Health Economics Evaluation of Cancer Intervention; a Review Paper

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ABSTRACT

The cost of new medical intervention are considerable to the healthcare system and also to the patients, however this new intervention can improve health outcomes substantially. In the past decades, multiple new medical interventions were introduced to treat cancer patients, as well as improve quality of life for these patients. However, most of interventions have considerable costs. In order to proper use of restricted health care resources, beyond the standard evaluations of safety and efficacy, it is essential to estimate the relative cost and benefits of new medical intervention and technologies. Assessing the health and economic effects of these interventions has been an interesting topic for the clinicians in last decade and such assessment involves a range of issues, methods and policy statements. This review discusses the main type of economics evaluation and it provides some example of published cancer intervention studies. Economic evaluations can be useful for decision makers because it can give “value-for-money” information about the allocation of restricted health care resources. Economic evaluation sets up the related cost and effects of health interventions, with basically goal of maximizing population health for the limited resources.

Key words: Economic evaluation, Cost analysis, Cancer intervention.

Introduction

Some factors such as the aging population, the HIV pandemic, the development of novelty (innovative) and the increased knowledge and expectation of healthcare consumers raised attention to the issues of cost and effectiveness on health needs of the patients [3]. The cost of new medical intervention are considerable to the healthcare system and also to the patients, however this new intervention can improve health outcomes substantially. In order to proper use of restricted health care resources, beyond the standard evaluations of safety and efficacy, also it is essential to estimate the relative cost and benefits (i.e., cost benefit analysis) of new medical intervention and technologies [22,30]. In cancer care, innovative interventions in cancer screening and diagnosis; surgery; medications; radiation therapy; and a wide range of ancillary, supportive, and palliative care services are derived from new technologies. New interventions have carried out important development to survival and quality of life for people with cancer. On the other hand, such development can come at a considerable cost.

There is some example of novel intervention that possibly will improve outcomes for specific populations but consequence in raised costs including $1,000 per contrast-enhanced magnetic resonance imaging screening, which is 10 times the cost of screening mammography in breast cancer [25]; $48,000 per patient per year for the use of intensity-modulated radiation therapy to treat prostate cancer; $1,800 per positron emission tomography scan for cancer staging [23,4]; $1,800 per month for gefitinib (Iressa) for the treatment of lung cancer; $50,000 per patient per year for trastuzumab (Herceptin) in the treatment of HER2-positive breast cancer [16,8] and more than $8,000 for a 6-day course of palifermin (Kepivance) in the treatment of oral mucositis.

Economic evaluation includes a set of methods that measure the costs and outcomes of comparative healthcare intervention. Assessing the health and economic effects of these interventions has been an interesting topic for the clinicians in last decade and such assessment involves a range of issues, methods and policy statements [29]. Economic analysis has been applied to health and medical intervention for more than a quarter century with dramatic growth in recent years [10].

Economic evaluation is often formed to compare one intervention with competing alternative. The standard of care is always chosen as the comparator for new medical intervention in most of cases; however, for the conditions don’t have effective
treatments, “do nothing” can show the standard of care. Obviously, progressions in technology caused to changes the standard of care. It can be found some examples in the studies that comparing the cost effectiveness of chemotherapy agents. For instance, earlier economic evaluation studies comparing the cost-effectiveness of treatment options for non-small-cell lung cancer (NSCLC) often chose best supportive care as the standard of care [9], while more recent studies have often used Cisplatin-based regimens as the standard of care for NSCLC [5].

Based on this procedure, to guide clinical decisions and also to inform health policy using economic evaluation was become a common tool. Economic evaluation sets up the related cost and effects of health interventions, with basically goal of maximizing population health for the limited resources. Nowadays, there are many economic evaluations that have recognizing how and where efficiency improvements could be made.

**Materials and Methods**

This is a systematic review study. An electronic search of English language articles was conducted in numerous data base using a combination of keywords: health economics, evaluation, cancer intervention, cost analysis, cost effectiveness, cost minimization, cost benefit. The database searched were online digital library including ScienceDirect, Medline&Ovid, Wiley Interscience, SpringerLink, SageOnline Journal,….

