Beyond Survival: Economic Analyses of Chemotherapy in Advanced, Inoperable NSCLC

Research shows that chemotherapy for inoperable non-small-cell lung cancer (NSCLC) improves survival. The economic implications of this treatment choice may be substantial. This paper reviews studies examining the cost-

Lung cancer is the primary cause of cancer-related mortality in the United States, accounting for almost 30% of all cancer-related deaths.[1] It is estimated that more than 177,000 cases of lung cancer were diagnosed in 1996.[1] Direct medical expenditures for lung cancer reached some $5 billion in 1996 and represented about 15% of all cancer-related costs.[1] In short, lung cancer presents a substantial challenge to clinicians and results in a significant human and economic burden.

Squamous cell, large cell, and adenocarcinomas of the lung comprise the class of tumors commonly referred to as non-small-cell lung carcinomas (NSCLC). Collectively, they represent more than 75% of all lung carcinomas.[2] Average 5-year survival rates for non-small-cell lung cancer are about 13%,[1] but prognosis is highly dependent on stage of disease. Five-year survival rates average about 5% for persons with stage IIIb disease and less than 2% for those with stage IV disease.[3]

Treatment Options and Dilemmas

Therapeutic options for persons with non-small-cell lung cancer are limited. Surgical excision of the tumor is the treatment of choice, and persons with stage I disease have a better than 70% survival rate at 5 years.[3] Yet, only 30% of patients are operable at presentation.[3] For individuals with unresectable locally or regionally advanced disease, radiotherapy, alone or in combination with chemotherapy, is the preferred option. For those with metastatic disease, the goals of therapy include palliation and extension of survival. Patients with metastatic disease typically receive supportive care with or without chemotherapy. However, controversy exists over the appropriate role of chemotherapy in this setting.

Recent studies comparing radiotherapy plus chemotherapy vs radiotherapy alone in patients with advanced disease but no clinically evident metastases have been inconclusive.[4-10] A meta-analysis of studies evaluating the addition of a cisplatin (Platinol)-based regimen to radiotherapy alone suggested a 13% reduction in the risk of death (hazard ratio, .87; 95% confidence interval [CI], .79 to .96).[11] This result corresponds to an absolute survival benefit of 2% at 5 years.[11]

Evidence of clinical benefit is also mixed when chemotherapy is compared to best supportive care (BSC) for stage IV patients.[12-19] A general trend favoring the use of chemotherapy has been reported, but only a few studies establish a statistically significant survival difference. In part, the equivocal results are related to the small sample sizes of the studies, [20] although meta-analyses support the finding of a modest benefit.[11,21-23]

Considering the dismal prognosis of these patients, some clinicians believe that even modest survival gains are important and should be aggressively pursued. Others disagree, maintaining that the minimal survival and palliative benefits from the use of these agents have little merit in clinical practice, especially in view of their associated toxicity and cost. These variations in belief and practice concerning the use of chemotherapy in inoperable non-small-cell lung cancer have been demonstrated by several studies.[24-28]

The purpose of this paper is to recount existing data on the economic consequences of chemotherapy in patients with inoperable non-small-cell lung cancer as they relate to the clinical risks and benefits of treatment. Data are presented that describe the cost-effectiveness of chemotherapy, and although chemotherapy's effect on quality of life is not a primary focus, this review addresses the importance of preferences in prioritizing benefits vs costs. We conclude by commenting on the role of chemotherapy in non-small-cell lung cancer and by identifying the limitations of analyses that should be taken into account by future studies.
Methods

MEDLINE (1980-present), PDQ (September 1997), Cancerlit (1989-present), EMBASE (1989-present), and the Nursing & Allied Health (1982-present) databaseS were searched in September 1997 for studies published in English through the use of the following key terms: cost, cost-effectiveness, chemotherapy, and non-small-cell lung cancer. The reference list of relevant articles was also scrutinized, and several authors of economic analyses of therapy for non-small-cell lung cancer were queried about the existence of other published or unpublished studies. Studies that included chemotherapy but focused primarily on the role of colony-stimulating factors or antiemetics were excluded. Those evaluating patients with lung cancer, instead of non-small-cell lung cancer, were also excluded.

