Hepatic resection as a treatment for liver metastases in colorectal cancer
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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 hepatic resection in patients with colorectal cancer and liver metastases.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with colorectal cancer and liver metastases.

Setting
The setting was a hospital. The study was performed at the Trent Institute for Health Services and Research, UK.

Dates to which data relate
The effectiveness data were collected from 1984 to 1996. The authors did not state the dates to which the resource utilisation and costs related. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies.

Outcomes assessed in the review
For the standard chemotherapy, the authors reported several survival rates at 3 and 5 years. These were obtained from different case-series studies included in the review. The authors considered one study (Wade et al.; see Other Publications of Related Interest) as providing the most appropriate comparative data for potentially resectable patients. They also reported the different values that they found in the primary studies for the median survival, 5-year survival, operative mortality, and operative morbidity following hepatic resection. The outcomes for hepatic resection were assessed on the basis of 16 of the 21 published studies.

In order to assess the estimated benefits of the alternative strategies, two studies were chosen. One reported the benefits for patients undergoing resection with curative intent (Scheele et al.; see Other Publications Of Related Interest). The other reported the benefits of standard chemotherapy for a similar patient group (Wagner et al.; see Other Publications Of Related Interest). The authors used the areas under the survival curves to calculate the mean survival and the gain in survival for both a 5-year and a 10-year follow-up.
Study designs and other criteria for inclusion in the review
The authors reported that there were no randomised controlled trials available relating to the intervention under study. Therefore, they had to rely on case-series studies. Case-series that reported survival results for more than 100 patients, and those with recently published data covering specific patient cohorts, were included in the review.

Sources searched to identify primary studies
The sources searched were MEDLINE, EMBASE, the Cochrane Library, HMIC (Department of Health, King's Fund, HELMIS), the NHS Centre for Reviews and Dissemination (DARE, NHS EED and HTA databases), and between 20 and 25 other information sources covering websites, personal contacts and literature databases.

Criteria used to ensure the validity of primary studies
The authors focused on the case-series studies that reported survival for at least 100 patients. The choice was justified on the grounds that the larger studies represent best practice and have greater potential to identify significant sub-groups with differing chances of survival.

Methods used to judge relevance and validity, and for extracting data
An appropriate comparable group for those patients receiving liver resection was identified among the case-series studies included in the review. Therefore, the data seem to have been extracted based on this criterion.

Number of primary studies included
Fifty-nine case-series studies on the use of liver resection were found. Of these, 21 met the inclusion criteria and were included in the review.

Methods of combining primary studies
The results from the primary studies included in the review were reported using a narrative method.

Investigation of differences between primary studies
Differences between the primary studies were investigated in terms of the effectiveness outcomes reported. These mainly related to the expected survival for those receiving non-surgical treatment and for those receiving surgical treatment according to different prognostic indicators. The prognostic indicators were curative/non curative liver resection, the presence or absence of extrahepatic disease, the presence or absence of tumours in the margins of the resection, the size of the tumour, the number of metastases, the presence of satellite lesions, the presence of metachronous or synchronous metastases, and the type of resection. Differences in the rate of recurrence were also studied. Some of the differences were attributed to variation in the inclusion and exclusion criteria across the different studies identified.

Results of the review
The 5-year survival for patients with single, potentially resectable, liver metastasis who received standard chemotherapy was less than 5%, with a mean survival of 11 months.

The median survival following hepatic resection ranged from 20 to 37 months. The 5-year survival following hepatic resection ranged from 21 to 41%. The operative mortality with liver resection ranged from 0 to 7.6%. The operative morbidity following hepatic resection varied between 14 and 34%.

The mean survival at 5 years for those patients with less than 4 metastases receiving resection was 39 months. Similar patients receiving standard chemotherapy survived, on average, 19 months. Therefore, the gain in survival experienced by patients with less than 4 metastases receiving resection, compared with those receiving standard chemotherapy, was 20 months.
For those patients with 4 or more metastases, the mean survival at 5 years was 35 months if the patients received resection, and 13 months if the patients were treated with standard chemotherapy. The gain in mean survival experienced by those patients receiving resection, compared with similar patients receiving standard chemotherapy, was 22 months.

