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Cost-effectiveness analysis of colorectal cancer treatments

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Abstract

A concise overview is provided of the methodology of cost-effectiveness analyses, followed by a survey of published CEAs of colorectal cancer treatments. To gain credibility, the methodology applied in CEAs must be further improved. Costs are rarely estimated from the societal perspective, and little is known about how colorectal patients value their treatment and health.

Keywords: Cost-effectiveness analysis; Methodology; Survey; Colorectal cancer

1. Introduction

The last decades have shown a steady increase in the number of cost-effectiveness analyses that are published in the medical literature. No doubt, an important reason for this rise is the growing consciousness and concern about healthcare costs, but likewise the advancement of medical technology has raised questions about the appropriateness of healthcare. Moreover, the current shift towards interventions that improve quality of life, compared with life-saving interventions, provides more ethical scope to consider costs in medical decisions.

The subject of this paper is cost-effectiveness analysis (CEA) of colorectal cancer treatments. The paper consists of two major parts. First an introduction to the methodology of CEAs is provided, highlighting the choices that need to be made to produce a CEA. We aim to show that cost-effectiveness is not a clearly defined unequivocal concept, to provide some insight into the consequences of assumptions that are commonly made in CEAs, and to enable the reader to distinguish between proper and improper assumptions.

The second part of this paper consists of a survey of published CEAs of colorectal cancer treatments. These publications will be used to illustrate specific elements of cost-effectiveness analyses and to investigate existing methodological shortcomings. Only publications that explicitly compare costs and effectiveness were selected for the survey. Since cost-effectiveness is only one of the possibly relevant decision criteria, the publications should not be expected to provide a complete overview of the pros and cons of the considered colorectal cancer treatments.

2. Methodology of cost-effectiveness analysis

A cost-effectiveness analysis is an economic analysis in which two or more treatment options are compared by effectiveness and costs. A treatment is said to be dominant if it is both less expensive and more effective than the alternatives. A treatment is said to be cost-effective if it provides good value for money: it need not be cost-minimising, but compared with the alternatives the incremental costs should be outweighed by the incremental effectiveness. By incremental is meant that it is the differences in costs and effects that are relevant, not the absolute values. The decision whether a more effective treatment is also cost-effective is based on the incremental cost-effectiveness ratio (CE ratio). This ratio of the additional costs and the additional effectiveness should be acceptably small.

Cost-effectiveness analysis is one of several types of economic analyses [1,2], each with their specific merits and application. For example, cost-of-illness studies estimate the costs associated with a group of patients, without comparing different treatment options for these patients. Similarly, costing studies estimate the costs

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associated with only one particular treatment. Cost-minimisation studies do compare different treatment options but only by costs, without taking other outcome measures into account. Cost-benefit analyses estimate the monetary value of health outcomes and subtract these from costs to estimate the monetary net benefit of an intervention. Cost-effectiveness analyses estimate costs and effectiveness separately, facilitating comparison with other interventions.

The most straightforward type of CEA is one in which both costs and effects are estimated from data of a single randomised trial. For a number of reasons, this type of CEA is not very common. CEAs are usually conducted to support policy-making, which may not allow for the long delay frequently associated with randomised trials. Evaluating the possibly small or long-term differences by randomised comparison may be unfeasible or too expensive; or, however, many trials may exist with results that need to be reconciled; and finally, especially in the past, the idea to estimate costs may not have been incorporated into the original study design. As a result, CEAs typically use varying degrees of modelling, aggregating data from various sources. Such CEAs should be presented in a way that enables the reader to assess the validity and the impact of the modelling assumptions.

To standardise the methodology of economic analyses, a multidisciplinary panel appointed by the US Public Health Service in 1996 drew up a set of consensus guidelines that has from the start been widely accepted as the standard for CEAs [3–5]. The most important of the formulated guidelines is that CEAs aiming to support societal policy-making should be conducted from a societal perspective. This means that the analysis should not be restricted to the perspective of particular care providers or patient groups. It should include all health effects and medical and non-medical costs experienced by those that are significantly affected by the intervention.

2.1. Estimating costs

Cost equals volume times price. The skill in applying this simple rule is to match the level of precision to the importance of the cost item [1]. For example, in some studies it may be relevant to define the costs of consultations as the total consultation time times the price per hour, but in most cases it will be sufficient to multiply the number of consultations with the price per consultation. International incomparability of prices of healthcare underlines the importance of reporting not only the estimated costs of healthcare consumption, but also the separate volumes and prices.

