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Bogotá, D.C., Agosto 1 de 2006

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Ciudad

Estimado doctor Martínez:

Cordial saludo; por medio del presente enviamos copia del protocolo de investigación titulado "Palliative endobronchial brachytherapy for non small cell lung cancer" abalado avalado por el Grupo de Cáncer de Pulmón de la Colaboración Cochrane y promovido por el Grupo Colombiano de la Colaboración Cochrane, como parte del proceso de evaluación para promoción al segundo año de la subespecialidad de oncología clínica. Adjunto encontrará los avances en el artículo producto de la investigación, y una breve declaración de los autores sobre sus aportes en el desarrollo del mismo. Los textos se presentan en idioma ingles por requerimiento del Grupo Editorial de la Colaboración Cochrane; una vez sea terminado el artículo, será puesto a consideración para publicación en alguna revista internacional.

Agradecemos su atención y quedamos a la espera de sus comentarios.

Atentamente,

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GINS
02.A60.06

Participación dentro del proceso de elaboración del la revisión sistemática Palliative endobronchial brachytherapy for non small cell lung cancer

Dr. Andrés Felipe Cardona

- Diseño y desarrollo del protocolo
- Diseño de la estrategia de búsqueda en Medline y Embase
- Selección de estudios incluidos
- Integración de información
- Elaboración del documento de resumen (artículo para publicación)

Dr. Andrés Yepes

- Diseño y desarrollo del protocolo
- Búsqueda manual
- Auditoria al proceso de selección de estudios incluidos
- Integración de información
- Elaboración del documento de resumen (artículo para publicación)

Dra. Vanessa Ospina

- Búsqueda manual
- Selección de estudios incluidos
- Integración de información
- Elaboración del documento de resumen (artículo para publicación)
- Corrección del documento de resumen

PALLIATIVE ENDOBRONCHIAL BRACHYTHERAPY FOR NON-SMALL CELL LUNG CANCER

(Protocol)

Cardona AF, Reveiz L, Ospina EG, Ospina AV, Yepes A.

Date of most recent substantive amendment: 15 January 2006

This record should be cited as: Cardona AF, Reveiz L, Ospina EG, Ospina AV, Yepes A. Palliative endobronchial brachytherapy for non-small cell lung cancer. *The Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD004284. DOI: 10.1002/14651858.CD004284.

BACKGROUND

Lung cancer is one of the most common neoplasms for men and women in developed countries (Becket 1993;Boyle 2000;Globocan IARC 2000). Between 75% and 85% of patients have non-small cell lung cancer (NSCLC) (squamous cell, adenocarcinoma and large cell undifferentiated carcinomas), of whom only 10 to 20% will have tumours that are potentially curable, and at the time of diagnosis most tumours in patients with NSCLC are stage IIIB or IV and are not surgically resectable (Paradelo 1992).

External beam radiotherapy (RT) to the primary tumour in the chest has been used to treat patients for many years. About 90% of treatments for advanced NSCLC are palliative, of which 20-30% are radiotherapy (Emami 1997;Maher 1993). External beam radiation and/or systemic chemotherapy may reduce tumour size and provide symptom improvement. Nevertheless, the disease often recurs in these patients at the site of the initial lesion (Edell 1993).

Regimens for palliative radiotherapy evolved from clinical experience and although surveys undertaken in the 1990s found wide variation in clinical practice, treatments had not been rigorously evaluated in clinical trials until the late 1980s and 1990s (Macbeth 2002).

In a previous Cochrane review of the effectiveness of external beam palliative radiotherapy regimens, the authors concluded that the majority of patients should be treated with short courses of 1 to 2 fractions of radiotherapy. More research is needed to assess definitively efficacy and tolerability of palliative radiotherapy in NSCLC (Macbeth 2002).

In the management of endobronchial disease, brachytherapy, laser resection or endoluminal prosthesis placement may be beneficial in airway obstruction. These modalities can be used individually or in combination (Paradelo 1992; Shaw 1993). The aim of palliative brachytherapy is to deliver endobronchial radiation therapy with minimal injury to normal lung parenchyma. This approach entails placing a small catheter across the endobronchial cancer using a fibreoptic bronchoscope (Schray 1988).

Brachytherapy is usually used for palliation in a patient with persistent or recurrent dyspnoea, haemoptysis or cough and endoscopic evidence of an airway tumour. Radiation protocols differ depending on the dose being used. Low-dose brachytherapy consists of insertion of a strand of iridium 192 delivering doses less than 1 Gy/hr (total dose, about 30 Gy) in the bronchus (Schray 1988). High-dose brachytherapy provides greater doses of iridium 192, and delivery of more than 10 Gy/hr (total dose, 20 to 40 Gy). Two to four treatments are usually delivered about 1 week apart (Speiser 1993).

The most serious complications of brachytherapy are massive haemoptysis, formation of tracheoesophageal fistulas, bronchospasm, bronchial stenosis, and radiation bronchitis (Perez 1992).

- BRAQUITERAPIA
- RADIOTERAPIA
- NEOPLASIAS PULMONARES

The aim of this review is to determine in patients with symptomatic NSCLC, if endobronchial brachytherapy is more effective and less toxic than external beam palliative radiotherapy, and other endobronchial procedures. Additionally, we will evaluate what dose of endobronchial brachytherapy is most effective and least toxic.

OBJECTIVES

To evaluate the effectiveness and toxicity of palliative endobronchial brachytherapy in increasing survival and controlling thoracic symptoms in patients with advanced non-small cell lung cancer, compared with either external beam radiation or other alternative endoluminal treatments including laser, surgery and stent applications.

To establish the optimal dose or regimen of palliative endobronchial brachytherapy and best fractionation schedule.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised controlled trials of palliative endobronchial brachytherapy will be included. Concurrent cohort comparisons and other non-experimental designs will be excluded.