**Results:**

There are 4 main types of economic evaluation: cost analysis, cost minimization, cost benefit, cost effectiveness [7,30]. The selection of a type of economic evaluation depends primarily on the question to be addressed but may also be influenced by factors such as data availability or target audience. Subsequently, we discuss types of economic evaluation and the criteria used to select each. We also provide examples seen in published cancer studies [29].

**Cost Analysis:**

Cost analysis considers only the cost component related to competing interventions, in spite of the differences in the consequence of clinical outcomes; for instance, is it cheaper to treat patients with drug A or Drug B? Since, in the cost analysis does not consider the results of interventions (eg, survival rate) between compared alternatives, this type of analysis is considered a partial form of economic evaluation [7]. To survey the economic burden associated with a specific disease or condition or the economic impact of new intervention, often cost analysis will be conducted. Results of cost analyses can be presented either in terms of the “total” or “incremental” (additional) costs associated with interventions or diseases. The other approach of cost analysis is comparing cost between two situations, one of them with intervention and the other one without intervention. For example reporting estimated total cost of cancer by the National Institute of Health in the United State, is a type of cost analysis. The National Institutes of Health estimated that the total cost of cancer was $263.8 billion in 2010; of that, $102.8 billion was in direct medical costs, and $170 billion was in indirect costs, including $20.9 billion in morbidity costs and $140.1 billion in mortality costs [1].

An example of cost analysis that reports “incremental” cost can be found in the study by Elthin et al. [11] about using palifermin for the treatment of oral mucositis among the patients suffering hematopoietic stem cell transplantation. According to clinical trials data showing that palifermin decreased the duration and frequency of oral mucositis in the this population (as compared with placebo), the results of the study showed that palifermin prophylaxis was associated with an average savings of $3,595 per patient.

The study by Shih et al. [28] was another example of a cost analysis, in which the authors estimated the costs associated with uncontrolled chemotherapy-induced nausea and vomiting (CINV) for cancer patients of working age whose chemotherapy regimens contained at least one highly or moderately emetogenic agent. The estimated average monthly medical cost for a patient with uncontrolled CINV was approximately $1,300 higher than that for a patient whose symptoms of CINV had been controlled. A subgroup analysis in that study concluded that indirect costs per patient per month were $433 higher for those in the uncontrolled CINV group.

**Cost-Minimization Analysis:**

Cost-minimization analysis (CMA) is a method of economic evaluation that can be used when the consequence of two or more alternative was shown to be equivalent and it chooses the least expensive alternative. In this type of analysis the focus of evaluation is on the costs, because the clinical outcomes of all intervention are equivalent. For example Avritscher et al. [2] in their study used CMA. They compare the use of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) in the treatment of hospitalized cancer patients with deep venous thrombosis. The justification for using CMA in this study was shown in the previous studies, as these retrospective cohort studies had shown low-molecular-weight heparin and unfractionated heparin to have equivalent efficacy and safety in the management of deep venous thrombosis. The cost of LMWH is
significantly greater than UFH, the authors hypothesized that once-daily dalteparin, a LMWH, could decrease the cure cost of cancer patients with deep venous thrombosis by removing anticoagulation monitoring and shortening hospitalization. The mean total cost was $3,383 US dollars (95% CI= $2,683-$4,083) for dalteparin and $4,952 US dollars (95% CI=$4,718-$5,185) for UFH for inpatient care. Authors concluded shorter hospitalization among the dalteparin-treated patients (mean 3.19 versus 5.22 days) Caused considerable savings.

The other example of CMA could be found in the study by the Southwest Oncology Group in which they compared the use of vinorelbine plus cisplatin versus paclitaxel plus carboplatin in the treatment of advanced NSCLC found no statistically significant difference in survival rate or quality of life between the treatment arms. Then, they carried out CMA and concluded the cost of paclitaxel plus carboplatin considerably higher than vinorelbine plus cisplatin [24].

