Radiocirugía y radioterapia estereotáxica corporal

Eficacia, seguridad y eficiencia en cáncer de pulmón primario y oligometastásis pulmonares

Radiosurgery and stereotactic body radiation therapy. Efficacy, safety and efficiency in primary lung cancer and pulmonary oligometastases. Executive summary
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Executive summary

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Executive summary

**Title:** Radiosurgery and stereotactic body radiotherapy. Efficacy, safety and efficiency in primary lung cancer and pulmonary oligometastases.

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**Introduction**

Stereotactic body radiation therapy (SBRT) is an external radiation modality that uses a system of three dimensional references independent of the patient to achieve a precise location of the lesion. Stereotactic radiotherapy generates highly conformal, precisely focused radiation beams to administer very high doses of radiation without increasing the radiation to healthy surrounding organs or structures. When the procedure is carried out in one treatment session, the procedure is termed stereotactic radiosurgery, and when it is administered in several fractions, the radiation modality is termed stereotactic radiotherapy.

Stereotactic body radiation therapy is basically administered for nonmetastatic primary cancer in early stages (lung, prostate and renal cancer) and oligometastases (lung, liver, spinal and paraspinal metastases), using hypofractionated scheme, achieving high rates of local control while minimizing treatment toxicity and shorting the global time of treatment.

**Objectives**

Evaluate the efficacy, safety and efficiency of radiosurgery and stereotactic body radiotherapy in stage I non small cell lung cancer (NSCLC) patients and in the treatment of pulmonary oligometastases.

**Methodology**

To accomplish evidence-based response to efficacy and safety and efficiency objectives, an exhaustive search of the published literature in referencial data sources was performed. Studies regarding patients with stage I NSCLC or pulmonary oligometastases, treated with radiosurgery or SBRT were included in the assessment. The overall survival, local control rate, quality of life and toxicity were assessed. Design studies included were health technology assessment reports, metanalysis, systematic reviews, randomized clinical trials, non randomised controlled trial and observational studies.
The selection criteria of the studies in the efficiency assessment were economic evaluations of cost minimization, cost effectiveness, cost utility, cost benefit and budget impact analysis. Costs, incremental cost effectiveness ratios (ICER) in terms of life years gained (LYG) and quality adjusted life years (QALY) and budgetary impact were assessed.

Results

Eighteen documents were included in the systematic review of efficacy and safety of stage I NSCLC patients. Eight documents were included in the systematic review of pulmonary oligometastases.

A systematic review with metanalysis (Zhang et al.) was included in the assessment of stage I NSCLC patients. To update this review, 16 additional observational studies were assessed: one non randomised controlled trial, five case control studies and ten observational studies. A comparative metanalysis that pooled SBRT, conventional radiotherapy and particle (proton and carbon ion) therapy observational studies was also included (Grutters et al.).

The systematic review and metanalysis carried by Zhang et al. included non randomised controlled trial and observational studies. The calculated biologically equivalent dose (BED_{10}) for each study ranged between 51 and 196 Gy. The pooled estimate overall survival rate was 83%, 56% and 36 for one, three and five years, respectively. The pooled estimate local control rate was 95%, 88% and 76% for one, three and five years, respectively. The global rate of serious adverse events was 7.6%.

In the 16 additional observational studies, the values obtained for local control rates and overall survival rates were consistent with those described in the systematic review and metanalysis carried by Zhang et al. Main serious adverse events were pneumonitis, dyspnea, chest pain and rib fracture episodes. Three deaths related to treatment were described. In case control studies that assessed inoperable patients treated with SBRT vs. convencional radiotherapy, statistically significant differences were observed in the group treated with SBRT. Estimated values for overall survival rates were: 72% SBRT vs. 48% convencional radiotherapy and 71% SBRT vs. 42% convencional radiotherapy, for two and three years, respectively. In case control studies that assessed inoperable patients treated with SBRT vs. surgery (lobectomy or wedge resection) no differences in overall survival were observed between both treatments.

In the comparative metanalysis carried by Grutters et al. corrected pooled estimated for two and five years overall survival and disease specific survival were statistically significantly higher than those values for conventional radiotherapy (overall survival:70% vs. 53% and 42% vs. 19% for two and five years, respectively) (disease specific survival:83% vs. 67%
and 63% vs. 43% for two and five years, respectively). No significant differences were observed between SBRT and particle therapy.

A systematic review (Siva et al.) was included in the assessment of pulmonary oligometastases. Also, to update this review, seven additional observational studies were assessed, all of them were retrospective studies.

