Postoperative management of stage II/III colon cancer: a decision analysis

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
Different management strategies (7 in total) for patients with stage II or III resected colon cancer. Strategy 1 (S1) included adjuvant chemotherapy for patients after curative resection of stage III colon cancer and follow-up of patients with both stage II or III colon cancers. The other six strategies (described below) were variations of this strategy. Strategies 2, 3, and 4 were based on adjuvant chemotherapy only in stage III colon cancer (Tt.III) and were targeted at different groups included in systematic follow-up (F-U.): strategy 2 (S2): Tt.III + follow-up in patients younger than 75 years with stage II and III (F-U. II/III <75); strategy 3 (S3): Tt.III + follow-up in patients younger than 75 years and stage III with carcinoembryonic antigen (CEA) > 5 ng/mL (F-U. II/III <75, CEA >5), strategy 4: Tt: III + no follow-up (NOF-U). Strategies 5, 6, and 7 were based on adjuvant chemotherapy in stage II and III colon cancer (Tt.II/III) and targeted different groups for systematic follow-up: strategy 5 (S5): Tt.II/III + follow-up in all patients with stage II and III (F-U.II/III); strategy 6 (S6): Tt.II/III + follow-up in patients younger than 75 years and stage III with CEA > 5 ng/mL (F-U. II/III <75, CEA >5), and strategy 7 (S7): Tt.II/III + no follow-up (NOF-U).

Type of intervention
Treatment and palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
A hypothetical cohort of patients with stage II or III resected colon cancer.

Setting
A hospital setting. The economic analysis was carried out in France.

Dates to which data relate
Effectiveness data were obtained from literature published between 1976 and 1997. Resource use data were based on recommendations and protocols, published in 1995, from French institutions. The price year was not explicitly specified.

Source of effectiveness data
The evidence for the final outcomes was based on a review of the literature

Modelling
A decision analytic model was developed to estimate the costs and effects associated with each therapeutic strategy.
Outcomes assessed in the review
The following outcomes were assessed in the review:

- the proportion of the population with colon cancer stage II;
- the proportion of the population with colon cancer stage III subdivided into the proportion with preoperative CEA < 5 ng/mL, and preoperative CEA > 5 ng/mL;
- 5-year recurrence (with/without adjuvant chemotherapy) of stage II colon cancer;
- 5-year recurrence of stage III colon cancer when preoperative CEA < 5 ng/mL and preoperative CEA > 5 ng/mL;
- decrease in recurrence risk with adjuvant treatment;
- treatment of recurrences using curative surgery with intensive follow-up or with no follow-up;
- 5-year survival rate after recurrence resection using curative surgery or palliative treatment;
- perioperative mortality for age groups over 75 years and under 75 years;
- 5-year mortality rate (not cancer related) for age groups over 75 years and under 75 years;
- mortality rate related to adverse effects of chemotherapy;
- hospitalisation rate for severe adverse events associated with adjuvant chemotherapy;
- proportion of recurrences diagnosed during the first 2 years after colon cancer resection;
- the type and proportion of recurrences treated with a curative surgical intervention.

Study designs and other criteria for inclusion in the review
The authors analysed data on the efficacy of follow-up protocols, either comparative studies published since 1977 or noncomparative studies published since 1990 which included more than 500 patients. Data from a meta-analysis, from 2 randomised studies, and from cohort studies were used. Another randomized study was not used because of a high proportion of rectal cancers.

Sources searched to identify primary studies
The MEDLINE database was searched along with a manual search.

Criteria used to ensure the validity of primary studies
The criteria used to ensure the validity of primary studies were not reported.

Methods used to judge relevance and validity, and for extracting data
The methods used to judge relevance and validity were not reported.

Number of primary studies included
A total of 37 studies, including at least 5 randomized trials and a meta-analysis were included.

Methods of combining primary studies
In most cases, the adopted probabilities were based on mean values in the literature.
Investigation of differences between primary studies
An investigation of the differences between primary studies was not reported.

Results of the review
The outcome values were as follows:

proportion of population with colon cancer stage II, 54;

proportion of population with colon cancer stage III subdivided into proportion with preoperative CEA < 5 ng/mL, 22.4%, and preoperative CEA > 5, 23%;

5-year recurrence (with/without adjuvant chemotherapy) of stage II colon cancer, 17.1%/24.5% (95% CI: 21.6%-27.4%);

recurrence (with/without adjuvant chemotherapy) at year 5 of stage III colon cancer when preoperative CEA < 5 ng/mL, 31.4%/44% (95% CI: 38.9% - 48.1%), and preoperative CEA > 5, 46.4%/65% (95% CI: 58% - 71.6%);

decrease in recurrence risk with adjuvant treatment, 28.5%;

treatment of recurrences using curative surgery with intensive follow-up, 30% (95% CI: 26.2% - 37.6%), or with no follow-up, 18% (95% CI: 12.7% - 22.5%);

survival rate at year 5 after recurrence resection using curative surgery, 25%, or palliative treatment, 1.5%;

perioperative mortality for age groups over 75 years, 7%, and under 75 years, 3%;

mortality rate at 5 years (not cancer related) for age groups older than 75 years, 30%, and under 75 years, 8.4%;

mortality rate related to adverse effects of chemotherapy; 0.25% (95% CI: 0 - 0.6%);

hospitalization rate for severe adverse events associated with chemotherapy, 10%;

proportion of recurrences diagnosed during the first 2 years after colon cancer resection, 80%;

hospitalization rate for severe adverse events associated with chemotherapy for patients without curative resection of recurrence, 20%;

and the type and proportion of recurrences treated with a curative surgical intervention, hepatic metastases in 80% of cases and pulmonary metastases in 20%.

