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Comments and Critique

The Economic Evaluation of Cancer Treatments and Programmes

INTRODUCTION

THE ECONOMIC evaluation of any health care intervention involves the appraisal of both the inputs (costs) and outputs (consequences) of activities. The identification, measurement and valuation of costs and consequences of alternative treatments and programmes assists decision-makers by informing choices about the use of scarce health care resources. If the maximum benefits are to be obtained from the limited health care resources available, the evaluation of cancer treatments should not be excluded from such an approach.

Considerable progress is being made in the methods of economic evaluation and a growing literature in the economics of cancer is evident. However, it is important, especially for practitioners, to undertake and interpret studies with care if erroneous and misleading conclusions are to be avoided. The principles and methods associated with good economic appraisal of health care programmes have been outlined elsewhere [1, 2]. The aim of this paper is to focus specifically on the cancer literature in order to illustrate the role that economic evaluation can play in this field.

FORMS OF ECONOMIC EVALUATION

Several types of economic evaluation can be identified and classified according to the way in which costs and consequences are measured and valued (Fig. 1). The inputs to a health care intervention include not only the direct costs of providing treatment (such as the cost of radiotherapy, chemotherapy, surgery and associated length of hospital stay or outpatient visits), but also indirect costs arising from lost production if individuals have to withdraw from the workforce in order to undergo therapy. The importance of these costs will depend upon the site of cancer and the client group considered. For example, they are likely to be more significant for some lymphomas, which may affect younger people, than for advanced lung cancer, where patients tend to be elderly. The treatment itself may affect the quality of life of the patient during therapy and thus there are also intangible costs arising from the anxiety and pain associated with therapy. This is of particular importance in cancer as the adverse effects of some treatments such as chemotherapy and radiotherapy may be substantial.

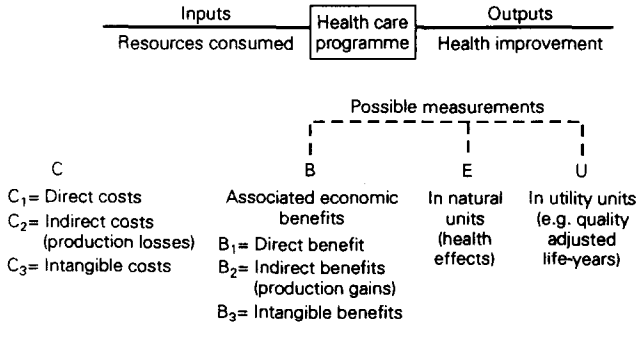

Fig. 1. Components of economic evaluation.

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Similarly, the benefits arising from a health care intervention can be measured in terms of the direct savings in treatment costs and can also include the indirect benefits associated with reduced production losses if the intervention allows the patient or family member to return to work. Economists are divided on the issue of including production losses in economic evaluations—on the one hand they might represent real losses in resources but on the other hand their inclusion will tend to bias the allocation of resources towards health care programmes which affect the economically active sector of the population [4]. Finally, the intangible benefits of reductions in morbidity associated with the intervention should also be considered.

The forms of economic evaluation differ in the extent to which they measure and value the benefits of treatment. If it can be shown that the health outcomes of the interventions being considered are equivalent, it is sufficient to consider, in a cost analysis, only the relative costs associated with each alternative in order to choose the optimum strategy. For instance, the costs of alternative treatments for prostatic cancer [5] have been compared on the basis of costs alone. Similarly, the costs of conservative breast cancer surgery (with adjuvant radiotherapy) have been compared with the costs of mastectomy on the grounds that there is considerable clinical evidence of their equivalence in terms of survival [6–8]. However, the assessment of quality of life as well as costs would obviously be of importance in this case.

More commonly, it is necessary to consider the costs in relation to the differential health benefits produced by alternative strategies. The simplest method, cost-effectiveness analysis, measures outcomes in "natural" units such as numbers of lives saved, years of life saved or cases successfully treated. In cancer, whilst some treatments may extend life, improvement in the quality of life is also an important outcome. Additionally, there may be occasions where the side-effects of treatment mean that life is extended at a price, in terms of reduced quality of life. In order to encompass this important aspect and in order to make the results more generalisable to allow comparisons with other types of health care interventions, cost-utility analysis incorporates a generic measure of outcome called the quality-adjusted life-year. Here data on both the length and quality of life gained by treatment are combined in a single measure (Fig. 2).