Cost Effectiveness Analysis:

Evaluating only the cost of an intervention will not help us whether it is cost effective. A cost effectiveness analysis will measure two parameter, cost and outcome (effect). Whereas two measured parameters showed the results of an economic evaluation, this will not necessary inform us which intervention option is ‘better’ same as the results of clinical trial. Intervention with the more effective result as well as lower cost, obviously it will be the most cost effective option. In this condition the most cost effective option can explained as being dominant. On the other hand, if the cheapest and lowest alternative is not the most effective then, the decision of which intervention to select is less clear. In this condition the results will usually obtain in the form of an incremental cost effectiveness ratio, expressed as the extra costs incurred for each extra unit of benefit. When no intervention is dominant, economic evaluation would inform you how much you should pay extra to improve your results [12].

In contrast to CBA, which have the both costs and consequences be used in monetary terms, the consequences of intervention in cost effectiveness analysis (CEA) would be presented in nonmonetary units for example effectiveness, benefits or outcomes. For describing the desired objective of an intervention, natural units are most appropriate. Survival, rate of complete response, progression-free survival, or number of adverse events avoided during cancer therapy is some example of outcomes of CEA. Consequently, CEA compares interventions in 2 different dimensions: cost and effectiveness. Many new interventions in cancer therapy are both more costly and more effective than older or ‘standard of care’ interventions. For CEA, the difference in mean cost between the 2 interventions (new cost minus old cost) is divided by the difference in mean effectiveness (eg, new survival rate minus old survival rate) to get an incremental cost-effectiveness ratio (ICER). For finding one extra unit of outcome (eg, 1 month increase in survival or 1 additional year of life) can be indicated the extra cost by ICER. Then, the selected threshold value would be compared to ICER to evaluate of cost effectiveness of the new intervention. The intervention would be considered as cost-effective, if the ICER has been less than the threshold value (for example, the additional cost of new intervention per outcome is lower than the accepted standard) [7,27]. However, the new interventions sometimes are not more costly and more effective than the old interventions. If the cost of new intervention is lower than old intervention and the effectiveness is more (the ideal case), after that, it can said the new intervention is dominant as compared to the older ones (more better outcome with less money). In contrast, if a new intervention is more costly and less effective (the worst possible case), then the new intervention is not dominant and it provides worst outcome with more cost, so is not likely to be of interest. It also can be possible both cost and effective are less than standard for the new intervention (for example, with less cost, it’s provide less health benefit than standard) [6].

It should also be noted that sometimes the ‘cost-effectiveness ratio’ has been produced by dividing the cost of intervention by its effectiveness without comparison by older/standard intervention. This ratio is not ICER because they didn’t compare one treatment with another. In this condition, it assumed that there is no intervention (zero cost and zero effectiveness) for comparison; this assumption is not true in many cases. Therefore, these ratios cannot be interpreted accurately and are not useful in economic evaluation.

One example of CEA in oncology was in the study by Ng et al. [21] in which using data from a clinical trial of adjuvant vinorelbine plus cisplatin compared with observation after resection of stages IB-II NSCLC. They collected direct medical utilization data from medical record of patients and clinical trial. Effectiveness was measured in terms of survival (life years). The cost of adjuvant chemotherapy was greater. The mean costs for treatments per patient were $23,878 and $31,319 in the observation and adjuvant chemotherapy, respectively while adjuvant therapy raised the mean survival of 12.5 months in the clinical trial. Therefore, the ICER (adjuvant chemotherapy to observation) illustrate CAD$7,175 per life year gain. The results showed adjuvant therapy is highly cost-effective for this population.