2.1.1. Volumes of healthcare

Estimates of volumes of care can be obtained from a variety of sources. The best warranty of validity is to obtain the estimates from the same patients from which effectiveness is estimated. This information can either be obtained from the patients themselves or from their providers of care, like physicians or hospitals. Patients usually have an overall view of the care that they consume and it is relatively easy to ask them using a questionnaire, a diary or an interview. The main disadvantage of asking the patients is that it requires them to remember, which may be a difficult task and may lead to inaccurate estimates [6]. Automated information systems used by providers of care may provide more accurate data. Their disadvantage is that existing databases may not contain precisely the required information and it may be laborious to obtain the information, especially if a patient has several relevant providers or if different patients have different providers. If no patient population is available for questioning, then estimates need to be obtained from other sources, like expert opinion, insurance companies or the literature. These data sources provide little opportunity for careful patient selection, so validity is a major problem.

2.1.2. Prices of healthcare

Prices are the cost per separate item of healthcare. To obtain a valid estimate of societal prices it is as a rule best to discern different cost categories, such as personnel, equipment, material, housing and overheads. The prices of separate categories are usually a better proxy for the societal price than the charge for the intervention as a whole. Unfortunately, conducting a detailed price analysis is laborious, and therefore often only applied to the primary intervention.

For interventions less prominent in the study, simpler valuation methods can be used. In some countries standard prices are available [7], from previously conducted detailed price analyses. Besides being ready for use, they have the additional advantage of facilitating comparison of different cost analyses. If appropriate standard prices are not available, then one may obtain price estimates from published studies. A last resort is to use charges, but these should be used as little as possible. The complex way in which charges are determined can seriously undermine their validity as estimates of the societal costs.

A final topic in pricing is the differential value of money through time. Costs in the future are preferable to costs now, for one reason because delaying provides the opportunity of obtaining interest. Reckoning with the differential value of money over time is called discounting. The consensus guidelines [3] advise use of a constant 3% discount rate, which means that the value of money decreases by 3% each year. For example, the value of \$100 in 10 years time is equal to $\$100/1.03^{10} = \$74$ now. Discounting is especially relevant in analyses with long time horizons, like in follow-up or prevention programmes.

2.1.3. Non-medical costs

From a societal perspective, medical treatment can lead to non-medical costs. CEAs from a societal perspective should also estimate these non-medical costs, unless there is enough evidence beforehand that there will be no difference between the treatment options. The main cost categories here are patient costs and productivity costs.

Patient costs include, for example, the costs of time and travelling, costs of informal care, and out-of-pocket costs. Time costs reflect that patients have other valuable things to do apart from being treated, so time can be a true factor for patients in deciding whether or not to undergo treatment. Travel costs can often be estimated without asking the patient, provided the means of transportation is known. Informal care and out-of-pocket costs, however, can only be estimated by asking the patient. Out-of-pocket costs include for example special clothing, diet costs or a waterbed for a patient with painful bone metastases. It should be realised that not all patient expenses are costs. Insurance premiums and disability pensions should be excluded because, from a societal perspective, these are income transfers without loss of resources.

Productivity costs can be estimated by valuing a patient's lost production by the patient's wages [8]. One should be aware that by including productivity costs an intervention that prevents illness among younger male patients is bound to be more cost-effective than that same intervention among older female patients. This discriminatory effect can be partly remedied by including unpaid labour as well.

2.2. Estimating effectiveness

Effectiveness of treatments can be measured in many ways, like the probability of cure, the number of complications, the probability of local recurrence or 5-year survival. A CEA on two different types of adjuvant treatment could for example render an estimate of the costs per prevented local recurrence. To choose between treatments with identical goals, a CEA with these effectiveness measures can provide valuable information about which treatment is more efficient in achieving that goal.

However, for policy-making on a broader scale, the effectiveness measure should be applicable and comparable for a wide range of treatments and should reflect the ultimate goals of health care: to improve both survival and quality of life. An effectiveness measure that aims to meet these criteria is provided by the concept of quality adjusted life expectancy, also published under the name of Q-TWiST. This measure can incorporate both advantages and disadvantages of treatments, which is especially useful in the assessment of the value of chemotherapy. An additional advantage of using quality adjusted life years (QALYs) is that there is some consensus on the fact that under normal circumstances $50 000 per QALY are acceptable costs. For example, the value of a prevented local recurrence is more difficult to determine because it depends on how much the effectiveness of treatment improves with earlier detection.

When QALYs are used to assess effectiveness, the cost-effectiveness analysis (CEA) is called a cost-utility analysis (CUA). The first step in estimating QALYs is to estimate non-adjusted life expectancy. The second step is to multiply the life expectancy in particular health states with the corresponding quality weights, also known as valuations or utilities. These quality weights are expressed on a 0 to 1 scale, with 0 representing the value attached to a state of death and 1 the value attached to optimal health. QALYs can be seen as the equivalent number of years in full health. For example, 5 years in a health state that is valued at only half of optimal health (i.e. as having a value of 0.5) can be thought of as being equivalent to 2.5 years in full health: $5 \times 0.5 = 2.5$ QALYs. Different methods to assess quality weights will be described here in some detail. For an overview of CUAs and assessed quality weights in oncology, the reader is referred to Earle and colleagues [9].