The most generalisable form of analysis, cost-benefit analysis

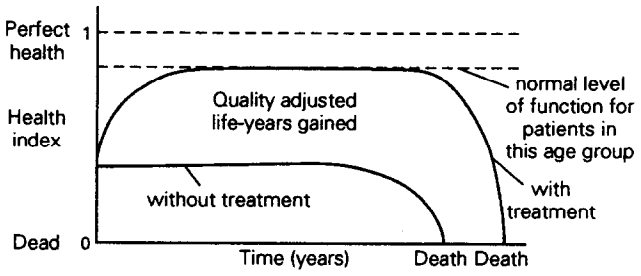

Fig. 2. Quality-adjusted life-years added by treatment.

translates all inputs and outputs to monetary terms which in principle allows comparisons both within and between different health conditions. However, the valuation of the intangible costs and benefits usually proves to be very difficult in practice and as a consequence, comprehensive cost-benefit analyses are not common in health care.

KEY METHODOLOGICAL ISSUES IN ECONOMIC EVALUATION

There are several key methodological features of a good economic evaluation. These are set out in Table 1 as a series of questions to ask of any published study. In this section some of the important methodological issues are illustrated by reference to examples from the cancer field.

Selection of alternatives

The economic evaluation of cancer treatments should involve the comparison of relevant alternatives. For example, screening options may be evaluated by comparing screening versus "do nothing", although it is important to note that the "do nothing" alternative will include the subsequent costs and benefits of treating people at a symptomatic stage. Two recent economic evaluations of breast cancer screening programmes in the UK [9] and Australia [10] compared screening with a "no screening" option. Cervical screening has also been investigated in this way [11, 12]. Other research in this area has focused on alternative approaches to screening (e.g. for various age groups or with various screening intervals). In a computer simulation using data synthesised from clinical trials, Van der Maas *et al.* [13] compared four alternative strategies for breast cancer screening. Similarly, alternative intervals for prostate screening were considered in a computer simulation by Love *et al.* [14].

Alternative methods of treatment may also be considered, and the majority of economic evaluations in the cancer field fall into this category. These include evaluations of surgery versus radiotherapy for glottic carcinoma [15], chemotherapy versus bone marrow transplant for leukaemia [16, 17] and surgery, radiotherapy or oestrogen therapy for prostatic cancer [5, 18, 19]. Other possibilities include the comparison of alternatives in the location of care, for instance home versus hospice or hospital care for the terminally ill [20, 21] or mobile versus fixed breast cancer screening [22].

Viewpoint for the analysis

An economic evaluation may be undertaken from several viewpoints, including those of the patient, the department providing the service, the whole institution within which the department is situated, the government or society as a whole. The range of costs and benefits included in the analysis will vary according to the viewpoint adopted, and although economists often argue for the widest viewpoint, most studies adopt a narrower perspective.

The potential dangers of adopting a narrow viewpoint can be illustrated using an example of the chemotherapeutic treatment of ovarian cancer with carboplatin versus cisplatin [23]. Carboplatin is the more expensive drug and thus, from the pharmacy viewpoint, treatment with cisplatin will always appear more cost-effective (assuming outcomes are equal). However, cisplatin requires inpatient admission for intensive hydration before and after treatment, whereas carboplatin can be administered on an outpatient basis. Thus, from the point of view of the hospital as a whole, cisplatin may be the less cost-effective option. Therefore, acting on the recommendations of a narrow evaluation based only on pharmacy costs would be inefficient. Similarly, although the cost to the hospital of delivering chemotherapy or radiotherapy on an outpatient basis may be cheaper than inpatient treatment [24, 25], a different conclusion may be drawn if the costs to the patient and their family of repeated visits to the outpatient department are considered. Another illustration of the distinction between health service and wider society costs was given in the study by Moskowitz [26] where published outcome data from American breast screening trials were incorporated into an economic analysis. If health care costs were considered in isolation, the costs to the health service per cancer detected were positive ($8851), whereas if the social costs and benefits of disability, lost production and replacement costs to industry were included, a net overall saving of $1000 000 was estimated. Although the methodology used in this study to estimate costs was deficient (being based on a charge for screening), it is useful to illustrate how not only the magnitude but also the direction of the conclusions can be altered by considering different perspectives.