Another example of CEA found in the study by Mittmann et al. [19] about the prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer. they carried out a cost-effectiveness analysis using prospectively collected
resource utilization and health utility data for patients in the CO.17 study who received Cetuximab plus best supportive care (N = 283) or best supportive care alone (N = 274). For the entire population and for the subset of patients with wild-type KRAS tumors, mean survival times were an 18 to 19 month period. The mean improvement for the entire study population in overall and quality-adjusted survival with Cetuximab was 0.12 years and 0.08 QALYs, respectively. The ICER was $199,742 per life-year gained (95% CI = $125,973 to $652,492 per life-year gained). The mean gains for patients with wild-type KRAS tumors in overall and quality-adjusted survival were 0.28 years and 0.18 QALYs, respectively. The ICER was $120,061 per life-year gained (95% CI = $88,679 to $207,075 per life-year gained). Only Cetuximab cost and patient survival was variables that influenced cost-effectiveness in a sensitivity analysis. The ICER was lower when the analysis was limited to patients with wild-type KRAS tumors. The ICER for Cetuximab of $199,742 per life-year gained is considerably higher than the jurisdictional thresholds of which we are aware. However, restricting Cetuximab to patients with wild-type KRAS tumors reduced the ICER to $120,061, indicating that the use of Cetuximab only in this group of patients would result in a more efficient use of health-care resources. Consequently, it would not be efficient to fund Cetuximab treatment for all patients with advanced colorectal cancer. Use of Cetuximab may be restricted based on a patient’s tumor KRAS status.

Another example of cost effectiveness was reported in the study by Wang et al. [31]. They study A Cost-Effectiveness Analysis of Adjuvant Chemoradiotherapy for Resected Gastric Cancer. The aim of this study was to perform a cost-effectiveness analysis of adjuvant chemoradiotherapy for resected gastric cancer. Data were collected from The Intergroup 0116 trial, in which demonstrated that adding post-operative chemoradiotherapy for gastric cancer resulted in a significant overall survival improvement of 9 months. Medicare reimbursement rates were used for chemotherapy and radiotherapy costs. Patient utilities were derived from published literature. The analysis of results reported in 2007 US dollars. Patients with surgically resected stageIB to IV (M0) gastric adenocarcinoma were randomized to receive postoperative chemoradiotherapy or no additional treatment. As can be seen in Table 1, Results of INT0116 showed that the adjuvant therapy arm had improved overall survival of 35 vs 26 months for the surgery-alone arm.

The primary outcome measure for this analysis was the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the number of QALYs saved (Table 2). The incremental cost was the difference in cost between the chemoradiotherapy arm and the control arm.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incremental cost of chemoradiation</th>
<th>QALYs gained</th>
<th>Incremental cost-Effectiveness ratio</th>
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</thead>
<tbody>
<tr>
<td>Incremental cost</td>
<td>$20,100</td>
<td>0.53</td>
<td>$38,400/QALY</td>
</tr>
<tr>
<td>Survival gain</td>
<td>9</td>
<td></td>
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</table>

Table 1: Quality adjusted life gained

Table 2: The primary result of ICER

Although for direct comparing between interventions with same outcome measure, CEA can be used but this method has 2 drawbacks. At first, if the effectiveness units (the outcome of evaluation) are differed in the studies then the results of CEA cannot be used to compare different interventions. For example, some studies may summarize the CEA results in terms of costs per life year saved, while others may report costs per additional complete response achieved. Secondly, when we are comparing the CEA between 2 interventions with same effectiveness, cannot show the qualitative differences between interventions. For instance, 2 chemotherapy regimens can have a same survival benefit but patients likely to choose the regimen with fewer side effects. However, the CEA cannot explicitly describe such quality of life differences.

