Cost-effectiveness of neoadjuvant multimodal therapy in patients with esophageal adenocarcinoma

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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
Adjuvant multimodal therapy, comprising chemotherapy plus radiotherapy, was evaluated in patients with oesophageal adenocarcinoma undergoing surgery. The dosing regimen for each course of chemotherapy consisted of fluorouracil, 15 mg/kg body weight daily for five days intravenously, plus cisplatin, 75 mg/m² body surface area for one day intravenously. The course of radiotherapy before surgery was 40 Gy, which was administered in 15 fractions over a 3-week period.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of patients with oesophageal adenocarcinoma undergoing surgery.

Setting
The setting was secondary care. The economic study was carried out in Italy.

Dates to which data relate
The dates during which the effectiveness and resource use data were gathered were not stated, but they were taken from a study published in 1996. The price year appears to have been 1997.

Source of effectiveness data
The effectiveness data were derived from a single study (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was carried out for the standard resource use related to the interventions. The costing used the same patient sample as that used in the effectiveness analysis.

Study sample
There were 58 patients with oesophageal adenocarcinoma, who were treated with two courses of chemotherapy and a course of radiotherapy before surgery. There were 55 controls with oesophageal adenocarcinoma that underwent surgery only. Power calculations to determine the sample size were not reported.
Study design
This was a case-control study. The length of follow-up was 3 years. The details of the study were published separately.

Analysis of effectiveness
The primary health outcome was the survival associated with the multimodal treatment and the standard approach. However, few details were provided. The details may be available in the original publication of the study.

Effectiveness results
The monthly percentage survival was derived from the published graph. This showed large differences in survival during the study follow-up. Survival at 10 months was 66.7% for the multimodal group and 56.4% for the control group. Survival at 20 months was 53.6% for the multimodal group and 30.8% for the control group. Survival at 36 months was 47% for the multimodal group and 8.9% for the control group.

Clinical conclusions
The clinical conclusions were reported in the original publication of the study. The reported results implied that adjuvant multimodal therapy had a continuous benefit on the monthly percentage survival.

Modelling
A parametric lifetime survival model (Gompertz function fitted through a non-linear weighted least-squares iterative fit), which used 3-year follow-up data, was employed. The details of the model were reported satisfactorily. The costs and the effectiveness of hypothetical groups of 100 patients undergoing multimodal therapy (preoperative chemotherapy plus radiotherapy) or surgery alone were estimated. The effectiveness evidence was derived from a published study.

Measure of benefits used in the economic analysis
The benefit measure used was the number of discounted life-years gained with the interventions. This was calculated using the area under the lifetime survival curve. The results of the survival fitting curve were also reported, in terms of the root mean squared error (RMSE) on the log-transformed survival percentage (SP) values and the RMSE on the SP values.

Direct costs
The costs relating to the treatment were assumed to occur exclusively during the first year of the patients' follow-up. Thus, discounting of the costs was irrelevant. The direct costs for treating 100 patients with either chemotherapy plus radiotherapy or no adjuvant therapy (for example, the costs of administration, nursing time, and devices) were analysed. The main cost items were drug acquisition, radiotherapy, hospitalisation, or day hospital attendance. The costs of surgery were excluded because the two patient groups were assumed to incur identical costs. The costs per cycle per patient were reported. The drug acquisition costs were estimated using actual data, which were derived from average wholesale prices in Italy. The hospitalisation costs reflected the average costs of Italian public hospitals. The source of the remaining costs was unclear. The price year appears to have been 1997.

Statistical analysis of costs
No statistical analysis of the costs was carried out.

Indirect Costs
No indirect costs were included in the analysis.
Currency
US dollars ($). The exchange rate in January 1997 was US$1 = Italian lira 1,594.

Sensitivity analysis
Sensitivity analyses were carried out to test the effect of the following:

- variations (+/-20%) in the total cost of the multimodal therapy, including drugs, radiotherapy and hospitalisation;
- undiscounted benefits; and
- survival from 0 to 3 years (thereby disregarding the extrapolated tail).

The analyses appear to have been univariate.

Estimated benefits used in the economic analysis
The benefits were discounted at an annual rate of 5% and normalised to a population of 100 patients. The area under the lifetime survival curve was 319.7 patient-years for the multimodal treatment group and 122.8 patient-years for the control group. Therefore, the incremental effectiveness of multimodal treatment modality was 196.9 discounted life-years per 100 treated patients. The RMSE on the log-transformed SP values were 1.5% for the multimodal group and 1.4% for the control group. The RMSE on the SP values were 6.0% for the multimodal group and 4.9% for the control group. The survival curve fit was excellent for both groups. The study results compared favourably with survival advantage in the study population when taking into account the median age at enrolment (65 years).

