The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation

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Scientific summary

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Background

Despite advances in treatments for primary cancers, many deaths from cancer are caused by metastatic burden. Survival rates vary, but survival beyond 5 years of patients with untreated metastatic disease in the liver is rare. Prognosis can vary according to the extent of the disease in the liver, and according to the site of the primary cancer. Treatment for liver metastases has largely been surgical resection, with 5-year survival figures ranging from 25% to 39% for patients with liver metastases from colorectal cancer. However, surgical resection is only feasible in approximately 20–30% of people. Non-surgical alternatives have been developed in recent years to treat some liver metastases; these alternatives to surgery can include various forms of ablative therapies and other targeted treatments.

Objectives

1. To conduct a systematic review of the evidence on the clinical effectiveness and cost-effectiveness of ablative therapies for liver metastases.
2. To adapt an existing or construct a de novo economic model to estimate the cost-effectiveness of different approaches to treating liver metastases.
3. To identify deficiencies in current knowledge and to generate recommendations for future research.

Methods

Fourteen electronic databases including MEDLINE, EMBASE and The Cochrane Library were searched from 1990 to September 2011. Experts were also consulted to identify additional studies and bibliographies of relevant papers were checked.

Titles and abstracts were screened for eligibility and inclusion criteria were applied to the full text of selected papers by two reviewers. Studies were included if they met prespecified criteria including any ablative or minimally invasive technology (1) used in the UK for treating liver metastases; (2) reported in comparative studies or a prospective cohort study with at least 100 participants; (3) where appropriate compared with surgical resection, chemotherapy or best supportive care; and (4) including outcomes of morbidity, mortality, survival, tumour ablation, local recurrence, or quality of life. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with differences resolved through discussion with a third reviewer. Studies were synthesised through a narrative review with full tabulation of results.

Results

Number and quality of studies

Searching identified 5381 references after deduplication, of which 16 met the inclusion criteria for the systematic review of clinical effectiveness. The included studies were either randomised controlled trials (RCTs) or prospective case series studies. Common reasons for exclusion were study design, including small sample sizes of prospective case series studies, irrelevant participants, irrelevant interventions, and irrelevant comparators. The overall quality of studies was weak and meta-analysis was not possible.

Summary of benefits and risks

Radio- or chemoembolisation

Seven studies provided evidence on the clinical effectiveness of radio- or chemoembolisation. Although these interventions resulted in statistically significant improvements in tumour response and time to disease progression relative to their comparators, benefits in terms of survival were equivocal. Radio- and chemoembolisation were generally well tolerated.

Microwave ablation

One RCT assessed a microwave ablation compared with surgical resection. It found no statistically significant difference between the interventions on measures of survival. Benefits were shown in terms of surgical invasiveness.

Radiofrequency ablation

One non-randomised comparison study and five case series studies assessed radiofrequency ablation. The non-randomised study reported few relevant data, and the case series studies differed such that comparisons of the relative benefits of radiofrequency ablation were not possible. Survival estimates ranged from median survival of 24–32 months from treatment of liver metastases to 44–52 months from diagnosis of liver metastases. Adverse events were generally mild to moderate only.

Laser ablation

Two case series from the same centre were included, although the populations under study differed. Estimates of overall survival were not reported consistently between the two studies meaning comparisons are difficult to make; however, survival rates at 5 years were in the region of 30–41%.

Studies unpublished at the time of the review

Eight studies were identified in searches but were published as abstracts only, and five ongoing trials of potential relevance to this review were identified.

Systematic review of existing cost-effectiveness evidence

Searches for economic evaluations of ablative therapies for liver metastases identified 108 references, of which two were included in the current review.

One economic evaluation compared radiofrequency ablation (with a range of treatment thresholds, retreatment and follow-up options), surgical resection (with a range of treatment thresholds and follow-up options) with no treatment in a population of people with surgically resectable or unresectable liver metastases. Gazelle and colleagues used microsimulation in a state transition model. Model parameters were derived from a range of studies. Strategies involving low treatment thresholds (fewer than three metastases for radiofrequency ablation and fewer than six for surgical resection) were dominated by strategies with higher thresholds, leading the authors to conclude that more aggressive strategies – particularly for surgical resection – were likely to be more cost-effective. Radiofrequency ablation was generally associated with lower quality-adjusted life-year (QALY) outcomes than surgical resection – for example, at a treatment threshold of six metastases and follow-up at 12 months, quality-adjusted life expectancy for a 65-year-old man with liver metastases undergoing radiofrequency ablation was 1.36 and the corresponding figure for surgical resection was 3.39.

The other economic evaluation compared hepatic artery chemoembolisation with palliative care for people with unresectable liver metastases. The absence of comparative studies demonstrating a survival benefit for hepatic artery chemoembolisation means that no firm conclusions can be drawn from the study – the study is further weakened by the absence of any adjustment for quality of life in estimating the benefits of the technology.

Both studies were conducted in the USA and both were modelling studies, deriving estimates of effectiveness (overall survival or quality-adjusted survival) from assumption or from microsimulation based on the surrogate measure of proportion of liver replaced by tumour. These studies have limited relevance to the NHS.

Systematic review of health-related quality of life in subjects with liver metastases

No comparative studies for the ablative therapies and the relevant comparators included in the current study were identified. No evidence of the impact on patients' health-related quality of life was found for most of these interventions. One before-and-after study was found related to one of the included ablative therapies and this reported no statistical significant difference before and 1 week, 1 month and 6 months after initiation of laser ablation in people with progressive disease undertaking second- and third-line chemotherapy.