Types of participants

Patients with histologically confirmed lung cancer of non-small cell type, locally advanced with observable endoluminal tumour of the trachea, main stem or lobar bronchi and with recurrent or persistent thoracic symptoms (haemoptysis, cough, dyspnoea, or post-obstructive pneumonitis).

Types of intervention

Endobronchial brachytherapy with palliative intent (i.e. with the intent of controlling symptoms, not cure) with different techniques, doses and fractions, compared with either external radiotherapy and other endoluminal procedures for non-small cell lung cancer, or with best supportive care. Combination treatment with external radiotherapy, laser photoresection and endobronchial surgery with or without diathermy will be considered.

Types of outcome measures

The following outcome measures will be considered:

- Improvement in major thoracic symptoms (degree and duration) as assessed by patient and doctor
- Quality of life (QOL) or functional status measured by standard and valid instruments (assessed using the ECOG scale or Karnofsky index)
- Radiological improvement
- Short- and long-term toxicity
- Survival from date of randomisation or first treatment
- Cause of death
- Degree of endobronchial obstruction if available.
- Patient convenience and acceptability

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Electronic databases to be searched include Medline, Embase, Cancerlit and the Cochrane library. The search strategies of the Cochrane Lung Cancer Review Group appropriate to each

of the databases will be applied and in addition the following specific search terms will be added to the search strategy for each respective database:

Medline (OVID)
1-25: see LCG Medline (OVID) strategy

26. Lung neoplasms
27. Non Small Cell Lung Cancer/
28. 26 or 27
29 . (Lung or pulmon$ or pneumo$).tw.
30. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
31. 29 or 30
32. NSCLC
33. exp radiotherapy/
34. exp radiotherapy, computer-assisted/
35. exp radiation dosage/
36. exp radiotherapy dosage/
37. exp radiotherapy, high-energy/
38.exp dose fractionation/
39. exp brachytherapy/
40. exp radiation oncology/
41. radiotherapy$.tw.
42. (thorac$ adj2 radiotherap$).ti,ab.
43. (radiat$ adj2 therap$).ti,ab.
44. (thorac$ adj2 radiat$).ti,ab.
45. irradiation.tw.
46.((endobronch$ or intralum$ or endolum$) adj2 (brachytherap$ or curietherap$)).ti,ab.

Embase
1-19: See LCG Embase (OVID)
20. Lung tumor/
21. Lung Non small cell cancer/
22. (Lung or pulmon$ or pneumo$).tw.
23. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
24. NSCLC
25. exp radiotherapy/
26. exp computer assisted radiotherapy/
27. exp radiation dose/
28. exp megavoltage radiotherapy/
29. exp adjuvant therapy/
30. exp radiation dose fractionation/
31. exp brachytherapy/
32. exp cancer radiotherapy/
33. Radiotherapy$
34. (Thorac$ ADJ radiotherap$).ti,ab.
35. Radiat$ ADJ therap$).ti,ab.
36. (Thorac ADJ radiat$).ti,ab.
37. Irradiaition.tw.
38. ((endobronch$ or intralum$ or endolum$) ADJ (brachytherap$ or curietherap$))

The Cochrane Controlled Trials Registry Central/CCTR
1. Lung neoplasms
2. Non Small Cell Lung Cancer/
3. 1 or 2
4 . (Lung or pulmon$ or pneumo$).tw.
5. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
6. 4 or 5
7. NSCLC
8. exp radiotherapy/

9. exp radiotherapy, computer-assisted/
10. exp radiation dosage/
11. exp radiotherapy dosage/
12. exp radiotherapy, high-energy/
13. exp dose fractionation/
14. exp brachytherapy/
15. exp radiation oncology/
16. radiotherapy$.tw.
17. (thorac$ adj2 radiotherap$).ti,ab.
18. (radiat$ adj2 therap$).ti,ab.
19. (thorac$ adj2 radiat$).ti,ab.
20. irradiation.tw.
21. ((endobronch$ or intralum$ or endolum$) adj2 (brachytherap$ or curietherap$)).ti,ab.

Additional strategies for the databases will be designed with the same criteria. Other strategies will be designed to include: references of review articles, books related to radiotherapy or brachytherapy and hand searches in the journals: International Journal of Radiation, Oncology, Biology and Physics; Radiotherapy and Oncology; Journal of Clinical Oncology; Clinical Oncology, Lung Cancer, Thorax and Chest from 1990 to 2003.

The editors of these journals will be contacted to give us the names, addresses and e-mails of researchers who submitted manuscripts of controlled trials that were not published. We will also consult local experts in the field. In the same way we will search in databases of ongoing trials such as www.controlled-trials.com.

Electronic addresses of radiotherapy and brachytherapy centres, societies and departments will be searched through Altavista using an advanced strategy, and will be contacted to find other ongoing or unpublished studies.

Relevant trial reports in all languages will be included.

METHODS OF THE REVIEW

Eligibility of the retrieved articles will be assessed from the title and abstracts. Where there is insufficient information for assessment, the full articles will be reviewed by authors.

All randomised clinical trials will be assessed independently by at least 2 reviewers (EO and LR) and (AC and JIM). There will be no blinding of the reviewer as to the origin, or conclusions of the article for eligibility assessment, data extraction or quality assessment.

Where necessary information will be sought from the principal investigator of the trial concerned. The data will be extracted by 2 reviewers independently to ensure validity, and if necessary discrepancies will be solved by an open discussion between all investigators.

Data will be extracted from the included studies (those that fulfill the inclusion criteria) using a specific methodology and a previously tested form. Methodological quality of included studies will be assessed according to the following aspects of trial quality:
1) Randomisation method: Any aspects of the randomisation method or characteristics of the data set which could imply inadequate concealment or differences in recruitment into the respective treatment arms will be noted and considered during article evaluation.
2) Adherence to intent-to-treat in the data set: The possibility of post-randomisation exclusions from or crossover between the treatment arms will be assessed.
3) Completeness of follow-up: The distribution of time since last information recorded will be rated and differences between treatment arms will be regarded as indicating less reliable follow-up.