A much debated question is whose values should be used. Clinical decision-making seeks to decide upon an optimal treatment policy for groups of similar patients or for an individual patient. Therefore, patient preferences are germane. Decision-making concerning healthcare resources in the public interest calls for incorporation of society's utilities in cost-utility analyses. Therefore, these utilities should be gathered from a representative sample of members of the community [3–5,10]. Their judgements should be informed, unbiased and competent, however, and in some instances the elicitation of preferences from persons experiencing a particular health state may be favoured, since they may be less biased.

2.2.1. Direct utility elicitation

The Time Trade-Off (TTO) and the Standard Gamble (SG) can be used to directly assess utilities from respondents (see Fig. 1). Both methods are difficult to administer without the help of an interviewer.

The TTO is based on the principle that a person in a less preferred health state will be willing to trade off a higher proportion of life expectancy to gain optimal health. The respondent is asked how many years y in optimal health she would consider equivalent to x years in the health state to be valued, a state that is usually worse than optimal health. The utility of the health state is then calculated as $U = y/x$. If y is small then also the measured utility is small, since the patient is willing to trade-off a large part of her life expectancy.

The SG is based on the principle that a person in a less preferred health state will be willing to accept more risk in order to gain optimal health. The patient is asked what risk of immediate death (or death within 1 week)

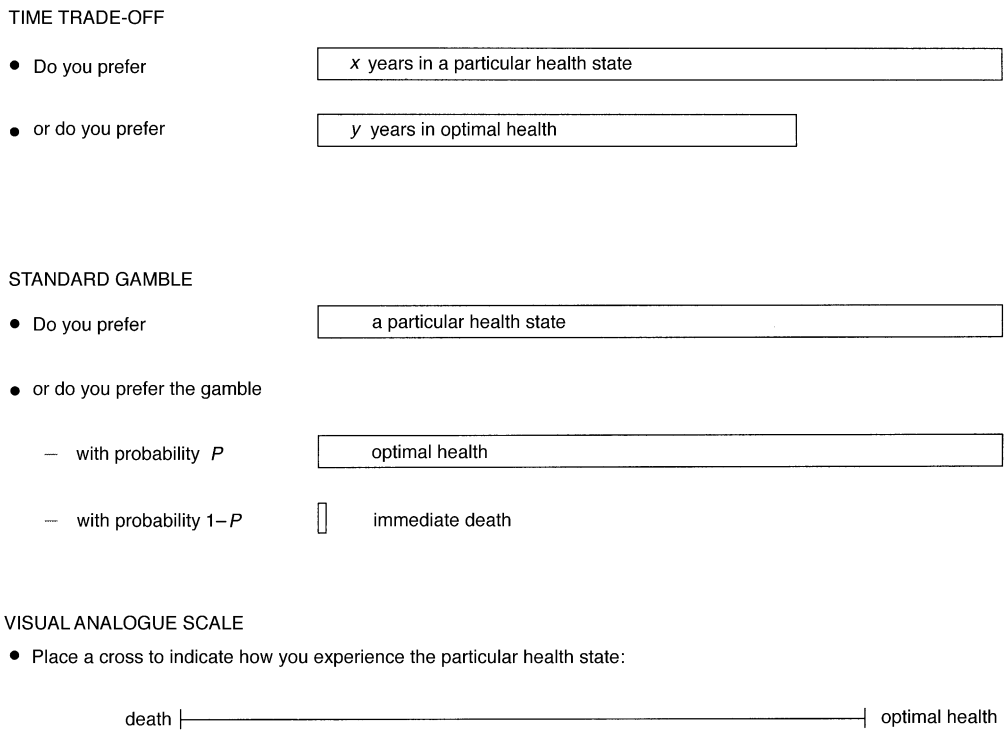

Fig. 1. The Time Trade-Off (TTO), Standard Gamble (SG) and transformed visual analogue scale (VAS) method. If the respondent is indifferent between both options, then her utility for the particular health state is $U=y/x$ for the TTO method and $U=p$ for the SG method. The non-transformed VAS score is the relative position of the cross on the scale, that is the distance between the left anchor and the cross divided by the length of the scale. The utility for the particular health state can then be calculated as $U=1-(1-\text{VAS})^{1.61}$.

she would be willing to accept, in order to gain optimal health. The question is framed as a choice between either the certainty of the health state to be valued or a gamble with probabilities p of optimal health and $(1-p)$ of immediate death. The utility of the health state is then calculated as the probability at which the patient is indifferent between the health state and the gamble: $U=p$. For more information on these methods see Stiggelbout and De Haes [10].

