósito Hernandez J

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[Intervention Review]

Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer

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ABSTRACT

Background

Non-small cell lung cancer is one of the leading causes of death in developed countries. Brain metastases are often seen in non-small cell lung cancer patients and although they are frequently multiple, a subset of patients with a solitary brain metastasis is regularly seen. Treatment of solitary brain metastasis has been surgery, when possible, but radiotherapy techniques, such as stereotactic radiotherapy using a linear accelerator or a high precision device of 201 cobalt-60 sources (gamma knife) have provided new treatment options.

Objectives

To determine the effectiveness of surgery compared to radiosurgery, either combined with whole brain irradiation or administered alone, for patients with a solitary brain metastasis from successfully treated non-small cell lung cancer.

Search methods

For this update we performed a new search in March 2009, using the following search strategy designed in the original review: Cochrane Central Register of Controlled Trials (CENTRAL) (accessed through *The Cochrane Library*, 2004, Issue 2), MEDLINE (accessed through PubMed), EMBASE and CINAHL (both accessed through Ovid). We also searched the Cochrane Lung Cancer Specialised Register.

Selection criteria

We considered for inclusion randomised trials comparing surgery (with or without whole brain irradiation) with all types of radiosurgery (with or without whole brain irradiation) for solitary brain metastasis from non-small cell lung cancer.

Data collection and analysis

Two review authors independently screened the search results to identify suitable trials.

Main results

Despite extensive searching we found no randomised trials suitable for inclusion.

Authors' conclusions

Based on the available evidence a meaningful conclusion cannot be reached. The term "single brain metastasis" is used to describe a brain metastasis found in patients presenting with an inoperable lung cancer or from an uncontrolled primary tumour some time after diagnosis, and the term "solitary brain metastasis" is used when the brain metastasis is diagnosed some time after radical, potentially

curative treatment. In the evaluated studies, we found that the criteria for the definition of solitary brain metastasis were not consistent. Some series combined patients with single and solitary brain metastasis. Some of the single arm or cohort studies came from single institutions where the availability of both techniques (radiosurgery and surgery) was not described. Therefore, it is possible that the most accessible technique might be used preferentially, reinforced by a general belief that the techniques are equivalent. This has prevented an appropriate treatment comparison, which should be made through a well designed phase III clinical trial.

PLAIN LANGUAGE SUMMARY

Surgery or radiosurgery for solitary brain metastases from non-small cell lung cancer

A solitary brain metastasis is the spread of cancer to the brain some time after successful treatment of the primary cancer. When the metastasis is caused by non-small cell lung cancer there are two main treatment options: surgery and radiosurgery. Radiosurgery consists of the use of high dose radiotherapy to the affected area guided by a three-dimensional computer and keeping the patient's head fixed, giving such precise treatment that it is considered "surgical". This review set out to compare both techniques. Our literature search has shown that a well-designed randomised trial comparing surgery and radiosurgery for patients with solitary brain metastasis has never been performed. Therefore, this review has been unable to show any advantage of one treatment over the other for this group of patients.

BACKGROUND

Non-small cell lung cancer (NSCLC) is one of the leading causes of death in developed countries (Parkin 1999). Patients die of local progression or recurrence of the primary tumour or because of metastatic spread. However, one of the distinctive features of the natural history of NSCLC is the very high incidence of central nervous system involvement in comparison to other malignant diseases. According to some authors 37% to 43% of brain metastases come from a NSCLC and it can be anticipated that the incidence will increase in the future due to better local control of the tumours (Chen 2007; Varlotto 2003). Although brain metastases from NSCLC are frequently multiple, a subset of patients with a single metastasis in the brain is regularly seen in clinical practice. At present the best tool for the diagnosis of a single brain metastasis is magnetic resonance imaging (MRI). Whether only MRI should be considered instead of computed tomography (CT) is a matter of debate (Yokoi 1999).

Brain metastases have three main clinical presentations:

1. a solitary brain metastasis developing some months or years after radical, potentially curative treatment of the primary tumour.

2. a single brain metastasis found in a patient presenting with an inoperable lung cancer.

3. a single brain metastasis from an uncontrolled primary tumour some time after diagnosis.

This review only includes patients with a solitary brain metastasis.

A renewed interest in the management of solitary brain metastasis from NSCLC has arisen from the development of better neurosurgical techniques (Koutras 2003; O'Neill 2003) and of radiosurgery (Muacevic 1999). Radiosurgery consists of delivering a very high dose of radiotherapy to a very small volume of tissue using a surgical fixation frame to keep the patient's head fixed during treatment. This method is generally used for treating tumours of less than 3 cm in diameter. There are three main types of radiosurgery: stereotactic linear accelerator-based radiotherapy with or without the use of a relocatable frame, and the gamma knife (Laing 1993; Simonova 2000). Sound clinical evidence of new radiotherapy devices, for example robotic image-guided radiosurgery systems or tomotherapy are awaited. (Calcerrada 2009; Gutierrez 2007).