Heterogeneity assessment
Homogeneity of the results for the various endpoints of interest will be explored using L'Abbe's (L'Abbe 1987) visual plot and through formal statistical testing. Heterogeneity in the results is expected to occur as the result of many potential factors (postulated a priori), and if this is indeed observed, the effect of the various potential sources of heterogeneity will be explored in an attempt to identify subgroups where the results are homogeneous. Meta-analysis will be undertaken if the results for the various endpoints of interest are sufficiently homogeneous. (Deeks 2001).

Potential sources of heterogeneity:
1. Quality of studies.
2. Full article publication only versus full and abstract publications.
3. Brachytherapy dose fractionation.
4. Proportion of patients with brain metastases.
5. Degree of bronchial obstruction.
6. Methods of symptom assessment (patient or doctor or both) and QOL assessment.

Sensitivity analysis
Sensitivity analysis will be performed by systematically excluding studies from the overall analysis based on the potential sources of heterogeneity hypothesised above and if homogeneous subgroups have not already been identified and analysed separately. (Lau 1997,Smith 2001).

Statistical considerations
Quantitative outcomes for dichotomous and continuous data will be evaluated using RevMan 4.2. Analysis based on intention-to-treat will be used. Outcomes of interest will be compared between the two treatment arms using the odds ratio with 95% confidence intervals. For survival analysis, estimation of the hazard ratio and its variance (Parmar 1998) will be used as the summary statistic where the data permits. The random effects model (DerSimonian 1986,DerSimonian 1996) will be used for the analysis. The number needed to treat (Cook 1995,McQuay 1997) will be calculated to represent the magnitude of any effect if identified. Assessment of publication bias (funnel plot) (Lau 1997) will be performed to evaluate the likelihood of publication bias in this topic.

Quantitative outcomes for dichotomous and continuous data will be evaluated using Revman 4.2 and appropriate tests for heterogeneity and robustness of data will be performed. Time to event analysis (time to death) will be approximated by either: analysing for different follow-up periods or calculating a weighted average of median survival duration across studies. If possible, sub-group analysis will be performed by dose or regimen of brachytherapy and co-interventions. A judgment regarding if and how to combine quality of life outcomes will be made depending on if and how this information is collected in each trial. If we cannot do a quantitative analysis we will conduct a qualitative review and synthesis of study results.

POTENTIAL CONFLICT OF INTEREST

None known.

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Palliative endobronchial brachytherapy for non-small cell lung cancer [Review]

Cardona AF, Reveiz L, Ospina EG, Ospina AV, Yepes A.

This review should be cited as: Cardona AF, Reveiz L, Ospina EG, Ospina AV, Yepes A. Palliative endobronchial brachytherapy for non-small cell lung cancer (Cochrane Review). In: The Cochrane Library, Issue 3, 2005. Oxford: Update Software.

Synopsis

Abstract

Background

The nearly epidemic proportions of lung cancer in the modern industrial world and the high mortality rate associated with this disease offer considerable challenge to the oncology community. The incidence of lung cancer has been increased significantly and represents one of the most common neoplasms for men and women in developed countries, ranking as the second among the conditions causing mortality, and also as the leading cause of cancer death (Becket 1993; Boyle 2000;Globocan IARC 2004). Although the search concerning early diagnosis and treatment of several cancer types has shown a great impact on survival, no considerable advance has been obtained with lung cancer.

Between 75% and 85% of patients have non-small cell lung cancer (NSCLC), of whom only 30% will have tumors that are potentially curable with surgical resection. However, in only 40% of cases can a fatal outcome be avoided because at the time of diagnosis 60% to 70% of these patients had distant metastases or local failure, that is also a significant problem in at least 20% of individuals undergoing curative interventions (Paradelo 1992; Huber 1995).

About 90% of treatments for advanced NSCLC are palliative, of which 20% to 30% received radiotherapy (Emami 1997;Maher 1993). Regimens for palliative radiotherapy had not been rigorously evaluated in clinical trials until the late 1980s and 1990s (Macbeth 2002), when research evolved from clinical experience to rigorous evaluation

in clinical trials investigating different palliative schedules in inoperable NSCLC that shows rates of symptoms relief between 48% to 80% (Maher 1992).

In a previous Cochrane review designed to evaluate which is the most effective and least toxic regimen of palliative external radiation therapy (XRT) in patients with locally advanced non-small cell lung cancer, the authors concluded that this treatment appears to be effective in controlling troublesome symptoms from intrathoracic tumor. They recommends that the majority of individuals should be treated with short courses of XRT (such as 10Gy/ 1 fraction or 16-17Gy/ 2 fractions) and in selected cases with good performance status, with higher dose regimens (such as 36Gy/ 12 fractions); nevertheless, more research is needed to assess definitively efficacy and tolerability of palliative external radiotherapy (Macbeth 2002).

Most patients with endobronchial lesions are not curable and for inoperable patients local treatment of bronchial occlusion may be beneficial, since obstruction is an important determinant of the quality of life, causing dyspnea, cough, hemoptysis, pneumonitis and postobstructive pneumonia. In the management of endobronchial disease, brachytherapy, laser resection, cryosurgery, electrocautery, endobronchial surgery or endoluminal prosthesis placement may be beneficial to reduce airway obstruction (Paradelo 1992; Shaw 1993).

Conventional endobronchial brachytherapy (EBB) has been used as one approach to improve local control, either alone or in combination with another treatment modalities, since the time Madame Curie discovered radium 100 years ago (Yankauer 1922). The theoretical advantages of BT be summarized briefly, in delivery of a high tumor dose in comparison with an external beam, rapid decrease of dose outside the treated volume, and precise dose localization and adaptability to tumor shape. The use of brachytherapy has increased in recent years due to several innovative technologic advances, including, low energy iodine-125 and palladium-103 radionuclides, HDR remote afterloading, computerized dosimetry, and utilization of newer imaging techniques (Schray 1988, Hilaris 1994).