Some economic evaluations have included very detailed analyses of the personal costs to patients and their families (in terms of transport, lost work or leisure time and also out-of-pocket costs) arising from cancer screening or treatment. For example, Ashby *et al.* [27] examined the personal costs to women attending screening clinics and outpatient facilities for breast cancer. The valuation of private costs such as lost leisure time is not straightforward, but it is important that evaluations should at least recognise explicitly that these costs exist and may influence the conclusions drawn. Indeed, such private costs may affect attendance for screening and hence the effectiveness of the programme.

Measurement and valuation of costs and consequences

Several issues in measurement and valuation of costs and consequences should be emphasised. First, the source of the cost data is important. Many studies, especially those undertaken in the US or other countries where health care is largely insurance-based, often report charges or billing figures rather than true resource costs. This general tendency has already been noted by others [28] but in cancer treatments the difference between costs and charges may be especially important. For example, charges or bills for radiotherapy treatment may not include an appropriate allowance for the capital equipment and depreciation of the equipment associated with radiotherapy or the specialised rooms needed to house the equipment, but these represent true resource costs which should be incorporated into the study. On the other hand, charges can overestimate true costs, if a hospital operating in a given locality feels that it has a competitive advantage.

The most important point in the assessment of outcomes is to

Table 1. Ten questions to ask of any published study [4]

1. Was a well-defined question posted in answerable form?
   (a) Did the study examine both costs and effects of the service(s) or programme(s)?
   (b) Did the study involve a comparison of alternatives?
   (c) Was a viewpoint for the analysis stated or was the study placed in a particular decision-making context?
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?
   (a) Were any important alternatives omitted?
   (b) Was (should) a "do-nothing" alternative (have been) considered?
3. Was there evidence that the programme's effectiveness had been established?
   Was this done through a randomised, controlled clinical trial? If not, how strong was the evidence of effectiveness?
4. Were all important and relevant costs and consequences for each alternative identified?
   (a) Was the range wide enough for the research question at hand?
   (b) Did it cover all relevant viewpoints (e.g. those of the community or society, patients and third-party payers)?
   (c) Were capital costs as well as operating costs included?
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, days lost from work or years of life gained) prior to valuation?
   (a) Were any identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
   (b) Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?
6. Were costs and consequences valued credibly?
   (a) Were the sources of all values (e.g. market values, patient or client preferences and views, policy makers' views and health care professionals' judgements) clearly identified?
   (b) Were market values used for changes involving resources gained or used?
   (c) When market values were absent (e.g. when volunteers were used) or did not reflect actual values (e.g. clinic space was donated at a reduced rate) were adjustments made to approximate market values?
   (d) Was the valuation of consequences appropriate for the question posed (i.e. was the appropriate type, or types, of analysis — cost-effectiveness, cost-benefit or cost-utility — selected?
7. Were costs and consequences adjusted for differential timing?
   (a) Were costs and consequences that occurred in the future "discounted" to their present values?
   (b) Was any justification given for the discount rate used?
8. Was an incremental analysis of costs and consequences of alternatives performed?
   Were the additional (incremental) costs generated by the use of one alternative over another compared with the additional effects, benefits or utilities generated?
9. Was a sensitivity analysis performed?
   (a) Was justification provided for the ranges of values (for key parameters) used in the sensitivity analysis?
   (b) Were the study results sensitive to changes in the values (within the assumed range)?
10. Did the presentation and discussion of the results of the study include all issues of concern to users?
    (a) Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
    (b) Were the results compared with those of other studies that had investigated the same questions?
    (c) Did the study discuss the generalisability of the results to other settings and patient/client groups?
    (d) Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences or relevant ethical issues)?
    (e) Did the study discuss issues of implementation, such as the feasibility of adopting the "preferred" programme, given existing financial or other constraints, and whether any freed resources could be used for other worthwhile programmes?

ensure that economic evaluations are based on good clinical evidence. Some studies are based on evidence arising from clinical trials [29, 30], whilst others use a synthesis of trial data from various sources [10, 31], especially where the study is based on computer simulations or decision-tree analysis [12, 13, 26, 32, 33]. When data from randomised trials are unavailable, some attempts have been made to ensure that patient groups are comparable by undertaking retrospective analysis with careful matching [34].