Various approaches to economic evaluation are possible.[29] Studies of chemotherapy in non-small-cell lung cancer have generally employed three types of analyses: costing, cost-minimization, and cost-effectiveness. Costing analysis describes the costs of providing a particular intervention and expresses the results in monetary units. Cost-minimization analysis compares the costs of competing strategies that achieve the same clinical outcomes and selects the approach with the lowest cost. This method is limited, however, since different treatments seldom produce truly equivalent outcomes. Cost-effectiveness analysis overcomes this limitation by simultaneously considering the comparative costs and outcomes of two or more treatment strategies. A ratio of cost to effectiveness is estimated. (The ratio has been defined as the incremental price of obtaining a unit of health effect from a given health intervention when compared to an alternative intervention. Results are reported as monetary unit per outcome gained.) Higher priority is given to interventions with lower cost-effectiveness ratios because they offer the maximum aggregate health benefit for a particular expenditure. Although any clinically measurable end point can be used, most analyses use years of life gained. We reviewed the economic evaluations for incremental cost-effectiveness ratios using life-years or quality-adjusted life-years (QALYs) gained.

Summary of Study Results

Seventeen studies were identified. Five were excluded from this review. Of the five, three were published only in abstract form,[30-32] and a fourth that considered the costs of using fazarabine for metastatic non-small-cell lung cancer was excluded because the drug had no demonstrable activity.[33] Rees reported a [notional patient benefit year cost] for two non-small-cell lung cancer chemotherapy regimens,[34] but we excluded this fifth study because the method of economic analysis used in the study is not a standard approach. Table 1 provides a summary of the key elements of the 12 included studies.[35-46] A wide variety of economic evaluation approaches were utilized, and most analyses were reported within the last few years. Earlier analyses compared certain regimens to best supportive care or to other available products. Many of the more recent evaluations projected the clinical and economic impact of gemcitabine (Gemzar) prior to its approval in the United States from data accumulated in phase II trials.

All of the analyses reported direct medical costs, with most taking the perspective of a third-party payor, such as the government or an insurance company. Only six reported cost-effectiveness ratios with life-years or QALYs gained as the outcome measure. In most of the identified studies, trial data were supplemented with data from other sources, such as surveys, published guidelines, or chart reviews, in order to produce the economic evaluation.

To provide a thorough discussion of the important findings and issues raised by these studies, we gave detailed consideration to four of the most comprehensive cost-effectiveness analyses. For three of these studies, researchers based their analyses on the results of individual clinical trials. The Jaakkimainen et al Study

In 1990, Jaakkimainen and colleagues reported the results of an economic evaluation of data from the BR-5 trial of the National Cancer Institute of Canada.[14,35] Patients in a three-arm section of this clinical trial were randomly assigned to receive vindesine and Platinol (VP); cyclophosphamide, Adriamycin, and Platinol (CAP); or best supportive care. A second study group comparing only the two chemotherapy regimens also was formed. For patients from the three-arm group, median survival durations were 119 days for best supportive care, 173 days for CAP, and 228 days for VP. This difference reached statistical significance for the comparison of VP to best supportive care (P = .012) and showed a favorable trend when CAP was
comparing to best supportive care (P = .051). However, chemotherapy also caused a significant
degree of leukopenia, severe vomiting, and, in the VP group, neurologic toxicity.
In their analysis, Jaakkimainen et al examined patients from the three-arm group. Direct medical
costs were split into four categories—chemotherapy, hospitalization, clinic visits, and
radiotherapy—and were analyzed for each patient from the point of randomization until death. Costs
were not specifically determined for toxicity alone but were assumed to be included in the other
categories.
Hospitalization represented the highest expenditure for each group. Both chemotherapy groups had
larger clinic and chemotherapy costs than the best supportive care group, while patients receiving
best supportive care had higher costs for hospitalization and radiotherapy. For the VP and CAP
groups, chemotherapy represented about 30% of their total treatment outlay.
Table 2 depicts cost and outcomes data from this and two other economic analyses, which were
based on the findings of single clinical trials.[38,40] In the study by Jaakkimainen et al, average costs
were highest for patients receiving VP and lowest for the CAP group. To facilitate comparisons
involving both cost and survival, incremental cost-effectiveness ratios were calculated. For any two
strategies, A and B, the following formula is used:
\[
\text{Cost-effectiveness} = \frac{(\text{Cost}_A - \text{Cost}_B)}{(\text{Survival}_A - \text{Survival}_B)}
\]
This approach explicitly considers the amount of additional resources needed to obtain any added
benefit offered by strategy A relative to strategy B and is especially useful when one treatment
alternative improves outcomes at an increased cost.
Results of the cost-effectiveness analysis are presented in Figure 1. Each treatment strategy is
graphed according to the average cost per patient and mean survival noted for that group. The slope
from one treatment group to another represents the incremental cost-effectiveness ratio comparing
those groups. For example, VP offers increased survival at an increased cost relative to best
supportive care. The slope from best supportive care to VP is the incremental cost-effectiveness ratio
of VP compared to best supportive care and represents the additional expenditure required for each
year of life gained by VP.
A surprising finding from this study was that CAP was able to extend survival at a decreased
absolute cost compared to best supportive care. This is graphed as a negative slope from CAP to
best supportive care.