Measure of benefits used in the economic analysis
Overall 5-year survival rates.

Direct costs
Costs were not discounted despite a 5-year time-frame considered for the cost analysis. Some quantities were reported separately from the costs. Cost items were reported separately. Cost analysis covered the costs of adjuvant chemotherapy treatment, systematic follow-up, and recurrence treatment, including hospitalisation for adverse events associated with chemotherapy. The perspective adopted in the cost analysis was that of the French National Medical Health System. The cost of each strategy represents the funds necessary for the 5 years of management of the cohort of patients with stage II or III colon cancer resected over a 1-year period in France. The costing of adjuvant chemotherapy and follow-ups was based on recommendations and protocols from French institutions. The cost of follow-up was calculated based on a 2-year follow-up period in 80% of patients with recurrence and for 5 years in the remaining
patients. Ambulatory costs were used to calculate costs of procedures employed for follow-up and chemotherapy. The price year was not explicitly specified.

**Indirect Costs**
Indirect costs were not included.

**Currency**
French francs (Ffr). The conversion rate was US$1 = Ffr 6.

**Sensitivity analysis**
A set of one-way sensitivity analyses was performed on some of the clinical and cost parameters.

**Estimated benefits used in the economic analysis**
Overall survival rate at 5 years was 60.6% in the reference strategy S1 (Tt.III + F-U.II/III). The corresponding values for the strategies 2 to 7 were 60.3%, 59.7%, 59.4%, 63.3%, 62.7%, and 62.3%.

**Cost results**
The total cost for the reference strategy, S1, was $68 million for the study cohort. The values for the strategies 2 to 7 were $58 million (2), $46 million (3), $42 million (4), $82 million (5), $61 million (6), and $58 million (7).

**Synthesis of costs and benefits**
Cost per surviving patient and incremental cost per additional surviving patient, as compared to strategy 4, were calculated as the measures of cost-effectiveness analysis. Cost per surviving patient was $10,768 for S1. The corresponding values for the strategies 2 to 7 were $9,118, $7,373, $6,781, $12,421, $9,308, and $8,954. The incremental cost per additional surviving patient as compared to strategy 4 was $0.208 million for strategy 1, $0.163 million for strategy 2, and $0.123 million for strategy 3. The corresponding values for strategies 5 to 7 were $0.098 million, $0.055 million, and $0.053 million. The order of the efficacy of strategies was insensitive to changes in the values of the variables studied. Sensitivity analysis suggests that the most influential variable for 5-year survival rate were the proportion of patients with advanced colon cancer, which emphasizes the importance of screening, and the efficacy of adjuvant chemotherapy, which strongly suggests that therapeutic trials should be performed.

**Authors' conclusions**
The current standard strategy may not be the most cost-effective strategy for the management of patients with resected colon cancer.

**CRD COMMENTARY - Selection of comparators**
Strategy 1 (S1), as the most commonly accepted strategy, was regarded as the comparator. The database user should consider whether this is a widely used health technology in their own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness results are likely to be internally valid given the systematic literature review, and the wide range of primary and meta-analysis studies (including randomised trials) used as the sources for the clinical probabilities. However, some methodological shortcomings can be highlighted in the study such as the absence of criteria used to ensure the validity of primary studies, and investigation of differences between primary studies. Furthermore, it was reported that some of the data in the literature were missing or inaccurate.
Validity of estimate of measure of benefit
The estimation of benefits was modelled. The instrument used to derive a measure of health benefit, (decision analytic model), appears to have been appropriate. However, it was mentioned that a Markov model could have been used instead of a decision tree model. Furthermore, it was admitted that the study model did not assess quality of life because of the lack of information in the literature.

Validity of estimate of costs
The good points of the study were that some quantities were reported separately from the costs and adequate details of the methods of cost estimation were given. With respect to the perspective adopted in the cost analysis, it appears that all important direct cost elements were included and the perspective adopted in the cost analysis was specified.

Limitations of the study were that the price year was not specified and it was not entirely clear whether the cost data were based on true costs or on charge/reimbursement data.

The effects of alternative procedures on indirect costs were not addressed.

Other issues
The authors' conclusions appear to be justified given the relatively comprehensive literature review, and the sensitivity analysis performed. However, the authors emphasised that the study results may need to be treated with some caution, even though they seem to be robust to variations in the parameters assessed. It was acknowledged that the cost of chemotherapy not only varies from one national health system to another but also changes within the country depending on individual hospital policy. An increase in the cost of chemotherapy could affect the ranking order of strategy costs. Some comparisons were made with other studies. It was reported that the study population and results were restricted to patients with stage II and III colon cancer. However, it was estimated that systematic population screening would result in an estimated decrease in the number of deaths at 5 years in the study model of 6%. Therefore, it was concluded that screening seems to be the most influential event for 5-year survival when all patients with colon cancer are considered. Furthermore, it was acknowledged that due to the 100% adherence rate considered for the stage III patients in the model for the adjuvant chemotherapy, the study model may have over estimated the expected efficacy in the study population.

Implications of the study
The study results suggest that survival could be improved by increased use of adjuvant chemotherapy and early detection of colon cancer. Research on these topics should be given priority over research on follow-up, which does not appear to improve survival. It would be useful to determine which threshold value for adherence to recommendations would influence the choice of the optimal strategy.

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