Reports of the use of surgery alone with or without whole brain irradiation, and/or radiosurgery or different combinations of these procedures, with or without systemic chemotherapy, have suggested that an increase in survival can be obtained in these patients, some of whom can achieve more than two years of disease-free survival, with a small proportion of patients (2.9%) living more than five years (Hall 2000; Wronsky 1995).

Because there are a variety of possible treatment options and balancing possible benefits and toxicities is so important, clinical decision making may be very difficult. The aim of this review was to clarify this topic.

OBJECTIVES

To determine the effectiveness of surgery compared to radiosurgery, either combined with whole brain irradiation or administered alone, for solitary brain metastases from NSCLC, in patients whose primary tumour has been successfully treated.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or controlled trials that compared surgery (with or without whole brain irradiation) with all types of radiosurgery (with or without whole brain irradiation) for solitary brain metastasis from NSCLC, independent of the chemotherapy treatment that had been administered.

We excluded prospective or retrospective cohort studies of patients with solitary brain metastasis from NSCLC.

We also excluded studies of multiple brain metastases and studies including patients with synchronous lung tumour and brain metastasis. Studies without computed tomography (CT) or magnetic resonance imaging (MRI) examinations (usually before 1980) were also excluded.

Types of participants

Patients included in the studies should have histologically proven NSCLC, be adults of more than 18 years old and have their primary tumour in complete remission when the diagnosis of a solitary brain metastasis (irrespective of its size) was made. It was also mandatory that the included patients have an MRI or a contrast enhanced CT scan (in the case of older series) as part of their initial evaluation.

We excluded patients with other clinical presentations of brain metastasis from NSCLC.

Types of interventions

We considered the following interventions:

- Linear accelerator stereotactic radiotherapy, with or without a relocatable frame, using single or multiple fractions and gamma knife radiosurgery. We also included studies with additional whole brain irradiation (WBI).
- Surgery: Any kind of complete tumour excision. We also included studies treating patients with complementary WBI.

We excluded studies that compared different chemotherapy combinations for the treatment of patients with a solitary brain metastasis.

Types of outcome measures

Primary outcomes

1. Overall survival from the diagnosis of a solitary brain metastasis.
2. Disease-free survival from the diagnosis of a solitary brain metastasis
3. Overall survival from the first diagnosis of NSCLC.

Secondary outcomes

Additional outcome measures to be considered when reported:

1. Survival free of brain relapse.

2. Treatment-related toxicity of radiosurgery and complications of surgery
3. Quality of life.

Search methods for identification of studies

We performed a search in March 2009 to update the original completed review. The databases and search strategies used were the same as in the previous version of this review. We include here the text published in Fuentes 2006:

"We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2004 Issue 2), MEDLINE (1966 to September 2005), EMBASE (1974 to September 2005), CINAHL (1982 to September 2005). We also searched the Cochrane Lung Cancer Groups Specialised Register. We searched databases using the recommended Cochrane search strategy for controlled trials (see also: Cochrane Lung Cancer Group Search) in addition to another search strategy (see Appendix 1)."

"We scrutinised reference lists from identified studies for any other additional studies. We conducted all searches without any limitation for language."

Data collection and analysis

All studies were evaluated by two reviewers in order to assess whether the studies matched inclusion criteria. We did not identify any studies that could be included in this update, nor did we identify any in the previous version of the review.

Methods that would be applied if trials are included in a future update of the review
Interventions would be classified as:

1.- Surgery alone
2.- Surgery and whole brain irradiation
3.- Exclusive radiosurgery, including any technique: radiosurgery using either gamma knife, radiosurgery using linear accelerator and stereotactic radiotherapy using any kind of relocatable frame.
4.- Any radiosurgery technique plus whole brain irradiation.

Statistical analysis

We would conduct a statistical analysis with the included RCTs. Where possible, we would combine outcomes from included trials using Review Manager. For dichotomous outcomes we would calculate a pooled relative risk (random-effects method) with 95% confidence interval. For survival analysis, we would use an estimation of the hazard ratio and its variance as the summary statistic if the data allowed. If the data were insufficient for this approach, we would conduct a secondary analysis with survival at five years. For continuous data, we would calculate a pooled standardised mean difference (random-effects method) with 95% confidence interval. We would describe quality of life data in the results but we would not perform a meta-analysis.

We would conduct the statistical analysis in accordance with the intention-to-treat principle. We would analyse patients in the groups to which they had been randomised, regardless of whether or not they had received the treatment they had been assigned or whether or not they had been observed until the completion of the follow-up period.