The Kennedy et al Study
Citing the modest survival benefits and severe toxicities associated with chemotherapy, Kennedy et
al performed a second economic evaluation of the BR-5 trial using cost data from a subset of the
original study population.[38] By incorporating a measure of preference for chemotherapy and best
supportive care, investigators expressed the results of their analysis as the cost per QALY gained.
QALYs denote the net health effectiveness of an intervention[47] and reflect both quantity and
quality of life.[48]
Quality-adjusted survival rates were determined by factoring in physician preferences for different
treatment strategies. Two scenarios were described: one for chemotherapy and the other for best
supportive care. Nine physicians from an oncology ward treatment team cited their preferences for
the scenarios. The average scores for the chemotherapy scenario were significantly lower than those
for best supportive care (P = .027).
Median total costs were lowest for best supportive care, followed by CAP and then VP.
Hospitalization, again, was the major expenditure in all of the treatment arms. When both
chemotherapy regimens were compared with best supportive care, CAP was a more cost-effective
approach than VP. In a direct comparison of VP and CAP, each year of life gained with VP cost an
additional $25,170.
These results changed dramatically when preferences were factored into the calculations, however.
Relative to best supportive care, each QALY gained with VP cost more than $400,000. When CAP and
best supportive care were compared, best supportive care dominated the comparison by producing
more QALYs at a lower total cost.

The Smith et al Study
Le Chevalier and colleagues reported on a trial of stage III and IV non-small-cell lung cancer patients
that compared VP with regimens utilizing vinorelbine (Navelbine) alone (NVB) or in combination with
Platinol (NVB-P).[49] Median survival durations for the three treatment groups were 40 weeks for
NVB-P, 32 weeks for VP, and 31 weeks for NVB. The NVB-P regimen conferred a significant survival
advantage compared to VP (P = .04) and NVB (P = .01).
Smith et al reported separately on the cost-effectiveness of these regimens.[40] They used mean
survival data. To better reflect current practice, the study assumed that cisplatin was being
administered on an outpatient basis. Results showed that drug and total treatment costs were highest for the NVB-P arm, and that chemotherapy alone accounted for about 50% of the total treatment costs for each group. Even though survival benefits were smallest with NVB, this regimen was also the least expensive. Relative to NVB, using NVB-P and VP would require an additional outlay of $17,700 and $22,100, respectively, for each year of life gained.

Incorporating physician- and nurse-rated preferences into the analysis showed that, when compared to NVB, the $17,700 cost per life-year gained with NVB-P increased considerably to $241,000 per QALY gained. Relative to VP, NVB improved quality-adjusted survival at a lower cost.

The Evans and Le Chevalier Study
While the three studies described above were based on the findings of individual clinical trials, Evans and Le Chevalier utilized clinical and economic data from multiple sources to examine seven treatment strategies: NVB; NVB-P (in both inpatient and outpatient settings); VP; etoposide (VePesid) and cisplatin (ETOP-CIS); vinblastine and Platinol (VLB-P); and best supportive care.[46] Using the population health model (POHEM) developed by Wolfson,[50] investigators analyzed the average cost of managing a patient with stage IV non-small-cell lung cancer and the resultant total cost to the Canadian health-care system for each of the seven approaches.

In 1993 Canadian dollars, best supportive care cost an estimated $27,348 per patient. Only VP ($30,539) and NVB-P administered on an inpatient basis ($29,880) cost more. For the other regimens, decreased costs associated with reductions in terminal care hospitalizations more than compensated for the additional cost of the chemotherapy agents.

Evans and Le Chevalier also examined the cost-effectiveness of each chemotherapy regimen relative to best supportive care. NVB, NVB-P administered in an outpatient setting, ETOP-CIS, and VLB-P were all found to extend survival at a decreased average cost per patient. Compared to best supportive care, each life-year gained from the inpatient administration of NVB-P cost $5,551, while VP was the least cost-effective approach at $11,876 per life-year gained.