A valuation method that can be used in questionnaires is the rating scale or visual analogue scale (VAS). The VAS asks the patient to indicate on a line the valuation of her health state, relative to two extreme health states like optimal health and death. The VAS score is not considered a utility because it does not ask for an explicit choice. In addition, it has undesirable scale properties [11]. Nevertheless, it does correlate with the direct valuation methods. In several studies a power transformation [12] has been suggested and used to convert the VAS to a TTO utility, like $U=1-(1-\text{VAS})^{1.61}$.

2.2.2. Health state classification systems

An indirect way to obtain utilities is to use health state classification systems. Examples are the Quality of Well-being scale [13], the Health Utility Index [14] and the EuroQoL [15]. Health state classification systems are customarily composed of two components: a descriptive system and a utility scoring formula. First the descriptive system is filled out by a patient to describe her health state, that is her level of functioning on a set of items pertaining to domains of quality of life or functioning (such as mobility, self-care or pain). Next, the scoring formula is used to calculate the utility of the described health state. This scoring formula is readily available from earlier studies, based on direct utility elicitation by samples of the general public [4]. Increasingly, the descriptive systems of such indexes are used in clinical trials, which increases comparability and enables cost-utility analyses from a societal perspective, using the preference weights from the general public.

3. Cost-effectiveness analysis of colorectal cancer treatments

We searched the literature for published cost-effectiveness analyses on treatment and follow-up of colorectal cancer. In the PubMed (1966 until April 2001), Current Contents (1995 until April 2001) and EconLit (1969 until February 2001) databases we first searched for publications on colorectal cancer that included cost(s) in the title.

This provided 279 distinct publications from which we successively excluded by hand 27 editorials, letters and comments, 50 publications without abstract, 44 publications that did not concern colorectal cancer, 25 publications that did not estimate costs, 16 cost-of-illness studies, 20 costing studies and 15 cost-minimisation studies. Of the remaining 82 cost-effectiveness analyses, we further excluded one on prevention, 51 on screening, and six on diagnosis. Finally, the 24 CEAs shown in Table 1 remained, of which three on primary surgery, five on adjuvant treatment, eight on follow-up and eight on treatment of advanced disease. Comparison with other reviews on economic analyses [9,16,17] did not render additional cost-effectiveness analyses. The median publication year was 1997.

3.1. Surgery

Surgery is the predominant curative option for colorectal cancer and the appropriateness of surgery is beyond doubt for potentially curable disease. As a result, the only CEA comparing surgery to no-surgery applies to very elderly patients. For patients more than 80 years old, Hobler [18] compared surgery with palliative treatment. The patients were not randomised. He showed that the gain in life expectancy from surgery was comparable to that for patients aged less than 80 years old. The hospital stay and total charges were both significantly higher, but only by 20%. Therefore, he concluded that the cost-effectiveness of surgery in the very elderly was comparable to that in younger patients, so surgery should not be restricted on the basis of age alone.

The non-randomised study by Musser and colleagues [19] compared different types of surgery. They concluded that laparoscopic colectomy compared favourably with open surgery. Neither quality of life nor long-term survival were estimated, but in laparoscopic procedures for cancer the number of resected nodes was higher and all margins were free. Although the operating room charges increased, both the overall hospital charges and the hospital stay were lower for laparoscopic surgery.

Jensen and colleagues [20] randomised patients admitted for colorectal surgery to obtain either white cell (WBC)-reduced blood or unfiltered blood. Effectiveness was measured by the number of complications and the duration of hospital stay. Costs of blood transfusion, filtering and hospital charges were estimated. The group of patients that received WBC-reduced blood had both lower costs and better effectiveness, almost comparable to the patients that did not receive any transfusion.

3.2. Adjuvant treatment

So far, no CEAs have been conducted on preoperative or postoperative radiotherapy, nor on immunotherapy. However, there have been quite a number of CEAs on adjuvant chemotherapy (ACT). This may reflect the commercial interests of the pharmaceutical industry. Based on the reported studies, there is no reason to believe that this has harmed the methodological validity of these studies. A relatively large number of these CEAs use QALYs as the outcome measure to balance improved survival against loss of quality of life.