We would test homogeneity of effect sizes among studies being pooled using the Chi^2 statistic for homogeneity, with $P < 0.1$ as the level of significance. We would conduct meta-analysis using the random-effects model if the data were sufficiently homogeneous, both clinically and statistically.

If meta-analysis was performed then we would conduct sensitivity analyses based on the following:
(1) Methodological quality: studies with inadequate or unclear allocation concealment would be excluded from meta-analysis.
(2) Methods of meta-analysis: random and fixed-effects models would be compared.

Assessment of risk of bias in included studies

Two review authors (XB, RF) would independently assess all included studies for risk of bias. A third reviewer (JE) would resolve disagreement. We would assess the risk of bias for every included study using the Cochrane risk of bias tool (Higgins 2008).

We would consider the following criteria:

1. Randomisation sequence generation. Was the allocation sequence adequately generated?

2. Allocation concealment. Was allocation adequately concealed?

3. Blinding of participants, personnel and outcome assessors. Was knowledge of the allocated intervention adequately prevented during the study?

4. Incomplete outcome data. Were incomplete outcome data adequately addressed?

Under each criterion, studies would be given a judgement according to the following:

i. 'YES'. (i.e. low risk of bias)

ii.'NO'. (i.e. high risk of bias).

iii.'UNCLEAR'. (uncertain risk of bias).

RESULTS

Description of studies

Two review authors evaluated all studies in order to assess whether they matched inclusion criteria.

Results of the search

In the first version of this review, we identified 686 references through electronic searching. After careful consideration, none of them could be included in our review. In the new search, we identified 892 references through electronic searching and we selected 56 for further evaluation. A second review cut down to ten the number of studies finally evaluated but none of them matched our inclusion criteria.

Included studies

We found no studies to be included in our review.

Excluded studies

Of the studies finally evaluated, one (O'Neill 2003) studied retrospectively two cohorts of patients treated with surgery or stereotactic radiosurgery for solitary brain metastases from different primary tumours. A different proportion of NSCLC patients was observed in the two arms (48% versus 54%) and radiosurgery was used more frequently on symptomatic patients (89% versus 74%). Although the authors concluded that radiosurgery provided a better local control than surgery, this comparison has many methodological shortcomings.

Auchter 1996 described the outcome of patients managed by radiosurgery but potentially candidates for surgical resection. As in the study of O'Neill 2003, it was performed in patients with a mixture of histologies: only 48% were NSCLC patients, 52% had extracranial metastases. Patients with single and solitary brain metastases were included in the same study. Bogart 1999 had a limited number of patients (15) but all of them had NSCLC and solitary brain metastases. However, the technique used in this study (surgical resection plus I-125 brachytherapy) did not match the criteria of our review. We considered three studies using surgery as the primary treatment of brain metastases (Granone 2001; Muacevic 1999; Wronsky 1995). All three were finally excluded because they treated patients of all types of primaries and were retrospective cohort studies. The reported one-year median survival time (MSV) was 46.3%, 53% and 80% respectively and operative/peri-operative mortality was 3% according to Wronsky 1995.

Maiuri 1998 reported a series of 240 patients with surgically resected solitary brain metastases during a period of 17 years (from 1976 to 1993). This is the largest series published. The study was excluded because it was retrospective, patients were evaluated by different diagnostic procedures (some with CT and others with MRI), all types of primaries were included and treatment varied from patient to patient, including radiosurgery and WBI that was not administered uniformly.

Li 2000 was a non-randomised comparison of three different radiation therapy techniques (radiosurgery or whole brain irradiation or both) for a single brain metastasis from small cell lung cancer (SCLC) and NSCLC. In this study, as in others, patients with a solitary metastasis and those with active extracranial disease were included, and a group treated with surgery alone was not included. Flannery 2003 used gamma knife stereotactic radiosurgery on NSCLC patients including two different populations: those presenting with a synchronous (single) brain metastasis and those with a metachronous (solitary) brain metastasis. The study reported a survival advantage for patients with solitary brain metastasis in comparison to single brain metastasis (one-year survival: 84.4% versus 40.5%, P = 0.001).

Results of different treatment options for NSCLC brain metastases were reported by Ohta 2002, but only 9 out of 23 patients met the criterion of having solitary lesions which were treated by different techniques.

Risk of bias in included studies

We did not include any studies and therefore could not assess risk of bias.

Effects of interventions

In summary we could not find any randomised study prospectively comparing surgery with radiosurgery for patients diagnosed with solitary brain metastases from NSCLC. No additional information could be obtained from the updated search.

DISCUSSION

Patients with NSCLC and brain metastases usually have a extremely poor prognosis. However, some authors have suggested that there is a subgroup of patients who may have a better prognosis if appropriately treated (Flannery 2008; Hu 2006). Therefore, two main questions arise: which is this group of patients and what can be considered the most appropriate treatment? At present there is no clear definition of the "best group".