Discussion
Our literature search identified 17 studies evaluating the costs associated with using chemotherapy for the treatment of inoperable non-small-cell lung cancer. Twelve were included in this review. These economic analyses were conducted from the perspective of those [who are responsible for allocating resources across programs for groups of patients.][51] Clinicians, who appropriately seek to maximize the welfare of individuals under their care, do not typically utilize this perspective in making daily decisions. However, findings from these studies do have important policy implications. For example, in a report by Evans,[36] stage IV patients represented approximately 40% of all cases of non-small-cell lung cancer diagnosed in Canada in 1984. When it was assumed that each stage IV patient received best supportive care, this group accounted for about 40% of total first-year management costs for NSCLC in Canada. This demonstrates that, even in the absence of chemotherapy, best supportive care is a costly management strategy, rivaling approaches that utilize surgery or intensive radiotherapy for patients with other stages of disease. Several studies identified hospitalization as the major portion of total costs regardless of the treatment strategy used.

Mixed Findings and Comparisons
Five of the studies examined the cost-effectiveness of chemotherapy relative to best supportive care.[35,37,38,43,46] Like clinical trials in this area, these economic analyses have produced mixed results. For example, Kennedy et al failed to confirm the finding of Jaakkimainen et al that chemotherapy could actually extend survival at a lower total cost relative to best supportive care, even though both groups of researchers used a subset of patients from the same clinical trial. While these conflicting results are disconcerting, decisions about the use of a specific treatment strategy rarely hinge on its ability to concurrently improve outcomes and decrease total costs. A more important issue, then, is to determine the relative value obtained from the various treatments. What is the cost of extending survival through the use of chemotherapy? Economic analyses have offered a consistent response to this question. Chemotherapy can be a cost-effective addition to best supportive care and, in some cases, may actually reduce the overall cost of treatment. In the five evaluations comparing chemotherapy to best supportive care, the cost per life-year gained with chemotherapy was less than $20,000.

In a recent review, the costs of various interventions per life-year gained were ranked in descending order.[52] However, caution must be exercised when evaluating league tables because of the
numerous potential methodologic differences in the studies from which the estimates are drawn.[53] Yet, ranking treatments in this manner can create a useful framework for interpreting therapy for non-small-cell lung cancer in light of other cancer treatments. For example, compared to standard chemotherapy for limited metastatic breast cancer, autologous bone marrow transplantation totals $116,000 per life-year gained. Cyclophosphamide, methotrexate, and fluorouracil, when compared to no treatment for breast cancer in 45-year-old women, costs $4,900 per life-year gained. Comparisons can also be made to other medical interventions, such as coronary artery bypass vs medical management for patients with left main disease and angina ($17,400 per life-year gained), in-center renal dialysis vs medical management ($50,000 per life-year gained), and cholestyramine for high cholesterol ($178,000 per life-year gained).

**Influence of Cost on Choice of Treatment**

It has been stated that cost should not negatively influence decisions about the use of chemotherapy for non-small-cell lung cancer.[35,43] The cost-effectiveness of chemotherapy in this setting compared to the cost-effectiveness of treatments for other diseases confirms this assertion. It also suggests that, in the face of budgetary constraints, decisions based on the cost-effectiveness of competing treatment alternatives would place a higher priority on chemotherapy for non-small-cell lung cancer than they would on many routine treatments and procedures for other diseases. However, these findings are tempered by two key issues. First, despite an increasing emphasis on assessing chemotherapy’s effect on quality of life, only two analyses[38,40] adjusted for the quality of survival gained with treatment. In each case, incorporating preference data decreased the cost-effectiveness of chemotherapy and altered treatment rankings. The impact of preferences on the findings of these studies highlights the need to address quality of life in future economic studies in non-small-cell lung cancer. Techniques for addressing treatment preferences range from holistic measures, such as the time tradeoff used by Kennedy et al and the simple estimates used by Smith et al, to multiattribute utility indices, such as the Health State Utilities Index, the Quality of Well-Being Scale, and the EuroQol, which address several components of a health outcome. In addition, the quality-adjusted time without symptoms or toxicity (Q-TWiST) method, used in studies of various types of cancer, may prove useful in non-small-cell lung cancer as well.

**Patient Preferences vs Physician Preferences**

According to the results of Kennedy et al, physician-rated preferences suggest that 1 month of survival on best supportive care is approximately equal to 2 months spent on chemotherapy. This explains much of the poor performance of the chemotherapy regimens relative to best supportive care in this study, but it also raises an important question: Whose preferences should be considered when assessing quality of life? Preferences elicited from physicians or nurses or from the general public can differ greatly from those of cancer patients. A survey published in 1987 reported that 85% of doctors who routinely treat lung cancer would not choose chemotherapy for themselves in the presence of symptomatic metastatic disease.[54] However, cancer patients themselves display a greater willingness to accept toxic therapies even when the probability or amount of benefit is small,[55-58] and this preference persists even after several weeks of chemotherapy.[55] Patient preferences are an important component of treatment decisions and should be factored into all economic analyses in this area. The second key issue is that much of the clinical data supporting the economic evaluations of chemotherapy vs best supportive care come from a single trial in which chemotherapy produced a survival advantage.[14] The cost-effectiveness of chemotherapy probably would have been less favorable if data had been derived from trials that failed to demonstrate this benefit.