The systematic review carried by Siva et al. included observational studies. Both single fraction stereotactic radiosurgery and hypofractionated radiotherapy studies were considered. In the radiosurgery series the mean weighted BED$_{10}$ was 87.1 Gy. Three serious adverse events (grade 3 pneumonitis) were reported. In the hypofractionated radiotherapy series BED$_{10}$ at isocenter ranged between 77 and 183 Gy. There was a grade 5 esophageal necrosis reported in one patient. The weighted rate of grade 3 or greater adverse events was 2.6%. For both series of studies similar weighted rates for two year local control and overall survival were obtained: 78 and 51%, respectively.

In the seven additional observational studies, the values obtained for local control rates and overall survival rates were consistent with those described in the systematic review carried by Siva et al. Grade 3 or greater adverse events were mainly pneumonitis episodes. There was documented a grade 5 pneumonitis.

Four documents were included in the systematic review of the efficiency of SBRT in the treatment of stage I NSCLC patients (one cost effectiveness analysis, two cost utility analyses and one cost analysis). The relative cost effectiveness analysis compared SBRT and surgical intervention. The cost utility analyses were used to compare SBRT vs. convencional radiotherapy and radiofrequency ablation and also comparing SBRT vs. particle and convencional radiotherapy. The cost analysis compared SBRT and conventional radiotherapy.

The cost effectiveness analysis showed that SBRT was less expensive than surgery but this resulted in an ICER of $7,753 per life years gained for surgery compared to SBRT. The incremental cost effectiveness ratios per QALY ranged from $9,806 to $19,264 for SBRT compared to radiofrequency ablation and compared to conventional radiotherapy, respectively. In the other cost utility analysis SBRT dominated (it achieved both cost and better health benefits) protons and conventional radiotherapy. Carbon ion therapy yielded the most QALYs per patient. SBRT was less expensive but this resulted in an ICER of €67,257 per QUALY gained for carbon ions compared to SBRT. The cost analysis indicated that SBRT was significantly less expensive than convencional radiotherapy but there were no association values for cost outcomes.
Conclusions

SBRT to treat Stage I NSCLC patients

- No randomised controlled trials that assess SBRT compared to other therapeutic alternatives (surgery, conventional or particle radiotherapy) have been found.
- The levels of evidence for studies of treatment with SBRT are low although the scientific production is high. The studies that were found are non randomised controlled studies and observational studies.
- Studies show high heterogeneity. There is variability in the fractionation schemes, patients treated and consequently in the efficacy and safety results.
- Main serious adverse events described are pneumonitis, dyspnea, chest pain and rib fracture episodes.
- There has been estimated an improvement in overall survival in inoperable patients treated with SBRT vs. conventional radiotherapy (outcomes assessed in case control studies and comparative metanalysis). No differences have been estimated in overall survival between patients treated with SBRT and surgery, and patients treated with SBRT and particle therapy.
- No solid conclusions of the efficacy and safety of SBRT can be drawn owed to low level of evidence of the comparative studies found.
- High methodological quality studies are needed to assess directly stage I NSCLC patients treated with SBRT vs. other therapeutic alternatives.
- There are four randomised controlled trials ongoing. These studies will assess properly SBRT vs. surgery (ROSEL study, STAR study and other phase III study) and SBRT vs. conventional radiotherapy (CHISEL study).
- The bibliography about efficiency results for stage I NSCLC patients is scarce and the comparative studies are low level evidenced. It can be concluded that results point out that SBRT treatment is efficient compared to radiofrequency ablation, conventional radiotherapy and protons radiotherapy in terms of cost utility (two studies) and that SBRT is efficient compared to conventional radiotherapy in terms of cost (one study). On the other hand, in the cost effectiveness analysis surgery appears to meet the standards for cost effectiveness compared to SBRT, under many methodology considerations (this results should be confirmed in a randomized controlled trial).
SBRT to treat pulmonary oligometastasis

- No randomised controlled trials that assess SBRT compared to other therapeutic strategies (surgery or conventional radiotherapy) have been found.
- The levels of evidence for studies of treatment with SBRT are low. The studies that were found are observational studies without control group.
- Studies show high heterogeneity. There is variability in the fractionation schemes, patients treated and consequently in the efficacy and safety results.
- Main serious adverse events described are pneumonitis episodes.
- No solid conclusions of the efficacy and safety of SBRT can be drawn owed to low level of evidence of the studies found.
- High methodological quality studies are needed to assess directly pulmonary oligometastases treated with SBRT vs. other therapeutic alternatives.
- No efficiency studies that assess SBRT compared to other therapeutic alternatives in patients with pulmonary metastases have been found.