From the available literature, there are different groups of patients with brain metastases: those with single brain metastases, synchronous with the primary tumour or from an uncontrolled primary tumour, and those with true solitary brain metastases, developing some months or years after successful management of the primary tumour. We decided to establish a narrow focus for our review, including only patients with a true solitary brain metastasis. This definition only includes patients with a single brain deposit without any evidence of disseminated disease at the time of diagnosis of brain metastasis. We realised that this clear concept has many different interpretations in the literature and in almost all reviewed papers there was a mixture of patients, most frequently with single and solitary brain metastases in the same cohort. Despite the fact that NSCLC is the leading cause of brain metastases and common enough to accrue representative groups of patients, many studies included in the same group patients with other histologies such as breast cancer, melanoma, hypernephroma and SCLC, making interpretation of the data extremely difficult.

As solitary brain metastasis is a radiological concept, new imaging techniques, including MRI and possibly positron emission tomography (PET) scan can question the validity of previous studies in which diagnoses were made by older radiological equipment, meaning that patients supposed to have solitary deposits may have had unsuspected multiple lesions causing a stage migration (Feinstein 1985).

Neurosurgery under expert hands has little margin for technical deviations. However, radiosurgery has a very wide range of technical possibilities as described in the literature, the most frequently used being the gamma knife, single dose and fractionated stereotactic radiotherapy with or without the addition of whole brain irradiation. Not only is there variability in technique and dose, but also in dose prescription, varying widely from one centre to another. New devices for delivering high precision radiotherapy will increase radiotherapy options during the next few years. However, proof of their clinical effectiveness has not yet been demonstrated.

Finally, our decision to exclude non-randomised studies resulted in a systematic exclusion of all the identified papers because they were all retrospective. Some provided non-randomised comparisons that were considered unacceptable for informing an evidence-based recommendation. In the absence of direct evidence of the clinical effectiveness of surgery compared to radiosurgery for solitary brain metastases from NSCLC we conclude

that further specific research by prospective randomised trials should be carried out.

AUTHORS' CONCLUSIONS

Implications for practice

As surgery has never been compared to radiosurgery in a prospective, randomised trial, there is no evidence to determine which is the best option for patients with solitary brain metastases from NSCLC. The clinical impact of new radiotherapy technologies needs to be assessed using properly designed clinical trials.

Implications for research

There is a need for comparative randomised clinical trials assessing the role of neurosurgery and radiosurgery. The studies should be limited to patients with NSCLC, with a solitary brain metastasis diagnosed by the best neuroimaging technique available. The type of radiosurgical treatment should be defined in advance and variables of radiotherapy dose definition and delivery should be carefully controlled.

ACKNOWLEDGEMENTS

To Jose Expósito (Managing Editor of the Cochrane Lung Cancer Group) for his assistance.

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APPENDICES

Appendix 1. Search strategy

1. exp radiosurgery/
2. Radiosurg*.tw.
3. Stereotactic surgery.tw.
4. Stereotactic radiotherapy.tw.
5. Whole brain irradiation.tw.
6. Whole brain radiotherapy.tw.
7. WBI.tw.
8. or/1-7
9. exp brain neoplasms/
10. central nervous system neoplasm/
11. exp neoplasm metastasis/
12. brain adj5 metastas*.tw.
13. cerebral adj5 metastas*.tw.
14. intracranial tum*.tw.
15. (single adj5 metastas*).tw.
16. (solitary adj5 metastas*).tw.
17. or/9-16
18. #8 and #17
19. exp lung neoplasms/
20. exp carcinoma non-small-cell lung/
21. lung cancer.tw.
22. lung carcinoma.tw.
23. non-oat cell.tw.
24. non small cell.tw.
25. NSCLC.tw.
26. or/19-25
27. #18 and #26

WHAT'S NEW

Date	Event	Description
3 December 2013	Review declared as stable	A new review looking at all brain metastases will be completed at the Neuro-oncology Subgroup of the Gynaecological Cancer Group.

CONTRIBUTIONS OF AUTHORS

RF had the idea to develop the review. XB and RF reviewed the abstracts. RF wrote the review and XB and JE provided feedback and assisted with revisions of the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Institut Català d'Oncologia, Spain.
- Iberoamerican Cochrane Centre. Hospital de la Santa Creu i Sant Pau, Spain.

External sources

- No sources of support supplied

NOTES

This review will no longer be updated. It will be replaced by a review looking at all brain metastases that will be completed at the Neuro-oncology Subgroup of the Gynaecological Cancer Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Lung Neoplasms; *Radiosurgery; Brain Neoplasms [secondary] [*surgery]; Carcinoma, Non-Small-Cell Lung [secondary] [*surgery]

MeSH check words

Humans