Brachytherapy for lung carcinoma will be categorized into interstitial and intraluminal techniques. Most commonly, interstitial implantation is used at the time of surgical resection, placed percutaneously or by thoracoscopy. Intraluminal techniques were introduced in the early 1920s; EBB is divided into low, intermediate, and HDR applications and refers to the temporary placement of the isotope into the tracheobronchial tree (Schray 1988, Speiser 1999, Burt 1987).

Actually, radiation protocols differ depending on the dose and isotope being used. Low-dose EBB consists of insertion of an isotope strand delivering doses less than 1 Gy/hr (total dose, about 30 Gy) in the bronchus, and high-dose EBB provides doses of more than 10 Gy/hr (total dose, 20 to 40 Gy) (Schray 1988). Two to four treatments are usually delivered about 1 week apart.

In earlier studies EBB was particularly used as palliative treatment in case of endobronchial recurrences after XRT. Later, was also combined with XRT and another interventions achieving response rates of 99% for haemoptysis, 85% for cough, 86% for dyspnea and 99% for postobstructive pneumonia and atelectasis (Seagren 1985, Chang 1994). Recently, a systematic overview of radiation therapy effects in NSCLC reveals that endobronchial brachytherapy appears to be not superior to external beam radiotherapy (Sirzen 2003). The most serious complications described with EBB are massive haemoptysis, formation of tracheoesophageal fistulas, bronchospasm, bronchial stenosis, and radiation bronchitis (Perez 1992).

The aim of this review was to determine if EBB is more effective and less harmfully than external beam radiotherapy or other endobronchial interventions in patients with symptomatic NSCLC. Additionally, we will evaluate what dose of EBB is most effective and least toxic.

Objectives

The primary objective of this review was to assess the effectiveness of palliative EBB in increasing survival and controlling thoracic symptoms in patients with advanced non-small cell lung cancer, compared with either external beam radiation or other alternative endoluminal treatments, including laser, cryosurgery, electrocautery, endosurgery and stent applications. Additionally, we evaluated the optimal dose regimen of palliative EBB, best fractionation schedule and rates of adverse events associated with this treatment.

Criteria for considering studies for this review

Types of studies

Studies were included if they were a journal publication of a RCT of palliative EBB for advanced NSCLC. Other sources of information like abstracts and proceedings of relevant scientific meetings, or information achieved by direct contact with investigators were also considered. Reports of EBB for non palliative management of NSCLC, concurrent cohort comparisons and other non-experimental designs were excluded.

Types of participants

Patients with histologically confirmed lung cancer of non-small cell type, locally advanced with observable endoluminal tumor of the trachea, main stem or lobar bronchi and with recurrent or persistent thoracic symptoms (haemoptysis, cough, dyspnea, or post-obstructive pneumonitis).

Types of intervention

Endobronchial brachytherapy with palliative intent (i.e. with the intent of controlling symptoms, not cure) with different techniques, doses and fractions, compared with either external beam radiotherapy, other endoluminal procedures, chemotherapy or with best supportive care for advanced NSCLC. Combination treatment with external radiotherapy, laser photoresection and endobronchial surgery with or without diathermy were considered.

Types of outcome measures

The following outcome measures were considered in the review:

- Improvement in major thoracic symptoms (degree and duration) as assessed by patient and doctor
- Quality of life (QOL) or functional status measured by standard and valid instruments (assessed using the ECOG scale or Karnofsky index)
- Radiological improvement
- Short- and long-term toxicity
- Survival from date of randomization
- Cause of death
- Degree of endobronchial obstruction if available
- Patient convenience and acceptability

Search strategy for identification of studies

We systematically screened the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to December 2004) and EMBASE (1974 to December 2004) using the OVID software system. The search strategies of the Cochrane Lung Cancer Review Group appropriate to each of the databases were applied and in addition the following specific search terms were added to the search strategy for each respective database:

Medline (OVID)

1-25: see LCG Medline (OVID) strategy
26. Lung neoplasms
27. Non Small Cell Lung Cancer/
28. 26 or 27
29 . (Lung or pulmon$ or pneumo$).tw.
30. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
31. 29 or 30
32. NSCLC
33. exp radiotherapy/

34. exp radiotherapy, computer-assisted/
35. exp radiation dosage/
36. exp radiotherapy dosage/
37. exp radiotherapy, high-energy/
38.exp dose fractionation/
39. exp brachytherapy/
40. exp radiation oncology/
41. radiotherapy$.tw.
42. (thorac$ adj2 radiotherap$).ti,ab.
43. (radiat$ adj2 therap$).ti,ab.
44. (thorac$ adj2 radiat$).ti,ab.
45. irradiation.tw.
46.((endobronch$ or intralum$ or endolum$) adj2 (brachytherap$ or curietherap$)).ti,ab.