Southampton Health Technology Assessments Centre economic evaluation

A survival model was developed to estimate the cost of ablative therapies or other non-invasive therapies in cohorts of adult patients with surgically resectable, or unresectable liver metastases. Limitations in the evidence base (lack of comparative studies or limitations in reporting survival outcomes) meant that not all identified therapies were included in the model.

The limitations of the evidence base need to be borne in mind when interpreting the results of the economic evaluation. The model includes separate comparisons of two ablative therapies with surgery (microwave ablation compared with surgery and radiofrequency ablation compared with surgery) and one other non-invasive therapy (radioembolisation in conjunction with hepatic artery chemotherapy compared with hepatic artery chemotherapy alone). Each of these comparisons is based on a single study.

Clinical effectiveness data in the model were based on overall survival and progression-free survival functions estimated using linear regression on data extracted from survival plots reported in included studies.

Health state utilities for stable disease and disease progression, derived in our review of published quality-of-life studies, were applied in the model.

Resource use estimates were developed based on treatment intensity (number of treatments and length of stay), on-treatment management and post-discharge monitoring reported in included studies. Unit costs were derived from NHS reference costs – where these were inadequate, unit costs were sourced from a local NHS provider.

Radioembolisation plus hepatic artery chemotherapy compared with hepatic artery chemotherapy

The analysis comparing radioembolisation plus hepatic artery chemotherapy with hepatic artery chemotherapy alone showed improved outcomes (0.35 QALY gain) from radioembolisation plus hepatic artery chemotherapy at an increased cost (incremental cost of £12,945), resulting in an incremental cost-effectiveness ratio (ICER) of £37,303 per QALY gained. Although deterministic sensitivity analysis showed that results were sensitive to variations in survival functions, utility estimates and costs of palliative care, the ICER appeared fairly robust, varying between £34,000 and £40,000. Probabilistic sensitivity analysis showed that radioembolisation plus hepatic artery chemotherapy had a probability of being cost-effective of 0.1% at a willingness-to-pay threshold of £20,000 per QALY and 26% at a willingness-to-pay threshold of £30,000 per QALY.

Microwave ablation compared with surgical resection

In the analysis comparing microwave ablation with surgical resection, the incremental cost is negative (£327) – treatment of liver metastases with microwave ablation is slightly lower than treatment with surgical resection – resulting in an ICER of £3664 per QALY gained. It should be noted that this positive ICER is derived from negative incremental cost and incremental QALY values – that is to say, in this analysis microwave ablation is associated with reduced cost but also poorer outcome than surgical resection. The results appear to be most sensitive to variation in utility estimates applied in the model, variation in values of parameters in the survival functions (for treatment effect on overall survival and all parameters in the overall survival function), variation in procedure costs and to the cost of palliative care. Probabilistic sensitivity analysis showed microwave ablation had a probability of being cost-effective of 31% at a willingness-to-pay threshold of £20,000 per QALY and 30% at a willingness-to-pay threshold of £30,000 per QALY.

Radiofrequency ablation compared with surgical resection for solitary metastases < 3 cm

In the analysis comparing radiofrequency ablation with surgery for solitary metastases < 3 cm, the incremental cost for radiofrequency ablation compared with surgical resection is negative (£6290) – a reduction of around 25% in total costs. There is no difference in discounted life expectancy between surgical resection and radiofrequency ablation for patients with solitary liver metastases of < 3 cm. However, as surgical resection is associated with significant reduction in quality of life for up to 6 months post-operatively, surgical resection is associated with lower QALY outcome than radiofrequency ablation. The estimated gain in discounted QALYs associated with radiofrequency ablation is 0.06. The ICER is –£266,767 per QALY gained. In conventional terms this would indicate that radiofrequency ablation dominates surgical resection for the treatment of (surgically resectable) small solitary liver metastases.

The cost-effectiveness results appear to be generally robust to variation in parameters included in the deterministic sensitivity analysis. The results appear to be most sensitive to variation in values of parameters in the survival functions (for treatment effect on overall survival and all parameters in the overall survival function) and variation in the utility.

Radiofrequency ablation compared with surgical resection for solitary metastases ≥ 3 cm

The comparison of radiofrequency ablation with surgical resection for solitary metastases ≥ 3 cm showed that radiofrequency ablation was associated with poorer outcomes, through a reduced life expectancy (–1.43 years) and lower QALYs (–1.27 QALYs), and a lower incremental cost (–£3207). The reduced costs and poorer outcome associated with radiofrequency ablation result in an ICER of £2538 per QALY. Deterministic sensitivity analysis showed that the analysis was generally robust to variations in parameters, with ICERs ranging from £2000 to £4000 per QALY. Probabilistic sensitivity analysis showed that radiofrequency ablation has a probability of being cost-effective of 0% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

Conclusions

The available evidence of effectiveness of ablative and minimally invasive technologies for treating liver metastases was limited, with methodological weaknesses. As a consequence, it is difficult to differentiate between the different therapies. The analysis is therefore limited in its scope, with many uncertainties. The results of radioembolisation and hepatic artery chemotherapy versus hepatic artery chemotherapy and microwave ablation are presented; however, it is unclear whether or not these are currently relevant to current management of liver metastases in the NHS.

There is limited high-quality research evidence upon which to base any firm decisions regarding ablative therapies for liver metastases. It is a rapidly developing field and there is room for further trials comparing ablative therapies with surgery, in particular. Any study should assess the clinical effectiveness and cost-effectiveness of the different techniques, assessing measures of survival, response, recurrence, quality of life, adverse events and costs. Outcomes should be reported separately for the different groups of participants. A RCT would provide the most appropriate design for undertaking the evaluation and should include a full economic evaluation, but the group to be randomised needs careful selection.

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