Estimating survival gain for economic evaluations with survival time as principal endpoint: 
a cost-effectiveness analysis of adding early hormonal therapy to radiotherapy in patients 
with locally advanced prostate cancer

Neymark N, Adriaenssen I, Gorlia T, Caleo S, Bolla M

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 hormonal therapy, as an adjunct to radiotherapy, for the treatment of patients with locally advanced prostate cancer. Hormonal therapy with the luteinising hormone-releasing hormone-analog goserelin was administered as a 3.6-mg subcutaneous injection every 4 weeks. Radiotherapy comprised 50 Gy over 5 weeks, followed by a prostatic boost of 20 Gy over 2 weeks. The patients were also given an anti-androgen, cyproterone acetate, at a dose of 150 mg/day orally for 1 month, starting 1 week before the first dose of goserelin.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with histologically proven locally advanced prostate cancer (cT3-4, N0-2, M0), according to the tumour-node-metastasis classification system of the International Union against Cancer. The patients were younger than 80 years of age and had not undergone any earlier treatment for prostate cancer. Patients with a prior malignant disease (except for treated basal-cell carcinoma of the skin) and those with evidence of distant metastases were excluded.

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

Dates to which data relate
The effectiveness evidence and resource use data were derived from a study published in 1997 (see Other Publications of Related Interest). The data were collected between 1987 and 1995. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a single study published in 1997 (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was carried out retrospectively on a subsample of the patients used in the effectiveness analysis.
Study sample
Power calculations were performed in the planning phase of the study. A sample of 75 patients in each study group had to be followed until relapse to detect a statistically significant difference in the study outcomes. A sample of 415 patients with advanced prostate cancer was enrolled from 1987 to 1995. There were 208 patients with a median age of 70 years (range: 51 - 80) in the RT group. There were 207 patients with a median age of 71 years (range: 54 - 80) in the COMB group.

Study design
This was a phase III randomised controlled trial carried out in several sites. The patients were stratified according to institution, clinical stage of the disease, and irradiation technique. The randomisation was performed using the minimisation technique. The median follow-up was 45 months. Fourteen patients (10 in the RT group and 4 in the COMB group) were not evaluated, but were considered eligible for the final analysis.

Analysis of effectiveness
The basis of the clinical analysis was intention to treat. The primary health outcome used in the analysis was overall survival from randomisation to death, or the most recent follow-up assessment. The study groups were well balanced with respect to age, WHO performance status, and clinical conditions.

Effectiveness results
The overall survival at 5 years was 79% (95% confidence interval, CI: 72 - 86) in the COMB group and 62% (95% CI: 52 - 72) in the RT group, (p=0.001).

For overall survival, the hazard ratio was 0.50 (95% CI: 0.33 - 0.76).

The authors stated that these results were generally confirmed in a more recent update of the analysis.

Clinical conclusions
The analysis showed that adjuvant therapy with goserelin, started at the beginning of external irradiation treatment and continuing for 3 years, may improve the 5-year overall survival of patients with locally advanced prostate cancer.

Modelling
The mean survival time in the two patients groups was estimated using the restricted means model.

Measure of benefits used in the economic analysis
The benefit measure used in the economic analysis was the mean survival. This was derived from the effectiveness analysis and was then recalculated using the restricted means method.

Direct costs
A 3% discount rate was used as the costs were incurred over more than two years. The unit costs were reported. The economic analysis included the costs of days of hospital stay, visits to day clinics, outpatient visits, surgical operations performed, drugs used for treatment or disease progression, palliative radiotherapy and sulfur-89 given for palliation. The cost/resource boundary adopted was that of the French public health insurance system. The costing was carried out retrospectively on a sample of 90 patients recruited into the trial by the Centre Hospitalier Universitaire of Grenoble in France during the study period. The costs were estimated using actual data derived from the national French Nomenclature, and represented tariffs for services provided by the few for-profit hospitals in France. The drug costs were estimated from acquisition prices.
Statistical analysis of costs
No statistical test of the difference between the costs was carried out. As censoring also represents a problem for analysis of the costs, the authors used a specific method to calculate the average per patient costs. This involved subdividing the survival period of interest into several subintervals (of one day, for example) and then calculating the average cost for each subinterval. All the costs were reported in 1998 values.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
French francs (Ffr).