Embase

1-19: See LCG Embase (OVID)
20. Lung tumor/
21. Lung Non small cell cancer/
22. (Lung or pulmon$ or pneumo$).tw.
23. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
24. NSCLC
25. exp radiotherapy/
26. exp computer assisted radiotherapy/
27. exp radiation dose/
28. exp megavoltage radiotherapy/
29. exp adjuvant therapy/
30. exp radiation dose fractionation/
31. exp brachytherapy/
32. exp cancer radiotherapy/
33. Radiotherapy$
34. (Thorac$ ADJ radiotherap$).ti,ab.
35. Radiat$ ADJ therap$).ti,ab.
36. (Thorac ADJ radiat$).ti,ab.
37. Irradiaition.tw.
38. ((endobronch$ or intralum$ or endolum$) ADJ (brachytherap$ or curietherap$))

The Cochrane Controlled Trials Registry Central/CCTR

1. Lung neoplasms
2. Non Small Cell Lung Cancer/
3. 1 or 2
4 . (Lung or pulmon$ or pneumo$).tw.
5. (Cancer or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).tw.
6. 4 or 5

7. NSCLC
8. exp radiotherapy/
9. exp radiotherapy, computer-assisted/
10. exp radiation dosage/
11. exp radiotherapy dosage/
12. exp radiotherapy, high-energy/
13. exp dose fractionation/
14. exp brachytherapy/
15. exp radiation oncology/
16. radiotherapy$.tw.
17. (thorac$ adj2 radiotherap$).ti,ab.
18. (radiat$ adj2 therap$).ti,ab.
19. (thorac$ adj2 radiat$).ti,ab.
20. irradiation.tw.
21. ((endobronch$ or intralum$ or endolum$) adj2 (brachytherap$ or curietherap$)).ti,ab.

Additional strategies for LILACS (from 1982 to the 40th edition) (Castro 1997), and BIOSIS (from January 1980 to December 2004) were designed using similar criteria. Other strategies were employed to include references of review articles, and chapters of books related to lung cancer brachytherapy. Moreover we conducted an additional search using disease terms combined with the most frequent brachytherapy adverse effects.

Leading researchers involved in the field were contacted by e-mail to obtain additional published and unpublished data (an electronic survey of authors found in Medline and Embase was conducted). Electronic addresses of radiotherapy and brachytherapy centers, societies and departments around the world, were searched through Altavista using structured strategies, and were contacted to find other relevant ongoing or unpublished studies.

In addition we searched in clinical trials registers such as Meta-Register of Controlled Trials, www.clinicaltrials.com, www.clinicaltrials.gsk.com, and LATINREC (Latin American Trials Register). Grey literature such as conference abstracts/proceedings from international lung cancer meetings, published lists of theses and dissertations worldwide letters and other literature outside of the main journal literature were searched where possible, but only were considered if data provide sufficient information for the analysis.

There were no language or date restrictions in the searches.

Methods of the review

A total of 752 references obtained from all databases were imported to the bibliographic package, Reference Manager (Version 8). The titles and abstracts of each article were studied and relevant studies (including review articles) selected according to whether they met the inclusion criteria and the full text of these articles was obtained.

Each randomised trial identified by the search was read independently by a pair of two reviewers (CAF / RL and OE / MJI) and assessed for inclusion in the review considering the quality of the methods against pre-determined criteria (randomisation, blinding, statistical methods, methods for assessing symptoms and quality of life, completeness of data and follow-up), and for results. Discrepancies were resolved by consensus between all reviewers, and reasons for excluding studies were noted.

From the included studies key outcome results were identified and collected using a designed form that contents publication details, patient population, randomisation/allocation concealment, details of blinding measures, description of interventions and results. Methodological quality was assessed by the Critical Appraisal of Studies and Collecting Data in the Cochrane Collaboration Handbook, version 3.0.2, with the CONSORT Statement as a basis (Begg 1996). No formal scoring system was adopted. Where necessary information was sought from the principal investigator of the trial concerned. Differences in quality assessment were resolved by referring back to the original article. If necessary, a third party was consulted.

Quantitative outcomes for dichotomous and continuous data were planned to be evaluated using the Revman 4.1 and appropriate tests for heterogeneity and robustness of data be performed. Time to event analysis (time to death) was planned to be approximated by either analysing for different follow-up periods or calculating a weighted average of median survival duration across studies. A fixed effects model was planned to be used for the primary analysis. We also planned to conduct sensitivity analysis using trials of borderline quality if relevant, and also sub-group analysis. A judgement regarding if and how to combine quality of life outcomes was planned to be made depending on if and how this information was collected in each trial. We planned to conduct analysis by intention to treat and to asses publication bias using the funnel plot model.

If it is not possible to carry out a quantitative analysis because of the multiple sources of heterogeneity between included studies (quality of studies, full data publication, tumour stage, brachytherapy total dose and fractionation schedule, degree of bronchial obstruction, methods of symptoms and quality of life assessment) we will try to conduct a qualitative review and synthesis of the selected reports.

Description of studies

From the results of the extensive literature search, 752 citations were initially identified as potentially relevant. Thirty three references were considered as possible randomized controlled trials (RCTs) of EBB alone or in association with other interventions, for the palliation of symptoms related with advanced NSCLC.

Manual culling reduced this number of references to 18 eligible trials and 16 reports were excluded. Ten were duplicate publications of already included data, three were not randomized and the others considered curative brachytherapy interventions. Some of the studies included in the review were partial reports presented as conferences abstracts.

Complementary strategies to identify another relevant studies, unpublished data or ongoing trials were not effective.

The studies considered in the review compared EBB with XRT, diverse fractionation schedules of high dose rate (HDR) EBB, XRT versus HDR EEB, HDR EBB versus HDR EBB plus chemotherapy and combined Nd-YAG laser/HDR EBB versus Nd-YAG laser alone. Non randomized clinical trials that compared palliative EBB with best supportive care, cryosurgery, electrocautery, endosurgery and stent applications were found.

XRT versus XRT in combination with HDR EBB

Four randomized controlled trials (RCTs) that compared external radiotherapy vs. external radiotherapy in combination with HDR EBB met the inclusion criteria. Three of the reports were duplicate publications of already included data published as preliminary analysis (Huber 1990; Pollinger 1996, 1997); the other two trials were presented as conference abstracts (Sharma 1998, Baas 1994), and their authors could not be contacted to obtain unpublished additional information on the results.