For a follow-up period of 10 years, the median survival for those patients with less than 4 metastases who underwent resection was 57 months. Therefore, resection generated 38 additional months when compared with standard chemotherapy.

For patients with 4 or more metastases, the median survival with resection was 50 months. The gain in survival when compared with standard chemotherapy was 37 months.

**Measure of benefits used in the economic analysis**
The measure of benefits used in the economic analysis was the life-years gained (LYG).

**Direct costs**
The resource quantities and the costs were reported separately. The direct costs included in the analysis were those of the hospital. The costs included for liver resection were the pre-operative costs (including diagnostic work-up), the variable costs of the resection procedure, and the longer-term follow-up costs. The costs related to adjuvant chemotherapy following resection were excluded since this is not a current practice in the UK. The authors also excluded the costs related to potential re-resections, assuming that recurrences would be treated with conventional salvage chemotherapy. The authors also reported these costs from a purchaser's viewpoint, although they warned that these costs may be underestimations of the true costs. The costs included for conventional treatment were for ward stay, chemotherapy drugs, diagnostic tests, consumables and fluids. The authors reported the average costs and also the marginal cost of liver resection in comparison with standard chemotherapy. The costs were estimated from actual data. The costs of liver resection were obtained from the Royal Hallamshire Hospital (Sheffield), while the costs of systemic chemotherapy were derived from a published study (see Other Publications of Related Interest), and the current British National Formulary drug costs and local inpatient costs.

Discounting was not performed. The authors justifying this by stating that the costs of resection were incurred within the first year of treatment. Moreover, it appears that the long-term follow-up costs for those surviving patients were incurred over 2 years, which made discounting of these long-term costs irrelevant. The price year was not given.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
No indirect costs were reported.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
Sensitivity analyses were performed to take account of different resection survival data. The health benefits were discounted at a 6% discount rate. The authors also reported the survival that would have resulted had a 20-year follow-up been considered. Three alternative scenarios were proposed on the basis of the results from published studies. One considered the best scenario among the studies included in the review. The second considered the likely UK experience scenario. The third considered the worst-case scenario. The percentages of curative, non-curative and non-resected patients, and the number of LYG with liver resection, were reported for each of the alternative scenarios.
Estimated benefits used in the economic analysis
See the 'Results Of The Review' section.

Cost results
For the liver resection strategy, the average cost of the diagnostic work-up was 314, the average cost of the resection procedure was 5,820, and the average cost of long-term follow-up was 268. The total average cost of the intervention was 6,402.

For the standard chemotherapy strategy, the average cost per month was 2,223, and it was assumed that treatment was based on a 3-month period. Therefore, the total average cost of treatment for this intervention was 6,669.

The marginal cost-saving of liver resection in comparison with standard chemotherapy was 267.

Synthesis of costs and benefits
The authors only reported the cost per LYG for liver resection. This may have been because this intervention generated more benefits and had slightly lower costs than standard chemotherapy, and therefore, was a dominant strategy in comparison with standard chemotherapy (although the authors did not refer to this fact in the study).

Under the 'best-case' scenario, the percentage of curative patients would be 100%. Therefore, there would be no non-curative patients or patients without resection. The number of LYG with liver resection under this scenario would be 3, and the cost per LYG would be 2,134.

In the case of the 'likely UK experience', 83% of patients would have curative tumours, 17% of the patients would be non-curative, and none of them would be non-resected. The number of LYG under this scenario would be 2.5, and the cost per LYG would be 2,658.

The 'worst-case scenario' would have 50% curative patients, 40% non-curative patients and 10% non-resected patients. The number of LYG with liver resection under this scenario would be 1.5, and the cost per LYG would be 3,945.