In 1990, the United States National Institutes of Health recommended ACT for Dukes' C colon cancer patients. Following this recommendation, there have been four cost-effectiveness analyses comparing systemic levamisole + 5-fluorouracil (5-FU) therapy with no ACT. To estimate QALYs, Smith and colleagues [21] in 1993 used the TTO method to obtained health state valuations from 8 healthy respondents and 8 Dukes' C patients undergoing chemotherapy. This is the only study in our survey that reported on a detailed price analysis. They estimated that the 2.4 years gain in life expectancy corresponded to a gain of only 0.4 years in quality-adjusted life expectancy. The additional costs amounted to 17.500 Australian dollars per QALY (1 Australian dollar $\approx$ 0.5 American dollar). They concluded that, for the moment, it was perhaps more appropriate for the use of chemotherapy to be an option rather than the standard treatment.

In a later analysis in 1994, Brown and colleagues [22] used different cost and utility estimates. They obtained utility estimates for the chemotherapy period from generic studies and for the relapse period they assumed a 0.5 utility weight, that is a gradual decrease from full health to death. Apart from hospital costs, also the value of the patient's time while undergoing therapy was included. Their estimated gain per patient was approximately 1.8 quality-adjusted life years, with costs amounting to only $2.094 per QALY. Both studies show that the cost-effectiveness of ACT is acceptable, but the difference is considerable. Brown attributed the difference to the assumed limited detrimental effect of chemotherapy on quality of life, underlining the need for standardised methodology.

A study by Norum and colleagues [23] in 1997 applied to both Dukes' B and C patients. They measured utility in their patients by averaging the EuroQoL, VAS and European Organization for Research and Cancer Quality of Life-Core 30 (EORTC QLQC30) instruments, confirming the limited impact of ACT on quality of life. They also included travel costs that were considerable because their arctic study region was sparsely populated. The employed method was a so called threshold analysis: to make ACT cost-effective at £20 000 per QALY, the 5-year survival benefit needed to be at least 5% (£1$\approx$$1.5). The available estimates all suggested that this threshold was indeed attained.

Finally, based on longer follow-up data, Bonistalli and colleagues [24] in 1998 estimated an even larger gain of 2.8 quality-adjusted life years, at $1501 per QALY

Table 1
Summary of the CEAs included in the survey

Publication	Population	Treatment options	Included costs	Effectiveness measure	Cost-effectiveness (CE)
Surgery					
Hobler, 1986 [18]	At least 80 years old	Surgery or palliative treatment	Hospital costs	Life expectancy	CE ratio was found comparable to that of younger patients
Musser, 1994 [19]	Surgical patients	Laparoscopic or open surgery	Hospital costs	Resected nodes, margins, hospital stay	Laparoscopic surgery was dominating: comparable surgical result and reduced hospital stay and charges
Jensen, 1995 [20]	Surgical patients	WBC-reduced or unfiltered blood	Hospital costs, transfusion, filtering	Complications, hospital stay	WBC-reduced blood dominated, with better effectiveness and lower costs
Adjuvant treatment					
Smith, 1993 [21]	Dukes' C patients	Levamisole + 5-FU therapy or no ACT	Hospital costs, including a detailed price analysis	QALE, TTO-utilities elicited from 16 respondents	$17 500 Australian per QALY
Brown, 1994 [22]	Dukes' C patients	Levamisole + 5-FU therapy or no ACT	Hospital costs, patients' value of time	QALE, 0.5 utilities and utilities obtained from literature	$2 094 per QALY
Norum, 1997 [23]	Dukes' B and C patients	Levamisole + 5-FU therapy or no ACT	Hospital costs, travel costs	QALE, EuroQol/VAS-utilities elicited from 62 patients	Cost-effective at £20 000 per QALY provided the survival benefit is at least 5%
Bonistalli, 1998 [24]	Dukes' C patients	Levamisole + 5-FU therapy or no ACT	Drug acquisition, chemotherapy	QALE, 0.5 utility for all impaired health states	$1501 per QALY
Messori, 1996 [25]	Colorectal patients	Intraportal or no ACT	Chemotherapy	LE	$1210 per non-adjusted LY
Follow-up					
Sandler, 1984 [27]	Patients after curative resection	Carcinoembryonic antigen monitoring or no follow-up	Follow-up tests, resurgery	Diagnosed resectable recurrences	$24 799 per diagnosed resectable recurrence
Graham, 1998 [28]	Dukes' B2 and C patients after curative resection	Separate monitoring tests or no follow-up	Follow-up tests	Diagnosed resectable recurrences	Carcinoembryonic antigen monitoring $5696 per diagnosed resectable recurrence, chest X-ray $10 078 and colonoscopy $45 810
Staib, 2000 [29]	Patients after curative resection	Intensive follow-up or no follow-up	Follow-up tests	Diagnosed resectable recurrences	€ 300 000 per diagnosed resectable recurrence
Bleeker, 2001 [30]	Dukes' C colonic patients after curative resection	Separate monitoring tests or no follow-up	Follow-up tests	Diagnosed resectable recurrences	Ranging from $5200 per diagnosed resectable recurrences for Carcinoembryonic antigen monitoring to $60 450 for physical examination.
Ketteniss, 2001 [31]	Patients after curative resection	Specific programme or no follow-up	Follow-up tests	Diagnosed resectable recurrences	62 000 German marks per diagnosed resectable recurrences
Kievit, 1990 [32]	Patients after curative resection	2-year carcinoembryonic antigen monitoring or no follow-up	Follow-up tests, resurgery	LE, QALE, Utilities obtained from literature	LE gain between +7 and −5 days. CE-ratio ranging from most favourable $23 000 to $5 000 000 per QALY
Norum, 1997 [33]	Patients after curative resection	Limited 4-year follow-up or no follow-up	Follow-up tests, resurgery	LE, QALE, Utilities obtained from literature [22]	Between £11 476 and £19 508 per QALY
Park, 2001 [34]	Patients suspected of recurrence	Diagnosis by CT + FDG PET or by CT only	Diagnosis, surgery, chemotherapy	LE	LE gain of 10 days, at $16 400 per non-adjusted LY