A total of 290 patients were randomised in these RCTs. The two full published studies included slightly different patient groups. The German trial (Huber 1997) considered only candidates for palliative interventions, while the Langendijk study (Langendijk 2001) divided groups according to two fractionation schedules of external irradiation; one radical (60 Gy), for patients with stage I or II disease with a tumor diameter > 4 cm or stage IIIa and stage IIIb disease without supraclavicular lymph node metastases and a WHO (World Health Organization) performance status ≤ 2. The other group includes patients with a WHO performance status of 3, with supraclavicular lymph node compromise and/or distant metastases with symptoms related to intrathoracic tumor. These individuals were considered to have the worst prognosis and were selected for the palliative fractionation schedule using a smaller dose of external radiation (30 Gy). Inclusion of these patients could influence the assessment of effectiveness or toxicity and might affect the survival results. Only fifty two patients are Stage IIIB and met the inclusion criteria of the systematic review.

For patients treated according to the palliative schedule, the target volume was irradiated with 3 Gy per fraction (four times a week) up to a total dose of 30 Gy (Langendijk 2001). For patients treated according to the radical schedule, the aforementioned target volume was treated with fraction doses of 2,25 Gy (four times a week) to a total dose of 45 Gy, followed by a boost up to 60 Gy, using fraction doses of 2,5 Gy (four times a week) on the gross tumor volume. Patients allocated to treatment arm 2 (external radiation in combination with endobronchial brachytherapy) received an additional two fractions of 7.5 Gy with HDR EBB in weeks 1 and 2. The choice of the external fractionation schedule was left to subjective decision of the treating physician what facilitates a bigger selection bias.

Of the eligible patients (Langendijk 2001), 47 were randomized to receive XRT alone and 48 to XRT and EBB. In 75 patients (79%), the radical fractionation schedule and in 20 patients (21%), the palliative schedule was used. Survival, respiratory symptoms (dyspnea), changes in quality of life (QoL), re-expansion of atelectasis, compliance to treatment and complications were assessed.

The Huber's trial (Huber 1997) included 98 patient with inoperable advanced non small cell lung cancer proven by histology or cytology, located in the trachea, mainsteam or lobar bronchi, with not further concurrent tumor treatment and Karnofsky performance status greater than 50%. Forty two patients were assigned to group 1, and were treated with a mean external radiation dose of 50,5 + / - 14,5 Gy; group 2, received a mean external radiation dose of 50 + / - 12,5 Gy followed by an additional dose of 7,44 + / - 2,6 Gy (at 10 mm depth) through endobronchial brachytherapy applied one week before, and three weeks after completion of external beam irradiation. Survival time was considered the principal end point of the study; assessment of local control, time until observed local recurrence and adverse effects were considered as secondary outcomes.

In both studies it is not mentioned that the selection of the patients had been made according to age, sex or histology. Brachytherapy procedure was performed using an Iridium-192 stepping source. In Hubar's study, all doses reported were calculated at a distance of 5 mm from the source axis, while in the other study, used doses were prescribed on a distance of 1cm. Only one of the trials mentioned that the application time ranged from 2 to 15 minutes, depending on the length of the irradiated area.

Follow up assessments differs significantly between the two studies. Both trials used the international staging system for lung cancer as recommended by the American Joint Comitte on Cancer, and only in one of them (Huber 1997), reference was made to the histological classification used in pathologic evaluation. In the clinical trial of Langendijk, the follow up began in the fourth week during radiotherapy, when a chest radiograph was made to evaluate whether it was necessary to change the original field set up for the boost, because of changes due to re-expansion of atelectasis or postobstructive pneumonia. In case of major changes because of resolution of atelectasis, a new planning CT scan was made and the treatment was adjusted.

In an opposed manner in the other study (Huber 1997) the first radiographic evaluation was carried out in the third month. Moreover, the scales used to evaluate the quality of life after the treatment was different. One of the studies used the index of Karnofsky (Huber 1997), while the other one (Langendijk 2001) used the Dutch version of the EORTC QLQ-C30 and the lung cancer module QLQ-LC13.

Different outcomes were measured and reported in these studies. The two trials reported survival as an outcome, even one of them considers it the main outcome, although in the context of a palliative treatment this may be less important than the measurement of symptom control and quality of life.

In the concise report of the study entitled prospective comparative study of external radiation plus HDR EEB versus external radiation alone in the palliative treatment of

bronchogenic carcinoma (Sharma 1998), the authors informed that 60 patients with inoperable NSCLC were included and randomized into two groups. All the individuals had endobronchial disease, and received a dose of 30 Gy of external beam radiotherapy divided in 10 fractions along two weeks. The endobronchial brachytherapy was delivered using micro-selectron HDR machine, and dose of 8 Gy at 1 cm from central axis of the source was administered in two sessions. The clinical profile of both study groups appears to be comparable. No additional information was obtained from authors or by the searches.

The other study (Baas 1994) was presented as an abstract in an international lung cancer meeting. In this short report, the authors scarcely describe the methodology used in the development of the study. However, it is clear that it corresponds to a prospective randomized multicenter trial with three arms, initiated to evaluate the additional effect of photodynamic therapy and high rate dose rate EBB associated with XRT, in the treatment of patients with advanced NSCLC. The patients should complete the following conditions to be included: weight loss <10% and functional status> 70%. The patients were treated using Photofrin (2 mg/Kg, 200 J/cm. 630 nm) and EBB (15 Gy at 1 cm distance along the tumor) 2 weeks before XRT (14 x 2,5 + 8 x 2,5 Gy to the tumor area in four weeks). Of the 43 patients included, only 37 presented stage III disease and the treatment were considered as palliative; of these, 12 patients received XRT alone, 12 external irradiation plus EBB and 15 photodynamic therapy with external XRT.

Comparison between diverse fractionation schedules of HDR palliative endobronchial brachytherapy

Five studies that compared diverse fractionation schedules of HDR palliative endobronchial brachytherapy were found by the search. Of them, one was published multiple times and it should be excluded by not having random assignment (Speiser 1992). Two of the reports were presented as summaries in international lung cancer meetings; in them the methods used for the selection of patients, the follow-up and the type of intervention are described marginally (Poellinger 2000, Calaguas 1997). It was impossible to contact the authors to obtain additional information.