Authors' conclusions
Liver resection seemed to produce survival advantages for patients with colorectal cancer and liver metastases, provided that the surgery rendered the patient tumour free and patients did not have extrahepatic disease. For patients with multiple liver secondaries, the prognosis was worst but they experienced a survival advantage from resection, provided they did not have extrahepatic disease and the entire tumour could be removed. There was no evidence of a survival advantage for those patients with extrahepatic disease, or for those in whom the entire tumour was not removed. Finally, the authors considered that liver resection is cost-effective when compared with many other health care interventions provided by the NHS.

CRD COMMENTARY - Selection of comparators
The comparator used was justified on the grounds that it is the standard practice in the UK for patients with colorectal cancer and liver metastases. You should decide if this is a widely used health technology in your own setting. The authors also mentioned other alternatives that have been studied as possible strategies for liver metastasis in patients with colorectal cancer, for example, local ablation with arterial chemotherapy, embolisation and cryotherapy. However, they justified the exclusion of these from the study on the grounds that they have not been proven to have a real impact on overall survival and long-term cure.

Validity of estimate of measure of effectiveness
The authors undertook a systematic review of the literature to derive effectiveness data. Therefore, the validity of the results is likely to be high. The effectiveness estimates were reported using narrative methods. Weighting was not applied to reflect the differences in sample sizes. The authors studied the differences between the primary studies and gave some explanations for the differences found. They also undertook sensitivity analyses to address variability in the data.

The authors acknowledged some limitations in relation to the effectiveness results obtained. For example, there was no randomised controlled trial available, and they therefore had to rely on case-series studies. In addition, there were difficulties in identifying a comparison group. The groups compared may not have been strictly comparable, thus limiting the conclusions to be drawn. Also, the studies included in the review differed in their inclusion and exclusion criteria, and in the treatments given to patients after resection. Finally, the retrospective nature of most of the studies included in the review introduced uncertainty into the reliability of the data (only four studies had a prospective data collection). These features complicate the interpretation of the results and introduce uncertainty into the reliability of the conclusions.

**Validity of estimate of measure of benefit**
The estimate of the benefits was obtained directly from the results of the review. The benefits were calculated from the results obtained from two studies. These studies were chosen because they represented a balance in terms of the patient numbers, proportion of patients treated curatively, the complexity of surgical procedures, and the availability of full survive curve data. The authors reported that the number of LYG for resection was estimated using a conservative assumption that disadvantaged resection, and therefore, the benefits derived from resection may have been larger.

**Validity of estimate of costs**
All the cost categories relevant to the perspective adopted appear to have been included in the analysis. The costs of adjuvant chemotherapy for patients following resection were excluded because, as the authors stated, this is not a current practice in the UK. Moreover, no costs for potential re-resection were included because the authors assumed that recurrences would be treated with conventional salvage chemotherapy. The resource quantities and the costs were reported separately, which may facilitate reflation exercises to other settings. On the other hand, the authors did not report the price year nor the dates during which the resource quantities and costs were collected. A sensitivity analysis of quantities was not conducted, which may limit the interpretation of the study findings. Discounting was not performed, but this was justified as those patients surviving more than 2 years incurred long-term follow-up costs within a 2-year period.

**Other issues**
The authors did not make appropriate comparisons of their findings with those from other studies, probably because of the lack of similar studies about this intervention. The issue of the generalisability of the results to other settings was not addressed.

**Implications of the study**
The authors recommend funding resections for a wider set of indications (i.e. patients with single or multiple metastases) for which curative resection can be realistically achieved. They state that district general hospitals should have a clear set of guidelines in order to deal with cases of liver metastases. They include referral guidelines in their study. A randomised controlled trial comparing liver resection and standard chemotherapy for patients with colorectal cancer and liver metastases that are potentially respectable, cannot be recommended because of ethical considerations. However, the authors suggest that a randomised controlled trial should be performed in order to determine the benefits and cost-effectiveness of regular follow-up of colorectal patients. Moreover, they argue that the cost-effectiveness of non-surgical treatment of liver secondaries for colorectal cancer should be evaluated, as the information available is insufficient.

**Source of funding**

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**Bibliographic details**

**Other publications of related interest**


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