Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of radiofrequency (RF) ablation and hepatic resection in patients with metachronous liver metastases from colorectal cancer (CRC) was examined. Several strategies were modelled in the analysis. Strategies for RF ablation differed in the maximum number of lesions that could be treated, the maximum number of repeat ablations allowed, and the frequency of follow-up imaging. Resection strategies differed in approach (segmental resection versus wedge excision), the maximum number of lesions or segments removed, and the frequency of follow-up imaging.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with CRC and liver metastases.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
Clinical evidence and some resource use data were estimated from studies published between 1978 and 2001. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A state-transition decision model was constructed, based on a published model, to assess the impact of the different treatment and follow-up strategies in a hypothetical cohort of 100,000 patients of 65 years of age (men in the base-case). The model tracked up to 15 individual hepatic metastases in each patient, specifying and updating tumour location, size, rate of growth, detection, and removal or ablation. The three health states considered were "alive_treat", "alive_notreat" and "dead".

Patients entered the model in the "alive_treat" state and were potential candidates for treatment (i.e. tumour ablation or resection). After treatment, the patients were either free of metastatic disease or had residual metastases, depending on the number and location of metastases detected, the location of metastases not detected, and the procedure performed.
Patients could also suffer surgical morbidity or mortality associated with treatment. Patients moved to the "alive_notreat" state when they had either been found to be "untreatable" (i.e. to have more metastases than the threshold for treatment in the strategy being considered), or when they had had the maximum allowable number of treatments for the strategy under consideration. At the end of each cycle, patients returned to one of the three model states and this process continued until all patients in the initial cohort reach the "dead" state, at which point the simulation was terminated. The cycle length was one month and the time horizon was the patient's lifetime. The structure of the model and a full description of the model assumptions were given.

Outcomes assessed in the review
The outcomes assessed were:

the demographic characteristics of the patient cohort;
tumour characteristics (i.e. the number and size of metastases);
the mortality and morbidity after resection, laparotomy and RF ablation;
the length of stay;
the probability of tumour necrosis with RF;
the detection thresholds associated with different imaging techniques;
survival;
the hazard rates; and
quality of life decrements.

Study designs and other criteria for inclusion in the review
The authors stated that a comprehensive review of the English-language literature was undertaken to identify primary studies. However, limited information on the design and other characteristics of the primary studies was provided. Some data came from US life tables.

Sources searched to identify primary studies
MEDLINE was searched for primary studies, the bibliographies of which were also checked.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Approximately 30 references provided clinical data.

Methods of combining primary studies
The primary estimates appear to have been combined using a narrative method.
Investigation of differences between primary studies
Not stated.

Results of the review
Some of the clinical data derived from the literature are reported here.

The tumour volume doubling time was 155 days (range: 78 - 233).

The normal liver volume was 1,225 cm³.

Mortality was 5% (alternative value 10%) after resection and 0.3% after RF ablation.

Morbidity was 20% after resection, 4% after laparotomy and 2% after RF ablation.

The length of stay was 12 days after resection and 5 days after laparotomy.

The additional length of stay after resection complications, laparotomy complications, or RF ablation complications was 3 days in each case.

The probability of complete tumour necrosis with RF was 0.784 (alternative value 1) for tumours =≤ 2.5 cm, 0.472 (range: 0.75 - 1) for tumours >2.5 to 4 cm, and 0.316 (range: 0.5 - 1) for tumours >4 to 10 cm.

The sensitivity of computed tomography (CT) was 0.85 (alternative value 0.75).

The detection threshold was 0.5 cm (alternative value 1.0 cm) at CT and 0.3 cm (alternative value 0.5 cm) at intraoperative ultrasound (US).

The hazard rate was 0.7427 when less than 25% of liver volume was replaced by tumour (LVRT) and 1.3203 when at least 25% LVRT.

Patients with less than 25% (but more than 0%) LVRT were assigned a median survival of 11.5 months, while patients with LVRT of 25% or more had a median survival of 6.3 months.

In patients with metastatic CRC, quality of life declines rapidly at the end of life (median time for decline: last 12 days of life). Hence, quality-adjusted life years (QALYs) were estimated by subtracting a toll in the final cycle (month) before death, estimating that quality of life in the month prior to death was 60% of that for age- and gender-matched controls. QALY tolls were also assessed to account for decreased quality of life following RF ablation, hepatic resection, or laparotomy.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive clinical data that were not available from the literature.

Estimates of effectiveness and key assumptions
The mortality after laparotomy was 1%. No new liver metastases developed over time, as all patients were assumed to have undergone removal of their primary tumours. Each metastasis had an independent and equal probability of being located in each of the eight liver segments. Other assumptions were also made in the model.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of QALYs. This was obtained by combining expected survival and the utility weights derived from the literature. An annual discount rate of 3% was applied.
Direct costs
The analysis of the costs was performed from a societal perspective. The direct costs were analysed with the inclusion of costs relevant to the third-party payer. The health services included in the economic evaluation were liver resection, laparotomy, RF ablation, patient care for patients with and without metastases, CT, intraoperative US, morbidity associated with laparotomy or RF ablation, and postoperative death. Both hospital and professional costs were considered for all procedures.

The unit costs were not presented separately from the quantities of resources used for all items, and most costs were reported as macro-categories. Resource use was based on authors’ assumptions and published evidence. The costs of tests and procedures were derived from Medicare payment schedule, assuming that ablation procedures could be performed on an outpatient basis. The hospital costs came from Ambulatory Practice Center codes, while physician costs were estimated from Current Procedural Terminology. The costs of cancer care came from a study published in 1995. The costs were converted into 1998 values using the medical care component of the Consumer Price Index. Discounting was relevant since long-term costs were analysed, and an annual rate of 3% was applied.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs (i.e. productivity losses) were appropriately included in the analysis as a societal perspective was adopted. The daily wage rate was derived from the US Bureau of Labor Statistics. The number of days off work was not reported. As in the analysis of the direct costs, an annual discount rate of 3% was applied and the price year was 1998.