Cost results
The drug acquisition cost for chemotherapy (including anti-emetic agents) was $229.8 per cycle per patient. This was estimated on the basis of intravenous administration of ondansetron before and during cisplatin infusion, for a total of 24 mg per cycle. Overall, the cost of chemotherapy was $45,960 per 100 patients, assuming an average of two courses per patient.

Radiotherapy was assumed to cost $62.7 per session per treated focus. The total cost normalised to 100 patients was $94,050, assuming an average of 15 sessions per patient.

Chemotherapy required 7 days of hospitalisation per course, and radiotherapy an additional 10 day-hospital cases. Assuming a cost of $350 per day of hospitalisation and $150 per for a day-hospital case, the total cost of hospitalisation and day-hospital was $640,000 per 100 patients.

Thus, the overall cost in the multimodal treatment group was $45,960 plus $94,050 plus $640,000, i.e. $780,010 per 100 patients, whereas the controls had no such costs. Consequently, the incremental cost of the multimodal therapy over standard therapy was $780,010.

Synthesis of costs and benefits
The costs and the benefits were combined by an incremental cost-effectiveness analysis. The incremental cost-effectiveness ratio was $3,961 per life-year gained. A 20% increase in the total costs of multimodal therapy yielded a cost-effectiveness ratio of $4,754 per discounted life-year gained. A 20% decrease in the same costs yielded $3,169 per discounted life-year gained. The cost-effectiveness ratio was $13,732 per discounted life-year gained when no extrapolation beyond the 3-year follow-up was performed. The cost-effectiveness ratio was $3,063 per life-year gained in the case of undiscounted benefits (corresponding to a gain of 254.6 undiscounted life-years).

Authors' conclusions
The cost-effectiveness ratio of the multimodal therapy, i.e. $3,961 per discounted life-year gained, was favourable in comparison to surgery alone. The sensitivity analysis confirmed the robustness of this conclusion.
CRD COMMENTARY - Selection of comparators
The analysis of adjuvant multimodal therapy (chemotherapy plus radiotherapy) in patients with oesophageal adenocarcinoma undergoing surgery, compared with surgery alone, was justified on the basis of the beneficial results obtained from a recent controlled study. You should assess which standard therapy is currently implemented in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from a published controlled study. However, the information on the study design was insufficient to enable the validity of the estimates to be analysed.

Validity of estimate of measure of benefit
The choice of life-years gained as a measure of benefit was justified as a main area of intervention impact. The analysis was limited by the lack of a quality of life analysis. The benefits were estimated by extrapolating the results of the effectiveness evidence beyond the study follow-up. This assumption was tested in the sensitivity analysis.

Validity of estimate of costs
The costs appear to have been analysed from the perspective of the health care provider. The costs of the resources were calculated for standard treatment pathways and were not treated stochastically. A sensitivity analysis was performed on the total costs only. The cost estimates appear to have been somewhat specific to the study setting. Appropriate currency conversions were performed.

Other issues
The authors acknowledged that the use of costs relevant to Italian hospitals could have limited the generalisability of the cost-effectiveness estimates. However, this seemed unlikely when single costs, such as hospitalisation costs, were compared between countries. The authors compared their findings with those for other interventions, in order to conclude the favourable cost-effectiveness estimate. The results appear to have been reported selectively. The study's conclusions should be limited to the study population considered in the study.

Implications of the study
The authors suggested that the use of adjuvant multimodal therapy (chemotherapy plus radiotherapy) in patients with oesophageal adenocarcinoma undergoing surgery was cost-effective when compared with surgery alone.

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Supported in part by a grant from SIFO (Italian Society of Hospital Pharmacy).

Bibliographic details

Other publications of related interest
MeSH
Adenocarcinoma /surgery /therapy /radiography /drug therapy; Adult; Antineoplastic Combined Chemotherapy Protocols; Cisplatin /therapeutic use /economics; Combined Modality Therapy; Cost-Benefit Analysis; Esophageal Neoplasms /surgery /therapy /radiotherapy /drug therapy; Fluorouracil /therapeutic use /economics; Italy; Survival Rate

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