(*continued on next page*)

Table 1 (*continued*)

Publication	Population	Treatment options	Included costs	Effectiveness measure	Cost-effectiveness (CE)
Treatment of advanced disease					
Mellow, 1989 [35]	Rectal patients unsuitable for curative surgery	Endoscopic laser therapy or palliative surgery	Hospital costs	LE, complications	Endoscopic laser therapy dominated, with comparable LE and significantly less complications and charges
Glimelius, 1995 [36]	Inoperable colorectal patients	Best supportive care with or without chemotherapy	Hospital costs	LE, QALE, 0/1 utilities assigned by two observers	$9900 per QALY
Miller, 2000 [37]	Local recurrence	Non-operative, diagnostic or palliative, or surgical resection	Hospital costs	LE, QALE, SG-utilities elicited from 49 respondents	Diagnostic or palliative treatment dominated by non-operative treatment, surgical resection $56 700 per QALY
Beard, 2000 [38]	Resectable metastases	Hepatic resection or non-surgical cytotoxic treatment	Hospital costs	LE	£5236 per non-adjusted LY
Durand-Zaleski, 1998 [39]	Unresectable metastases	Hepatic arterial infusion, systemic or symptom control only	Hospital costs, absenteeism, disability living allowance	LE, QALY 0/1 utilities based on quality-of-life score	Hepatic arterial infusion and systemic chemotherapy both $24 000 per QALY
Iveson, 1999 [40]	Metastatic after 5-FU failure	Irinotecan or infusional 5-FU	Hospital costs	LE	£12 000 per non-adjusted LY
Levy-Piedbois, 2000 [41]	Metastatic after 5-FU failure	Irinotecan or infusional 5-FU	Hospital costs	LE	$10 000 per non-adjusted LY
Abramson, 2000 [42]	Metastatic unresponsive to systemic chemotherapy	Hepatic arterial chemoembolisation or palliative care	Hospital costs	LE	Cost-effective at $50 000 per non-adjusted LY provided the survival benefit is at least 5 months

WBC, white blood cells; 5-FU, 5-fluorouracil; Ly, life year; CT, computed axial tomography; FDG PET, [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography; ACT, adjuvant chemotherapy; QALE, quality-adjusted life expectancy; LE, life expectancy.

gained. However, they arbitrarily assumed a utility value of 0.5 during periods of toxicity and relapse. In addition, they included only the costs of drug acquisition and chemotherapy, so their results can not be compared with the other studies.

Intraportal adjuvant chemotherapy (mitomycin and fluorouracil) was studied by Messori and colleagues [25], also compared with no ACT. Based on 10-year follow-up data from a Swiss trial, they estimated a survival difference of 0.9 non-adjusted life years at costs of $1210 per non-adjusted life year. However, they also included only the costs of chemotherapy.

3.3. Follow-up

A wide variety of follow-up strategies exists for colorectal cancer patients after curative surgery. It is not difficult to show correspondingly large differences in costs [26]. The difficulty lies in estimating the differences in effectiveness. A number of papers have estimated the costs of follow-up per diagnosed resectable recurrence [27–31]. A major shortcoming of this type of studies is that they typically report CE ratios that are not incremental CE ratios. For example, a study could show that in 1000 patients a particular follow-up strategy would find 25 resectable recurrences at $50 000 costs, that is $2000 per resectable recurrence. An alternative follow-up strategy would find 50 resectable recurrences at $500 000 costs, that is $10 000 per resectable recurrence. From these numbers, the apparent conclusion would be that the first strategy is more cost-effective because the costs per resectable recurrence are lower. Instead, the conclusion should be that using the more expensive strategy yields 25 extra resectable recurrences at $450 000 extra costs, that is $18 000 per resectable recurrence. Although the costs per resectable recurrence are higher, the more expensive strategy may still be worth the extra costs. This raises the question how much a diagnosed resectable recurrence is allowed to cost: a question that is not answered in these studies.