Sensitivity analysis
Given the stochastic nature of the sampled data, the uncertainty of the estimated costs and benefits was analysed using a bootstrap resampling technique, repeated 5,000 times. As a result, the cost-effectiveness acceptability curve was mapped. This showed the probability that the new treatment would be considered cost-effective, as a function of hypothetical threshold values reflecting the decision-makers’ willingness to pay for an increase in survival.

Estimated benefits used in the economic analysis
The mean survival estimated by the restricted means method was 7.05 years in the COMB group and 5.99 years in the RT group. Thus, the gain in survival with COMB over RT was 1.06 years.

Using the Gompertz function, the estimated survival was 11.42 years in the COMB group and 7.36 years in the RT group, with a difference of 4.06 years. The corresponding figures when using the Weibull distribution were 13.76 years (COMB) and 8.02 years (RT), respectively, with a difference of 5.74 years.

The authors stated that it was not possible to determine which was the best estimate of mean survival.

Cost results
The mean costs per patient were Ffr 81,676 in the COMB group and Ffr 69,907 in the RT group during the full study period.

When the costs were estimated over the same restricted period as that used to estimate survival with the restricted means method, the mean costs per patient were Ffr 58,297 in the COMB group and Ffr 71,013 in the RT group.

Synthesis of costs and benefits
An incremental analysis was carried out to combine the costs and benefits of the interventions. However, no incremental ratio was calculated as the COMB-based treatment was dominant, being more effective (longer survival) and less costly than radiotherapy alone. The 5,000 bootstrap replications showed that COMB was dominant in 76% of the cases and there were cost-savings in 84% of the cases. Survival was improved in 89% of the cases.

Authors’ conclusions
The study provided strong evidence in favour of the addition of immediate hormonal therapy with goserelin to radiotherapy for patients with locally advanced prostate cancer. The combined therapy led to an increase in mean survival, and a reduction in the costs from the perspective of the French health insurance system. However, the authors noted that "the exact results of the analysis depend decisively on the time point chosen for the analysis and on the method used for estimating the difference in mean survival".
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. RT was selected as this was standard practice. You should assess whether it represents a valid technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the analysis was ensured by the performance of a phase III randomised controlled trial. The method of randomisation was appropriately reported, and power calculations were carried out in the planning phase of the study. The study groups were comparable at baseline. The analysis of the clinical study was conducted on an intention to treat basis. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
Mean survival was used as the benefit measure in the economic analysis. It represents a valid measure, as it is generally used in the case of treatments for cancer. The analysis showed that the method used to calculate mean survival may be crucial. The mean survival values calculated using other approaches were presented for comparative purposes.

Validity of estimate of costs
The analysis of the costs was carried out from the perspective of the French health insurance system, and all the relevant categories of costs were reported. The unit costs were reported and the price year was given. The source of the cost data was reported and the cost estimates were somewhat specific to the study setting. The costs were treated deterministically. However, sensitivity analyses were not carried out to assess the impact of single cost items on the estimated total costs, but a bootstrap technique was performed to determine the robustness of the overall cost-effectiveness of the interventions. The authors acknowledged that the method used to estimate the costs represented a great improvement, compared with the methods usually used to estimate the costs in the presence of censored data, but it should not be considered as the only solution since other approaches have been proposed.

Other issues
The study results were not compared with those from other studies. The authors stated that they were unaware of any publications related to the method of assessing average survival. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses on specific variables were not carried out. Thus, the external validity of the study was limited. A sample of patients with advanced prostate cancer was enrolled and this was reflected in the conclusions of the analysis.

Implications of the study
The authors suggested that the restricted means method should be used to estimate the mean survival. This method avoids any problem in using extrapolation processes, at the expense of producing conservatively biased estimates of the mean survival in each study group. A further study is currently being carried out by the authors. This focuses on a simulation approach to determine the most appropriate method to estimate survival in the presence of censored data.

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**Other publications of related interest**

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