Currency
US dollars ($).

Sensitivity analysis
Extensive univariate sensitivity analyses were performed to investigate the robustness of the cost-utility ratios to variations in the model inputs. These included patient age and gender, mortality hazard rates (for patients with and without metastases), the number of metastases, tumour size and doubling time, and diagnostic test sensitivity. Other model inputs varied were maximum tumour size treatable with RF ablation, success in achieving local control of treated lesions, the costs of ablation, resection and laparotomy, the costs of patient care, and the discount rate used for the costs and QALYs. Multivariate sensitivity analyses of selected values were also performed. The alternative ranges of values were either derived from the literature or set by the authors.

Estimated benefits used in the economic analysis
After eliminating dominated and weakly dominated alternatives, five strategies remained. The number of QALYs was:

1.1327 for RF ablation with 12-month follow-up and up to 3 metastases treated;
1.3255 for RF ablation with 12-month follow-up and up to 5 metastases treated;
1.3575 for RF ablation with 12-month follow-up and up to 6 metastases treated;
3.2634 for resection with 12-month follow-up and up to 6 metastases treated; and
3.3923 for resection with 4-month follow-up and up to 6 metastases treated.
Cost results
The estimated costs per patient were:

- $24,700 for RF ablation with 12-month follow-up and up to 3 metastases treated;
- $24,800 for RF ablation with 12-month follow-up and up to 5 metastases treated;
- $24,800 for RF ablation with 12-month follow-up and up to 6 metastases treated;
- $57,000 for resection with 12-month follow-up and up to 6 metastases treated; and
- $61,000 for resection with 4-month follow-up and up to 6 metastases treated.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and QALYs of the five non-dominated strategies.

The incremental cost per QALY in comparison with the next less effective strategy was:

- $300 for RF ablation with 12-month follow-up and up to 5 metastases treated;
- $1,300 for RF ablation with 12-month follow-up and up to 6 metastases treated;
- $16,900 for resection with 12-month follow-up and up to 6 metastases treated; and
- $31,200 for resection with 4-month follow-up and up to 6 metastases treated.

The sensitivity analysis showed two significant trends. First, the cost-utility ratios of RF ablation versus the no-treat strategy were less than $5,000 per QALY and, with very few exceptions, the cost-utility ratios of resection versus RF ablation were less than $30,000 per QALY. Second, when all possible RF ablation and resection strategies were considered, more aggressive surgical strategies were superior to RF ablation (i.e., they resulted in more QALYs gained). For example, in most cases, the cost-utility ratios of even the most aggressive surgical strategies were less than $35,000 per QALY.

A further finding was that some of the less aggressive RF ablation strategies (e.g., the treatment of one to two metastases) were both less expensive and more effective than the no-treat strategy.

Authors' conclusions
Both radiofrequency (RF) ablation and hepatic resection were relatively cost-effective strategies for the management of patients with limited hepatic metastases from colorectal cancer (CRC). In general, more aggressive strategies (i.e., the treatment of patients with more tumours, more frequent post-treatment follow-up regimens, and surgery rather than ablation) were superior to more conservative strategies and were cost-effective using standard threshold values. The results of the analysis were sensitive to changes in the number of metastases present, the size threshold above which lesions were considered untreatable with RF ablation, and the cost of RF ablation.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as all relevant strategies for the management of metastatic CRC were compared. Different follow-up timeframes were considered. All interventions were compared with the reference strategy of no treatment. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies. However, the methods and conduct of the review were not reported clearly. Moreover, no information on the design and characteristics of the primary studies was provided. Thus,
it was not possible to assess the validity of the primary estimates. The methods used to extract the data from the primary studies and to combine the clinical estimates were not described. Some opinions were also used to derive clinical data because of the lack of published evidence. Sensitivity analyses were performed to assess the robustness of the final cost-effectiveness estimates to variations in the clinical data.

**Validity of estimate of measure of benefit**

The benefit measure used in the analysis was appropriate, as QALYs capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life) for patients with CRC. Further, QALYs are comparable with the benefits of other health care interventions. Discounting was applied in accordance with US guidelines for economic evaluations. Some details on the source of the utility weights and the approach used to calculate QALYs were provided.

**Validity of estimate of costs**

The choice of adopting a societal perspective in the analysis was appropriate as all the costs were included in the analysis. The costs were presented as macro-categories and a detailed breakdown of the cost items was not reported. This might limit the possibility of replicating the analysis in other settings, but it is quite common when the long-term costs of cancer care are assessed. The source of the data was reported for all costs, but information on resource use was mainly based on authors' opinions. No statistical analyses of the costs were performed, but the issue of uncertainty in resource consumption and cost estimates was extensively addressed in the sensitivity analysis. Discounting was appropriately performed and the impact of variations in the discount rate was investigated. The price year was reported, which will facilitate reflation exercises in other settings.

**Other issues**

The authors did not compare their findings with those from other published studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. The authors stated that the main limitations of their study were the necessary simplification of reality required in the decision model and the uncertainty surrounding some parameters. However, extensive sensitivity analyses were performed. Finally, patient heterogeneity was not investigated, owing to the lack of detailed data, and extra-hepatic metastases were not modelled.

**Implications of the study**

The study results suggested "physicians performing ablation and resection should be encouraged to select patients for therapy on the basis of technical feasibility rather than numerical thresholds and to pursue repeat treatment when new lesions are identified after initial therapy". Further, since there are generally no other potentially curative therapeutic options for these patients, RF ablation of larger lesions should be encouraged.

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