**Assumptions Underlying Economic Analysis Models**

Although the studies we identified provide important and timely information, improvements in several areas of methodology are necessary. For example, more than half of the studies modeled costs and outcomes by using data from multiple sources. Economic models provide a flexible, inexpensive alternative to conducting a prospective study when necessary data are lacking or a head-to-head trial cannot be conducted. They are also helpful when the results are intended to inform broad policy decisions. Yet, this approach requires many assumptions about such factors as patient demographics, clinical outcomes, and resource utilization patterns. For instance, the model used by Evans et al included only those tests believed to be essential to diagnosis.[37] Since many tests and procedures performed as part of the differential diagnosis of non-small-cell lung cancer can be clearly labeled as unnecessary in retrospect, the model may underestimate some health-care costs. Other costs were omitted because all diagnostic procedures and therapeutic interventions were assumed to occur without complication.
In addition, modeled algorithms do not account for the widespread variations in beliefs and practices that have been demonstrated by surveys of physicians who treat lung cancer,[24-26,28] as well as by a recent study of the management of non-small-cell lung cancer in Ontario.[27] Since many clinicians express reservations about the assumptions already present in even conservative economic analyses of individual trials, the results of models may be met with skepticism.

**Applying Cost Information to Clinical Data**

While four studies identified by this review utilized data from individual clinical trials, only one involved a prospective collection of economic data. This trend of applying cost information to previously gathered clinical data stems from several factors, including a lack of funding for economic analyses[59] and the often conflicting goals of clinical and economic trials.[60,61] For example, the desire to generalize the results of an economic study may lead investigators to recruit a wide variety of patients and to limit protocol-induced medical practices. These choices, however, would hinder the examination of efficacy and safety considerations.

Yet, in spite of these difficulties, progress is being made toward concurrent collection of clinical and economic data. For instance, a Health Economics Unit has been established by the European Organization for Research and Treatment of Cancer,[62] and the Cancer and Leukemia Group B has formed a Clinical and Economics Committee.

All of the studies that we identified were limited by a lack of comprehensive, patient-specific resource utilization data and by the difficulty of combining these data when several centers were involved. In the study by Smith et al, patients had been enrolled and treated in Europe, but economic information was gathered from the charge data of patients treated at the Medical College of Virginia Hospitals. This approach is prone to error because differences in practice patterns have been shown to influence resource utilization patterns and, thus, economic outcomes.[63]

The wide variety of techniques used in these studies highlights the importance of clearly defining underlying conditions and assumptions before comparing the results of separate economic analyses. It also points to the need for a set of standards and guidelines for the conduct and reporting of these evaluations.

This topic was addressed recently in recommendations published by the Panel on Cost-Effectiveness in Health and Medicine convened by the US Public Health Service and by the *British Medical Journal.*[29,64] Careful attention to these suggestions will greatly aid in standardizing the methods and improving the merits of the results obtained. During this period of refinement and standardization, transparent presentation of data, assumptions, and calculations will be extremely important.

**Conclusions**

In summary, through evidence-based approaches to clinical decision-making, policies have been developed to maximize the quantity and quality of health benefits. These decisions often fail to account for resource limitations. Chemotherapy for non-small-cell lung cancer has come under close scrutiny because of the high cost and modest benefit associated with its use. Examination of the value of this approach through cost-effectiveness analysis should aid in making decisions regarding its use.

Although relatively few studies in non-small-cell lung cancer have examined economic end points, these analyses serve to identify the costs associated with numerous treatment strategies and to determine the expenditures necessary to achieve various clinical outcomes. These studies indicate that, compared to best supportive care, chemotherapy can be a cost-effective approach for stage IIIb and IV non-small-cell lung cancer. Relative to many treatments for other types of cancer or for other diseases, expenditures for chemotherapy in this setting can be justified based on the survival benefits achieved.

Application of these findings may be hindered by the wide variety of techniques used and by several methodologic issues. Future economic analyses should place increased emphasis on quality-of-life considerations, including the impact of patient preferences for various treatments. Although the above findings will not end the controversy surrounding the role of chemotherapy in this setting, they suggest that, in addition to clinical and quality-of-life considerations, economic end points can play an important role in resource allocation decisions.

**References:**


Source URL:
http://www.physicianspractice.com/review-article/beyond-survival-economic-analyses-chemotherapy-advanced-inoperable-nsclc

Links: