Prophylactic cranial irradiation revisited: cost-effectiveness and quality of life in small-cell lung cancer

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer (SCLC) who had achieved complete remission.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients with limited-stage SCLC who had achieved complete remission. Complete remission was defined as the complete disappearance of tumour after treatment completion. Patients with mixed SCLC and non-SCLC were excluded.

Setting
The setting was a hospital. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness and resource use data were gathered from 1987 to 1998. The price year was 1992.

Source of effectiveness data
The effectiveness evidence was derived from a single study and authors’ assumptions.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not reported. Eligible patients were identified from a provincial cancer database, and their charts were reviewed. The study sample included 98 radically treated SCLC patients who had achieved complete remission. There were 66 patients (55% men) in the PCI group and 32 (56% men) in the no PCI group. The median ages in the two groups were 64 years (PCI) and 68 years (no PCI), respectively.

Study design
This was a retrospective cohort study that was carried out in the Canadian province of Saskatchewan. A study team comprising four radiation oncologists, two medical physicists, one health economist, one epidemiologist and one health records technician reviewed the patients' charts. The treatment response was evaluated by serial physical examinations and chest radiographs in all cases, computed tomography (CT) in 43 patients, bronchoscopy in 1 patient, and autopsy in 4 patients. Details of the follow-up were not reported.

**Analysis of effectiveness**
All of the patients included in the initial study sample were considered in the analysis of effectiveness. The outcome measures used in the study were:

- overall survival, from time of diagnosis to the date of death;
- disease-free survival, from the last treatment date to the date of recurrence of any symptoms, signs, or definitive investigation results;
- the development of brain metastases; and
- the number and duration of acute toxicities.

Both overall survival and disease-free survival were calculated using the Kaplan-Meier method. The study groups were comparable at baseline and had similar distribution of known prognostic factors. Further, a regression analysis showed that gender, age and biologically effective dose were not significant predictors of survival.

**Effectiveness results**
The mean overall survival was 33.5 months with PCI and 20 months with no PCI. The mean difference was 13.5 months (95% confidence interval, CI: 5.2 - 21.9; p<0.01).

The median overall survival was 20 months with PCI and 19 months with no PCI, (p>0.01).

The 2-year overall survival was 43.9% with PCI and 21.8% with no PCI, (p<0.05).

The 5-year overall survival was 12.1% with PCI and 6.2% with no PCI, (p<0.05).

The mean disease-free survival was 29.5 months with PCI and 16.3 months with no PCI. The mean difference was 13.2 months (95% CI: 4.8 - 21.5; p<0.01).

The median disease-free survival was 14.7 months with PCI and 10 months with no PCI, (p>0.05).

The 2-year disease-free survival was 25.6% with PCI and 10.1% with no PCI, (p<0.005).

The 5-year disease-free survival was 11.5% with PCI and 5.1% with no PCI, (p<0.05).

The proportion of patients who later developed brain metastases was 67% in the PCI group and 50% in the no PCI group.

Of the 66 patients in the PCI group, 46 (70%) had acute toxicities. More specifically, 23 nausea, 23 anorexia, 20 fatigue, 6 vomiting, 4 headaches, 4 skin reactions, 4 ear problems, 3 confusion, 1 light-headedness, and 1 sensation of fullness in the head. Some patients had multiple symptoms.

The mean total duration of the acute toxicities was 1.8 months (median 2.5).

**Clinical conclusions**
The effectiveness analysis showed that PCI improved survival in comparison with no PCI, although it was associated
Methods used to derive estimates of effectiveness
The authors made some assumptions to derive quality of life values which were not available. In particular, the utility weights associated with time with toxicity (TOX) and time after relapse (REL) until death were estimated, to calculate the quality time without symptoms and toxicity (Q-TWiST).

Estimates of effectiveness and key assumptions
The utilities associated with TOX and REL were varied from 0.25 to 1. The utility associated with TWiST was assumed to have been 1 (perfect health).

Measure of benefits used in the economic analysis
The summary benefit measures were overall survival and quality-adjusted survival. These were based on data derived from the single study or authors' assumptions. No discounting was applied because of the short life expectancy of the patients included in the study.

Direct costs
Discounting was not relevant since most of the patients died within 2 years, thus costs were not incurred in the long term. The unit costs were presented for most items, but details on the quantities of resources used were unclear for all items. The economic evaluation included the costs of services from the initial referral to the cancer centre until the time when all investigations and therapies had ceased. Investigations comprised blood or urine test, radiograph, electrocardiogram, echocardiogram, nuclear medicine liver scan, ventilation/perfusion scan, gated cardiac wall motion scan or bone scan, ultrasound liver scan, cranial CT or chest/abdomen or planning CT scan, and pulmonary function test.