Although data relating to length of survival may be obtained retrospectively from the literature, quality of life data, which are also important in view of the increasing recognition that cancer and associated treatment will have a major impact on the patient, cannot be so obtained. There is a growing literature relating to this topic and ongoing debate about the most appropriate methods of measuring and valuing the quality of life of cancer patients [35, 36]. The extensive literature cannot be reviewed here, but several key points should be noted. First, it is possible to use either disease-specific or generic measures of quality of life in the evaluation of cancer treatments. The former group include measures such as the Functional Living Index — cancer [37] and the Rotterdam Symptom Checklist [38]. The latter group include such measures as the Nottingham Health Profile [39] or Sickness Impact Profile [40]. Generic measures allow comparisons to be made across different patient and disease groups, and are thus very useful. However, unless a valid method of weighting and summing scores obtained across different dimensions of a profile is available, then it may be impossible to say (overall) how outcomes compare, as different treatments or patients may score higher and lower on the various dimensions than others. Whilst information relating to a whole range of dimensions of quality of life certainly provides a rich and fruitful source of data, a single measure which incorporates not only the effects on quality of life, but also the effect on survival is often sought in economic evaluations.

One method used in economic evaluation is to weight the length of time spent in various health states by the "utility" value of that state as judged by doctors, patients or society on a scale from zero (dead) to unity (completely healthy). More details of this approach can be found elsewhere [4, 41], but its potential relevance to the evaluation of cancer therapy can be easily illustrated. McNeil *et al.* [42], in investigating preferences

for laryngectomy or radiotherapy for laryngeal cancer, revealed that although the surgical option produced better survival rates, people placed less value on these years of survival than those produced by radiotherapy due to the poor quality of speech associated with the surgical option.

Cost-utility analysis has been used in an economic evaluation of a clinical trial of different chemotherapy regimens for small cell lung cancer in Canada [30]. In this case, the clinical trial had demonstrated a small, 6-week survival benefit for one regimen but as this was potentially associated with higher costs but also improved quality of life, an economic analysis was also undertaken. Six relevant health states were presented to 7 patients undergoing chemotherapy and to 14 health professionals familiar with the treatment. The utility weights were elicited via the standard gamble and category rating methods [41]. It was found that the high-cost regimen was associated with higher quality adjusted survival and therefore an assessment would have to be made of whether these extra benefits outweigh the extra costs. This judgement can be made by comparison with other health care interventions [43].

One drawback of utility measurement is that it can be resource intensive requiring lengthy interviews by trained staff and it may not be possible to incur these additional costs in order to undertake the full economic evaluation. One alternative may be to use utility values for various cancer health states which are available in the literature, or a prescaled generic utility measure [41, 44, 45]. These can then be incorporated into an economic evaluation where appropriate without undertaking any direct measurements. Values for mastectomy [46] and for five cancer-related health scenarios [47, 48] have been reported.

Some researchers argue that it is more correct to elicit patients' preferences for a complete profile, of health states stretching into the future, rather than to obtain values for each state and then multiply by the time spent in each. In part this is because the length of time spent in each state, and the overall prognosis, affect patients' valuations. Mehrez and Gafni propose a measure called the "healthy years equivalent" [49]. A variant of this has been used by Gerard *et al.* in an evaluation of breast cancer screening [50].

Identification of marginal costs and consequences

The concept of the "margin" is central to economic analysis. The marginal cost or benefit of one strategy, compared with the alternative, is represented by the incremental or extra cost or benefit incurred or achieved.