Cost Benefit Analysis:

In the cost benefit analysis, both cost and outcome (benefit of intervention) value with the same units. It means that since the costs are valued in monetary terms, the health outcomes of interventions are also expressed in monetary terms. It means that life and suffering have been replaced with monetary values [20]. In CBA, by using monetary value for both costs and outcomes, it allows us to comparing directly interventions with different objectives. With subtracting the costs of intervention from value of outcome in dollars, then it give us the net benefit of intervention. In this method, if the net benefit is positive (outcome minus cost), an intervention is worth implementing. The largest net benefit will be chose among interventions with positive net benefit. An alternate approach in CBA can be found by
The example of CBA could be found in the study by Halpern et al. [13] in which they performed the costs of workplace-based smoking cessation programs for a cohort of 10,000 employees. For manufacturing facility in the southern United State, the smoking cessation program would cost $1,193,322 over 10 years. However, combining medical care saving and workplace saving (indirect cost) the program is projected to save $2,575,511 over 10 years. Thus, the program yields $2,575,511 divided by $1,193,322 or approximately $2.16 in savings for every dollar spent on cessation. With a benefit-cost ratio greater than 1, the authors recommended implementing the smoking cessation program.

Another example of CBA could be found in the study by Jansman et al. [15]. Capecitabine is an oral prodrug of 5-fluorouracil and has been studied for the treatment of colorectal cancer. In 2 Phase III trials, Capecitabine was at least as effective as 5-fluorouracil plus leucovorin and had a more favorable toxicity profile. They used CBA to assess the pharmacoeconomic profile of Capecitabine compared with 5-fluorouracil/leucovorin for colorectal cancer patients treated in the Netherlands. Data were examined to determine the numbers of outpatient visits for 5-fluorouracil/leucovorin administration, health care use and medication to manage adverse effects, and travel distance to and from the hospital. The mean total costs of palliative treatment were €4004 with Capecitabine and €5614 with 5-fluorouracil/leucovorin. The costs of adjuvant treatment were €3770 for Capecitabine and €4704 for 5-fluorouracil/leucovorin. The cost savings were primarily related to the number of outpatient visits for Capecitabine versus the number of day-care treatment days for 5-fluorouracil/leucovorin, despite the higher acquisition costs of Capecitabine. Based on this analysis, the treatment of colorectal cancer with oral Capecitabine is cost saving in the Netherlands compared with 5-fluorouracil plus leucovorin administered according to the Mayo regimen.

When we placing monetary value in improving symptoms for conditions that do not reduce life expectancy, there were fewer ethical problems. For example Dyspepsia is very common and the sufferers are willing to spend more money on over the counter medications to improve their symptoms. Many people ask to get more antacids or Hantagonists and in the UK around 1.5 million spend in year [18]. It suggests that for such products people more willing to spend money to release from the symptoms. One of the advantages of CBA is that non-health related benefit can be addressed. For instance, some parts of the process of care not just outcome. For most of people, waiting 30 min to meet a doctor in the outpatient clinic is undesirable and many people willing to pay small amount of money to be seen sooner. However there is no loss of health by sitting in a waiting room so QALY cannot evaluate this issue [20].

An alternative method to describe the economic value for an intervention/year of life is called the willingness to pay (WTP). In a WTP analysis, some information about a real or hypothetical intervention would be provided for participants in the study, including its potential to increase life expectancy. Then, participants are asked to specify the maximum amount of money they would be willing to pay for the intervention. The net benefit of the intervention is calculated by subtracting actual cost from values based on the WTP responses. For example the study by Leight et al. [17] about willingness to pay in use of oral epidermal growth factor receptor tyrosine kinase inhibitors for patients with advanced NSCLC in Canada. Oral epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are new agents in the treatment of advanced non-small cell lung cancer (NSCLC). Phase II studies demonstrate objective tumor responses and symptom improvement, combined with minimal toxicity and the convenience of an oral agent. Fifty-seven advanced NSCLC patients and 54 healthy subjects participated in a structured interview and bidding exercise. The median amount both groups were willing to pay for a month of oral EGFR TKI therapy was $100 CAD (range $0–5000 per month). A minority of NSCLC patients received employment income, the majority relying on disability, pension income, and social assistance for financial support. Affordability of these agents was a key concern for both advanced NSCLC patients and healthy subjects. These investigators reported that both NSCLC patients and healthy subjects were willing to pay more for these agents but were willing to pay only a small proportion of their market price.