Three studies have attempted to estimate the effect of follow-up on (quality adjusted) life expectancy. These studies all use a high degree of modelling to aggregate estimates from different data sources. Reasons why modelling is especially important in the assessment of follow-up are the long time horizons, the large number of feasible strategies and the possibly small differences between the strategies. An additional advantage of using models is that, when recurrence rates change due to improvements in primary treatment, new preliminary estimates of the value of follow-up can be obtained promptly by changing the parameters of the model. However, the divergent results of these three studies illustrate that careful scrutiny of the modelling assumptions is required.

The first study by Kievit and Van de Velde [32] in 1990 compared 2-year carcinoembryonic antigen monitoring with no follow-up. In addition to the advantage of salvage surgery, this study also included disadvantages of follow-up, like 5% operative mortality and decreased quality of life after diagnosis of recurrence. Utility values were obtained from the literature. Depending on the type of patient and the chosen assumptions, the estimated influence of carcinoembryonic antigen monitoring on life expectancy ranged from an increase of 7 days to a decrease of 5 days. The estimated CE ratio ranged from the most favourable $23 000 per QALY to worse than $5 000 000 per QALY. As a result, they concluded that there was insufficient evidence to support routine carcinoembryonic antigen monitoring.

Norum and Olsen [33] in 1997 compared no follow-up with a limited 4-year follow-up strategy consisting of carcinoembryonic antigen monitoring, ultrasound of the liver, chest radiography and colonoscopy at regular intervals. Health state valuations were obtained from their earlier study on adjuvant chemotherapy [23]. They only considered advantages of follow-up and assumed that the gain from finding resectable recurrences was either 10 years for 2% of the patients or 1.2 years for 10% of the patients (that is an average increase of 73 or 44 days per patient). The corresponding CE ratios were £11 476 and £19 508 per non-adjusted life year, and they concluded that their limited follow-up strategy looked cost-effective.

For patients suspected of having a recurrence based on carcinoembryonic antigen monitoring, Park and colleagues [34] in 2001 studied the cost-effectiveness of the use of [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography (FDG PET), in addition to computed axial tomography (CT). They also only included advantages of follow-up in the model. Under the baseline assumptions, the addition of FDG PET to CT increased the life expectancy by 10 days, with $429 additional costs. The incremental CE ratio was $16 400 per non-adjusted life year, so they concluded that the use of FDG PET is potentially cost-effective in the management of recurrence.

3.4. Treatment of advanced disease

Quite a number of studies have considered patients in different stages of advanced disease. Mellow [35] studied patients for whom for several reasons curative surgery was no option. In a non-randomised study he concluded that endoscopic laser therapy seemed to be a cost-effective alternative for palliative surgery. Quality of life was not estimated, but survival and complications after laser therapy were similar. Hospital charges were lower, mainly due to shorter hospitalisation.

In inoperable gastrointestinal cancer patients, including colorectal cancer patients, Glimelius and colleagues [36] compared best supportive care with or without chemotherapy. Quality adjustments were assigned by two observers that assigned either value 1 or value 0,

based on a quality-of-life questionnaire. Overall, the use of chemotherapy resulted in a statistically significant gain in (quality-adjusted) life expectancy. For colorectal patients, chemotherapy increased the life expectancy by 60% and more than doubled the quality adjusted life expectancy, at the acceptable costs of approximately $9900 per QALY.

Only one study, by Miller and colleagues [37], considered the cost-effectiveness of local recurrence treatment. They studied three groups of patients: non-operative patients, patients with diagnostic or palliative surgery, and patients with surgical resection. The SG technique was used to elicit utilities from 24 healthcare providers and 25 patients. The health state 'Pain and complications after recurrence' was the worst health state, valued at 50% of normal health by healthcare providers and 78% of normal health by the patients. Compared with the non-operative group, the diagnostic and palliative patients had worse (quality-adjusted) survival and higher costs. The resected patients also had higher costs, but with better quality-adjusted survival, at $56 700 per QALY. They concluded that purely diagnostic or palliative treatment should be avoided when possible, and that resection may be a cost-effective use of resources. However, since the study investigates different groups of patients instead of investigating different treatments for one group of patients, the validity of these conclusions depends on the comparability of the groups.

For patients with resectable distant recurrences, Beard and colleagues [38] compared hepatic resection with standard non-surgical cytotoxic treatment of liver metastases. They estimated that resection provides a survival benefit of 1.6 non-adjusted life-years, with an estimated £8378 difference in costs. The corresponding CE ratio of £5236 per life-year gained was considered highly cost-effective.