Thus in comparing alternative screening strategies, the relevant question may not be how much does each strategy cost in total, but rather how much extra does it cost (and how much is gained) to screen, for example every 2 years rather than 5 years? The simulation study undertaken using a synthesis of data for breast cancer screening illustrated that the marginal cost per life year gained increased dramatically as the intensity of screening (defined by the screening interval and invitations issued) increased [13]. Thus, although the average cost per life year gained for 2 and 4 year intervals were very similar ($4050 and $4850, respectively), the marginal costs differed substantially ($4050 versus $6050) and this increased even more when 1 year intervals were considered and marginal costs were estimated to be as high as $14 800.

Clarke and Fraser [9] also estimated marginal costs and benefits in relation to breast screening, but in this case they examined the extra costs and benefits associated with the addition of a clinical examination to the mammography screen. They illustrate that even though the extra variable costs associated with the addition of the examination were quite modest (£1300 for 1000 cases), the extra number of cases detected was also low (0.2 per 1000 cases) and thus over £6000 was needed to detect one more cancer by adding examination as a modality.

A further way in which the concept of the margin is important is illustrated in the following examples. First, there are currently developments in radiotherapy practice which suggest that for some types of treatment (particularly palliative care), a small number of radiotherapy treatments may be as effective as 10 or more treatments [50]. Secondly, Levine *et al.* [51] showed that when patients presented with cancer of unknown primary origin it was more cost-effective to undertake a limited search of those cancer sites for which effective systematic therapy existed, rather than to undertake a comprehensive search of all possible sites.

FUTURE DEVELOPMENTS IN ECONOMIC EVALUATION

This review has indicated that there is still some way to go in improving the range and quality of economic evaluations in the cancer field. It is therefore worth noting that, with the exception of the research on breast cancer screening, there are few examples of multidisciplinary working to date. The main tasks are as follows.

Identifying the relevant alternatives for evaluation

Since economics is about choice it is important that key alternatives in therapy, or the organisation of cancer services, are evaluated. Clinical researchers could help economists by identifying those therapies or programmes whose effectiveness is uncertain or which appear relatively resource-intensive in relation to the benefits produced. These could include some forms of adjuvant therapy or palliative strategies for end-stage disease, or certain comprehensive diagnostic procedures where no effective cure exists.

Also, economists need help in identifying situations where the relative effectiveness of alternative therapies is known, or is under study. This would facilitate an assessment of whether an evaluation would be worthwhile undertaking. For example, if two drugs have similar effectiveness and are of similar cost, it would probably not be worthwhile undertaking a full economic evaluation in order to demonstrate small differences in cost-effectiveness, unless the treatments were being given to large populations of patients.

On the other hand comparisons between surgery, radiotherapy or chemotherapy (or combinations of these) for the same condition may involve a wide range of different costs and outcomes. Therefore, it may not be immediately obvious, without performing an economic evaluation, which treatment is the most cost-effective. The same is probably true for choices in the settings for care, which involve a mixture of costs borne by the health and social care system and the patient and their family.

Linking economic evaluation with clinical trials

Economic evaluation can only be as good as the medical evidence upon which it is based. Since randomised controlled clinical trials produce the highest standard of evidence, they should more often be considered as a vehicle for economic evaluation. An increasing number of trials now include quality of life as an endpoint. However, it was mentioned above that disease-specific quality of life measures do not lend themselves easily to economic evaluation, unless the comparisons to be made are restricted to the particular form of cancer being studied.

In general, economic evaluations are undertaken to inform broader choices in the allocation of scarce resources. Therefore, they would benefit from inclusion of more generic quality of life measures, such as health utilities. Furthermore, few clinical trials include prospective gathering of cost data, so conclusions on the relative cost-effectiveness of treatment options can only be drawn if a costing study is undertaken retrospectively.

However, prospective economic analysis alongside clinical trials poses a number of methodological challenges [53]. Firstly, trial protocols may differ from regular clinical practice, so cost data collected during trials may have to be adjusted. Secondly, many cancer trials are multicentre trials, sometimes involving a number of countries. Therefore, an economic analysis based on such trials would need to take account of differences which occur from setting to setting, including relative prices and variations in the availability of health care resources. Finally, on occasions the sample size required to show differences between two treatment options in the economic parameters may be larger than that required to show a difference in the clinical endpoints. Therefore, care has to be taken to ensure that trials have sufficient power when economic endpoints form part of the primary analysis.