Another example of willingness to pay could be found in the study by Iskedjian et al. [14] in which they examined participants WTP in Methylnaltrexone in the Treatment of Opioid-Induced Constipation in Cancer Patients Receiving Palliative Care. This WTP study had two components: a decision board explaining treatment options (Component A) and a questionnaire to measure individual WTP using a bidding game approach (Component B). Component A had two options: Option 1 (laxatives only) and Option 2 (laxatives methylnaltrexone injection). Only participants choosing Option 2 were invited to complete Component B. The results of the WTP
survey were then incorporated into a CBA. Within a hypothetical cohort, additional monthly premiums that individuals were willing to pay for methylnaltrexone were compared with the monthly costs to the insurer for providing methylnaltrexone to all patients who would potentially be using it. A total of 401 Canadians were participated in the study, 60% percent of them preferred the treatment with Laxatives plus methylnaltrexone injection. They are willing to pay in additional monthly insurance premiums of Canadian dollar (CAD) $8.65 (95% confidence interval: CAD$6.17-CAD$11.13). The CBA resulted in additional CAD$ 89,307 with a cost of CAD$139,840 and benefits of CAD$ 229,147. A set of 10,000 Monte Carlo simulations resulted in average CBA savings of CAD$ 145,011 with a 99.86% probability of dominance. The present CBA provides pharmacoeconomic evidence for the adoption of methylnaltrexone for treating opioid-induced constipation in terminally ill cancer.

**Discussion & Conclusion:**

Economic evaluations can be useful for decision makers because it can give “value-for-money” information about the allocation of restricted health care resources. In particular, the more useful method is economic evaluations to identify interventions which are worth implementing and those are not. These evaluations also can be used with other approaches to assist set priorities, such as program-budgeting.

<p>| Table 3: strength and limitation of economic evaluation methods |
|---------------------------------|--------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Measurement effect for unit</th>
<th>Strengths</th>
<th>Limitation</th>
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| CMA  | No effects measured.        | There is only a need to collect cost data. | -Few treatments have identical outcomes.  
-Researchers would likely need to collect the effect data to verify the “equal effect” assumption. |
| CEA  | One effect measured in “natural units”. | There is one outcome and it is measured in its “natural units.” | Only one outcome will represent the effect of treatment; however, other outcomes may be relevant.  
Most CEA applied in clinical trial that shows the efficacy, do not show how much it cost to society or can be covered by health insurance? |
| CBA  | All effects measured in dollars. | The net benefit (NB) is easy to interpret. For example, a new treatment’s extra benefits are worth. | It is difficult to measure the value of all health outcomes in dollars.  
There may be moral objections about the impact of ability to pay in the process of valuing the effects. |

Robinson [26]

CBA is more useful for the highest level of decision making, for example the U.S. Congress decides how to allocate scarce resources towards programs with disparate outcomes. And to compare outcomes of different programs (e.g., defence and health), converting outcomes into a common unit (e.g., dollars) is necessary. CEA can be more useful for lowest level (Health Clinic), this model describes the scheme of decision making to simplify the process and to explain the typical uses of economic evaluation. It is not meant to use each form of economic evaluation to a specific level. For example, CEA can be used by Congress to assess the effectiveness of current policy concerning inpatient length of stay for Medicare (cost per life year saved). Similarly, a public health clinic director might use CBA to determine whether to construct a new facility or buy new equipment for an existing facility. For the most appropriate clinical research and economic evaluation to be carried out properly, independence should be granted through special funding. Savings due to the utilization of the results of such studies could be used to fund other studies and enhance further development and efficiency in cancer care.

**Recommendation for further studies:**

- Focus on cancers that are highly preventable and curable;
- Better data are required to analyze both outcomes and cost assessments;
- There is a need to collect data from population not just of clinical trials;
- Reliable data and accurate methods to assess the economic costs of uncompensated care are lacking.

**References**