The categories of costs considered were hospitalisation (including also fixed costs), radiotherapy and chemotherapy (investigations and drugs). The costs for both primary treatment and relapses were included. The authors stated that non-medical costs were not included in the analysis because their estimation could not be precise. Similarly, the cost of a lodge provided for cancer patients travelling a long distance for treatment was not considered because its impact was modest. Other cost categories, such as services provided by family doctors, were not included because of the perspective adopted. The cost/resource boundary of the study was that of the cancer centre. The costs and resource use data came from a cancer centre participating into the study and the sample of patients derived from the provincial registry. All of the costs were adjusted to 1992 values, which was the middle of the study period (1987 to 1998).

Statistical analysis of costs
A statistical analysis was carried out to test the statistical significance of differences in the total costs.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
Canadian dollars (Can$).

Sensitivity analysis
Sensitivity analyses were carried out by varying the assumed values of the utility weights for TOX and REL between 1 and 0.25.
Estimated benefits used in the economic analysis
The mean overall survival has been reported already (see the 'Effectiveness Results' section).

The mean quality-adjusted survival (Q-TWiST) ranged from 33.5 months to 23.9 months with PCI and from 20 months to 12.7 months with no PCI, depending on the assumptions on utility weights (higher weights led to higher Q-TWiST values).

The differences in quality-adjusted survival were statistically significant.

Cost results
The mean incremental cost per patient was Can$18,834 in the PCI group and Can$17,885 in the no PCI group, (p>0.05).

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of PCI versus no PCI.

The incremental cost was $70 per month of incremental overall survival. The incremental cost was Can$70 per month of quality-adjusted survival (or Can$840 per quality-adjusted life-year, QALY) if the utility weights for TOX and REL were assumed to have been 1, and Can$85 per month of quality-adjusted survival (or Can$1,020 per QALY) if the utility weights for TOX and REL were assumed to have been 0.25.

Authors' conclusions
The use of prophylactic cranial irradiation (PCI) in patients with small-cell lung cancer (SCLC) who have achieved complete remission was cost-effective. The cost-effectiveness of PCI compared favourably with other well-accepted chemotherapy strategies.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was consistent with the objective of the study. Thus, the comparison carried out in the analysis was appropriate. You should decide whether no PCI is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a retrospective series of patients which, as the authors noted, generally has a weak internal validity. However, it was stressed that the study groups were comparable at baseline, despite the lack of randomisation. The authors noted that the retrospective review of patients' charts has the advantage of reflecting “real world” treatment patterns, as opposed to artificial situations created in clinical trials. In addition, the authors undertook a regression model to assess potential confounding. The authors highlighted that the use of multiple chemotherapy therapies could have represented a potential confounding factor, but it reflected the full range of clinically available options.

Validity of estimate of measure of benefit
The use of overall survival and quality-adjusted survival as summary benefit measures was appropriate. In addition, such measures are comparable with the benefits of other health care interventions. Authors’ assumptions were used to estimate gains in quality of life. Since this represented a weak source of values, the results were reported for different values of utility weights.

Validity of estimate of costs
The authors stated implicitly the perspective that was adopted in the study, and justified their exclusion of some cost
categories. Extensive details of the cost analysis were provided, especially unit costs. The information on resource use was less clear. The source of the data was reported. The price year was reported, which aids reflation exercises in other settings. The authors stressed that the analysis followed closely the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. Discounting was not relevant because of the poor life expectancy of the patients included in the analysis. The cost estimates were specific to the study setting and were not varied in the sensitivity analysis.

**Other issues**
The authors pointed out that their clinical findings were comparable to those observed in a clinical trial. They also compared their cost-effectiveness findings with those from other studies published in Canada and the UK. The issue of the generalisability of the study results to other settings was not addressed and limited sensitivity analyses were carried out, which reduces the external validity of the study. This study refers to patients with limited-stage SCLC who had achieved complete remission.

**Implications of the study**
The study results supported the use of PCI to improve quality-adjusted survival in patients with SCLC who had achieved complete remission.

**Source of funding**
Supported by a Saskatchewan Cancer Agency Research Grant.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Brain Neoplasms /prevention & control /secondary; Carcinoma, Small Cell /prevention & control /drug therapy /mortality /secondary; Confidence Intervals; Cost-Benefit Analysis; Cranial Irradiation /economics; Female; Humans; Lung Neoplasms /drug therapy /mortality; Male; Middle Aged; Prognosis; Quality of Life; Remission Induction; Research Support, Non-U.S. Gov't; Retrospective Studies; Survival Rate

**AccessionNumber**
22002000189