In conclusion, this research has illustrated that there have been a number of economic evaluations of cancer treatments and programmes to date. A number of the key methodological issues have been outlined and possibilities for future developments identified. Further progress in methodology will be more easily achieved if there is greater collaboration between clinical and economic researchers working in this field.

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Treatment of Early Ovarian Cancer

THE PAPER by Chiara and coworkers (p. 1211) is a good example of a cooperative multicentre effort to study a relatively rare gynaecological tumour. The basic problem of early ovarian cancer is the lack of referral to cancer centres where clinical research programmes are being conducted. This is quite understandable from a clinical point of view as the diagnosis of early ovarian cancer is often made at the time of laparotomy for other reasons and therefore unexpected. From the research point of view it is dramatic. It necessitates to undertake multicentre trials with many different institutions and with all the difficulties and problems to get various policies and clinical circumstances into the same direction. The Italian paper shows some of these difficulties.

The studied population combined patients treated primarily in one of the GONO institutions with women who were referred after prior surgery elsewhere. The latter category, in which surgical staging was not performed according to preset criteria, formed 17% of the total group. Surgery in these non-GONO hospitals was considered inadequate and these patients were restaged at second-look surgery after chemotherapy. A total of 15 patients underwent incomplete initial surgery. The indication for second-look surgery was made at the discretion of the responsible gynaecologist. A total of 40 second-look procedures was performed, but only in 10 of the 15 patients with an inadequate initial operation. This is confusing. Only 10 of 15 patients with inadequate staging underwent restaging later and 30 of the remaining 69 patients had a second-look procedure on the basis of personal preference of the gynaecologist in charge. These figures cast some shadow over the value of the relapse-free survival reported in the study.

The criteria for adequate staging in the study suggest that a difficult compromise was reached between participating institutes. It is not clear why multiple random biopsy samples were not taken from the paracolic gutters a side at high risk for implantation metastasis [1]. Furthermore, retroperitoneal lymph node sampling was only performed in the case of clinically suspicious nodes. The Miami group has, already some time ago, demonstrated that the diameter of metastatic lymph nodes for the greater part overlap that of non-metastatic lymph nodes in women with gynaecological cancer [2]. Recently it was shown again in a large GOG study of patients with early ovarian cancer that the clinical impression of the lymph node status (negative or positive) is an unacceptably poor discriminative tool [3].

It remains difficult to define staging criteria in ovarian cancer that are both scientifically sound and also feasible and acceptable in a multicentre study. The EORTC gynaecology group has debated the various staging steps extensively and has formulated the criteria that an optimal staging procedure should fulfill [1].

The composition of the study population in the Italian study also deserves some attention. A total of 87 patients with stage I and II ovarian cancer were treated. 28 of these patients had a stage IIb or IIc disease that cannot be reckoned among the early stages of ovarian cancer. In virtually all series, stages IIb and IIc are considered the same and treated identically as compared to advanced stages III and IV. 48 of the remaining 59 patients were in stage Ic and 7 in IIa. This leaves only 4 patients with Ia and Ib disease, definitely too small a number to permit any conclusion on tumour behaviour of these stages. The relatively large number of patients with Ic disease results from the new FIGO classification in which former Ia2 and Ib2 tumours are now defined as stage Ic. Furthermore, the new FIGO classification Ic does not distinguish between surgical rupture at operation, tumour rupture before surgery, malignant peritoneal washings or malignant ascites. It is therewith, a compilation of patients with different prognostic factors, hampering valid conclusions on the biological behaviour of early ovarian cancer.

So, what does the study of Chiara *et al.* teach us in the end? It shows that six courses of cisplatin-containing combinations, is a feasible treatment with acceptable morbidity in patients with minimal or non-residual ovarian cancer at the time of chemotherapy. The study confirms the findings of others that tumour

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