The other study (Huber 1995, interim results), corresponds to a preliminary report of a clinical trial designed by Huber and collaborators, in which 93 patient with central tumors (substantial occlusion evidenced by bronchoscopic examination) with no alternative treatment options such as surgery, external radiotherapy or chemotherapy, and with no concurrent tumor treatment underway, were treated with two different fractionation schedules of endobronchial palliative brachytherapy. There was no selection of patients regarding age, sex, histologic findings, tumor stage, or Karnofsky performance status. Upon entering the study, all patients were staged according to the international staging system for lung cancer as recommended by the American Joint Committee on Cancer. Histologic classifications were done following the guidelines of the WHO.

The first group received brachytherapy with a total dose of 15.4 Gy, delivered in four fractions of 3.8 Gy at 10 mm from the source axis at weekly intervals. The second group received brachytherapy with a total dose of 14.4 Gy in fractions of 2x7.2 Gy at 10 mm from the source axis with an interval of three weeks.

Of the 93 patients included, 44 subjects were in group 1 divided in 36 (81,8%) men and 8 (18,2%) women, and 49 in group 2 divided in 34 (69,4%) men and 15 (30,6%) women. Eighty nine patients had advanced disease; of them 65 had NSCLC (31 in the group 1 and 34 in the group 2). The two major histologic types were squamous cell (52,3% and 46,9% respectively), and adenocarcinoma (18,1% and 22,4%). In group 1, 88,9% and in group 2, 92,7% of the patients had undergone pre-treatment, principally with XRT (group 1, 47,2% mean irradiation dose of 41,8 Gy; group 2, 39%, mean irradiation dose of 52,3 Gy) and Nd-YAG laser (33,3% and 46,3%). More than 40% in each group underwent different combinations of these treatments.

The minimum observation time was 3 months with a median observation time of 2,5 years and survival time was considered the endpoint of the study. Causes of Death and local tumor control assessed three month after the end of treatment were also reported.

The other two reports correspond to abstracts. The first one (Calaguas 1997), try to determine the optimal treatment dose of EBB for primary NSCLC between 500, 700 and 900 cGy (individuals were randomly assigned in each arm), considering the clinical response, host performance status scores (not especified), bronchoscopic and radiologic improvement, and the complications related with the procedure. The number of included patients was 43 and all received XRT prior to the endoluminal treatment (the of urinates it cheats between the interventions was not reported).

The other RCT (Poellinger 2000) investigate different HDR after loading dose schedules for palliative radiation treatment of central lung tumors. (histologic subtypes and tumor stage are not specified); four times 3,8 Gy (administered at 1 cm depth from source axis) per week were compared to twice 7,4 Gy with a three weeks interval regarding survival, local control and side effects. One hundred and forty two patients were included either to group 1 (60 patients) or group 2 (82 patients). Randomization resulted in an equal distribution for both groups with respect to the age, gender, tumor stage, Karnofsky performance status and histology.

XRT versus HDR EBB

Six randomized trials that compared XRT with HDR EBB were identified. One of the trials (Stout 2000) includes 99 patients with histologically confirmed inoperable NSCLC that were prospectively randomized to receive EBB (a single exposure of 15 Gy at a distance of 1 cm from the iridium source in the bronchus) or XRT (eight exposures of megavoltage XRT over 10±12 days, giving 30 Gy). Treatment was given on an out-patient basis. Patients were evaluated before treatment and at 4, 8, 16, 26, 38 and 52 weeks and every 3 months thereafter. Performance status, survival, respiratory function,

and thoracic symptoms assessed either by patient and clinicians were evaluated in this study.

The second trial that compared XRT with HDR EBB (Moghissi 1999), include seventy-five patients with intraluminal microscopically confirmed NSCLC were eligible if they had received no previous thoracic XRT, and had partial obstruction of the trachea or partial or complete obstruction of a main bronchus, the right intermediate bronchus, or a lobar bronchus. Disease had to be locally too advanced for surgical resection or radical radiotherapy with curative intent.

Patients were randomized to XRT (the most frequently used regimen was 17 Gy in two fractions) versus endobronchial treatment. Before randomization, collaborating centres chose for each patient whether the endobronchial option should be brachytherapy, laser treatment or cryotherapy, according to which locally available modality was considered most appropriate. The details of treatment in both arms were decided by the local clinicians; therefore there was no homogeneity in the regimens provided. Endobronchial treatment could be given in more than one session if necessary. The trial measured WHO performance status, thoracic symptoms, survival rates and adverse effects.

The four additional studies were reported as abstracts in congresses of cancer treatment. Two of the trials (Barber 1993, Hopwood 1997) corresponds to partial informs of the article completely published by Stout. The Barber study and the Hopwood report contents additional information concerning quality of life assessed using the Rotterdam Symptom Checklist and Hospital Anxiety and Depression Scale.

Other short report of a parallel randomized clinical trial (Mogulkoc 2000) incorporated 96 patients with inoperable central NSCLC in two arms of treatment that compares the effects of XRT versus EBB. Patients assigned to endobronchial intervention (n = 64) received a single dose of 15 Gy at a radius of 1 cm from the center of the source, delivered by Iridium-192. The XRT patients (n = 50) received eight fractions of radiation therapy over 10 to 12 days, to a total of 30 Gy. The principal outcomes were lung function that was evaluated using espirometry and peak flow rate, before treatment and at 8, 16 and 26 weeks after therapy, and symptoms palliation assessed at similar intervals of time.

[redacted]

HDR EBB versus HDR EBB plus Chemotherapy

The search found only one study that compares (Ferstl 1997) HDR EBB versus EBB plus chemotherapy in nineteen patients with advanced central NSCLC, either inoperable or not suitable to external beam radiation. All patients had diverse grades of bronchial stenosis due to tumor growth and they were randomized in two groups. Group 1 (A) received three course of oral etoposide (150 mg/day during ten days, 12 days interval) and EBB at day five of the course 1 and 3, with 7.2 Gy at 10 mm distance from the source axis. Group 2 (B) received EBB alone 2 x 7.2 Gy with a three weeks interval. The one year survival, mean survival time and adverse effects were reported.

Combined Nd-YAG Laser/HDR Brachytherapy versus Nd-YAG Laser alone

Only one study compares Combined Nd-YAG laser plus HDR EBB versus Nd-YAG laser alone (Chella 2000). It enrolled 29 patients with NSCLC who had already undergone a previous conventional treatment (11 with surgery followed by external beam radiation therapy and 18 with chemoradiotherapy). The patients were randomized in two groups; fifteen patients in group 1 underwent Nd-YAG laser debulking only (an energy of 25–45 W, using pulses up to 1.2 s, was used for a mean total amount of 1850 J; range 1400–2200 J) and fourteen patients in the group 2 underwent HDR EBB 15–18 days after Nd-YAG laser debulking on an outpatient basis. The dose prescription was 5 Gy at 0.5 cm, with a total exposition time variable from 10 to 15 min. The treatment was repeated three times every 7 days, for a total dose of 15 Gy. The trial measured subjective responses (improvement in symptoms) and objective responses (radiological, pulmonary function tests, period free from disease progression, the number of further endoscopic treatments, costs, complications and adverse effects.

Methodological quality of included studies

XRT versus XRT in combination with HDR EBB

None of the four RCTs provides information about the methods used for randomization (Huber 1997, Langendijk H 2001, Sharma 1998, Baas 1994). Two trials described correctly sample size and power calculation (Huber 1997, Langendijk H 2001), and groups of intervention appears to be well balanced concerning baseline clinical characteristics. Huber's study (Huber 1997) had seven withdrawals in group one and the analysis was based on the remaining 98 patients under an intention to treat basis.

Other study (Langendijk H 2001) recruits only 59.4% of the required sample. This trial had three withdrawals and the analysis was based on the remaining 95 patients. The reasons for exclusion were the presence of distant metastases, cervical carcinoma in the history of one patient and no histologic confirmation of the diagnosis. Allocation concealment was unclear.

The abstract of the other two studies (Sharma 1998, Baas 1994) doesn't have information concerning the randomization method, withdrawals, group's distribution and allocation concealment.

Comparison of fractionation schedules of HDR brachytherapy.

(Huber 1995 interin results)

In this German trial (Huber 1995) there was no information on methods of stratified randomisation. Sample size and power calculation were not described. All cases were analysed on an intention to treat basis. No patients were reported to have dropped out or were lost to follow-up for the primary en point. There was no significant difference in the distribution of patient baseline characteristics between the two treatment groups.
Allocation concealment: unclear

(Pollinger 2000)
(Calaguas 1997)
(Barber 1993)

External radiotherapy vs HDR brachytherapy

(Stout 2000)
The paper from the United Kingdom (Stout 2000) provided a description of sample size and power calculation. There was no information on methods of randomisation. No patients were reported to have dropped out or were lost to follow-up. However nine, stratified separately, had relapsed after surgery and were excluded from the analysis. There was no significant difference in the distribution of patient characteristics between the two treatment groups.
Allocation concealment: unclear

(hopwood 2000)

(Moghissi 1999)
In the manchester trial (Moghissi 1999), there was no information on methods of randomisation. The trialist provided a description of sample size and power calculation. However they were able to recruit only 18.8% of the required sample. Of the 38 patients randomized to XRT, 11 (29%) did not receive it and of the 37 patients randomized to endobronchial treatment, five (14%) did not receive it.
Allocation concealment: unclear

(Mogulkoc 2000)
(Sur R 2001)

HDR brachytherapy vs HDR brachytherapy + Chemotherapy

(Ferstl 1997)
The German study (Ferstl 1997) was published as an abstract. There was no information on methods of randomisation and no description of the sample size or power calculation was described. This trial had no withdrawals and neither the patients and treating physicians were blinded to the interventions. Information was given regarding baseline characteristics, including age, sex, tunor stage, histology and Karnofsky performance state and there were no statistically significant differences between the two groups.
Allocation concealment: unclear

Combined Nd-YAG Laser/HDR Brachytherapy Versus Nd-YAG Laser

(Chella 2000)

In the paper from Italy (Chella 2000), there was no information on methods of randomisation. Sample size and power calculation were described. This trial had no withdrawals and neither the patients and treating physicians were blinded to the interventions. Baseline characteristics was given regarding clinical features (previous treatments, histology, symptoms, WHO performance status and radiology).

Allocation concealment: unclear

Results

XRT versus XRT in combination with HDR EBB

In Huber 1997, 42 patients were included in group 1 (external irradiation alone) and 56 in group 2 (additional brachytherapy). The difference between groups was explained due to the loss of seven patients in group 1 in the early phase of the study who were treated in other hospitals and, therefore, could not be followed and evaluated. The minimum observation time was 3 months, with a median observation time of 2,5 years. In group 1, 66,6% of all patients (only 19 patients had stage IIIb tumor disease) and 69,6% of all patients in group 2 (27 patients had stage IIIb tumor disease) had received no prior antineoplastic therapy. The overall

Comparison between diverse fractionation schedules of HDR palliative endobronchial brachytherapy

XRT versus HDR EBB

HDR EBB versus HDR EBB plus Chemotherapy

Combined Nd-YAG Laser/HDR Brachytherapy versus Nd-YAG Laser alone

Discussion

Reviewers' conclusions

Implications for practice

Implications for research

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Potential conflict of interest

None

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Cover sheet

Palliative endobronchial brachytherapy for non-small cell lung cancer Reviewer(s)
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Additional tables

Additional tables are not available for this protocol