For unresectable metastases, Durand-Zaleski and colleagues [39] compared hepatic arterial infusion (HAI) chemotherapy, systemic chemotherapy, and symptom control only. This is the only CEA that made an attempt to estimate productivity costs. However, instead of estimating the costs of the patient's lost productivity, they estimated the costs of absenteeism. As a consequence, the prolonged productivity period for HAI patients paradoxically led to increased costs. They also assigned either utility 1 or utility 0, depending on whether quality-of-life scores were above or below certain limits. The estimated CE ratios of HAI versus systemic chemotherapy and of systemic chemotherapy versus symptom control were both £24 000 per QALY, which was considered within the range of other accepted treatments.

Both Iveson and colleagues [40] and Levy-Piedbois and colleagues [41] compared irinotecan with infusional 5-FU therapy, in patients with metastatic colorectal cancer after 5-FU failure. The respective estimated CE ratios were at most £12 000 and approximately $10 000 per non-adjusted life year. They concluded that the limited increase of 2 months life expectancy from using irinotecan was obtained at acceptable costs, comparable to other accepted cancer treatments.

Finally, Abramson and colleagues [42] conducted a threshold analysis determining the survival benefit required from hepatic arterial chemo-embolisation to make it a cost-effective alternative for palliative care in patients unresponsive to systemic chemotherapy. A cost-effectiveness threshold of $50 000 per life year would require a survival benefit of 5 months. Whether this threshold was indeed attained was left open for future randomised trials to decide.

4. Discussion

The aim of CEAs is to support healthcare policy-making, facilitating a comparison of alternative ways of spending money. The basic objective is not to minimise costs, but to obtain good value for money. A prevalent rule of thumb is that $50 000 per QALY is acceptable, whereas $100 000 per QALY might not be acceptable. These thresholds originate from the debate in 1973 on the acceptability of haemodialysis for patients with end-stage renal disease [9]. Over the past decades, they have often been quoted in the international literature. In using such thresholds, it should be realised that cost-effectiveness is only one of many criteria for decision-making. Whether an incremental cost-effectiveness ratio is acceptable or not is determined in conjunction with those other criteria. For example, a screening programme with large budgetary consequences should be more cost-effective than a small-sized experimental programme with possibly large scientific benefits.

The dominant opinion at the moment is that CEAs used to inform the broad allocation of health resources should use a societal perspective, comparing differences in societal costs to differences in QALYs. Comparability and standardisation are compromised if studies use the narrower perspective of particular care providers or the patients at issue. In addition, the societal perspective is the perspective of those paying for medical care. However, estimating the aggregate societal consequences may disregard consequences for particular subgroups of society. For example, including productivity costs is potentially discriminating against older and female patients because they traditionally provide less paid labour. Measuring effectiveness by QALYs is potentially discriminating against older patients because they have less time for improvement. Furthermore, using a societal perspective ignores other perspectives, like the hospital perspective, that may be more important for successful implementation or rejection of an intervention. If these are issues of concern, then additional analyses from a different perspective would be justified.

Very few studies in the survey have actually used the societal perspective. Most studies estimated only hospital costs, sometimes even restricted to costs of diagnostics or the primary intervention. Only one study briefly reported on a detailed price analysis; the other studies either used charges or did not report the origin of the applied prices. Apart from occasional time and travel costs, patient costs were not included. Only one study attempted to include productivity costs. These methodological shortcomings can have considerable influence on the conclusions. For example, including productivity costs is likely to render more favourable CE ratios, since the more effective treatment is bound to have less loss of productivity.

Of the 24 considered CEAs, eight estimated non-adjusted life expectancy and nine estimated quality-adjusted life expectancy. The methodology used to value health leaves much to be desired. Only three studies actually elicited quality adjustments. Some studies used an arbitrary 0.5 adjustment for all impaired health states, or an arbitrary 0.0 adjustment for seriously impaired health states. The use of different outcome measures complicates comparison of the relative cost-effectiveness. Although not necessarily so, non-adjusted differences in life expectancy are usually larger. Hence, one must be aware that cost-effectiveness ratios for non-adjusted life expectancy should be judged by stricter thresholds.

Half of all cost-effectiveness analyses on colorectal cancer were published in the past 5 years, so the 21st century will definitely be a challenging century for cost-effectiveness analyses. To gain credibility, CEA methodology must be further developed and standardised, and applied in prospective randomised trials. A challenging task will be to investigate the cost-effectiveness of improved diagnostic procedures, with their possibility to tailor treatment to the individual patient. However, above all, there is a real need to gain more insight into how colorectal patients value their treatment and health.

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