The cost-effectiveness of beta-radiation therapy for treatment of in-stent restenosis: an analysis at 290-day follow-up

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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 health intervention examined in the study was beta-radiation therapy as an adjunct to percutaneous coronary intervention (PCI) for the treatment of in-stent restenosis. Radiation was delivered using the Guidant Intravascular Radiotherapy System, a phosphorus-32 emitter delivered with an automatic delivery unit into a centred catheter delivery system.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older, with angina or a positive functional study, undergoing an elective PCI procedure for treatment of a restenotic lesion within a previously implanted stainless steel stent in a native coronary artery. Patients were excluded if they had had acute myocardial infarction within the previous 72 hours, previous radiation treatment to the chest, evidence of thrombus by angiograms, or multiple lesions in the target vessel.

Setting
The setting was hospital. The economic study was conducted in the USA.

Dates to which data relate
Data on effectiveness and resource use were gathered from August 1998 to December 1999. The price year was 2001.

Source of effectiveness data
The effectiveness evidence came from a single study, whose details were published elsewhere (see "Other Publications of Related Interest" below).

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

Study sample
Power calculations suggested that a sample size of 310 patients was sufficient to show a 36% reduction in the primary safety endpoint, assuming a 50% 9-month rate of major adverse cardiac events (MACEs) in the PCI alone group and 32% 9-month MACE rate in the treatment group with 90% power and 5% significance level. Smaller sample sizes were
required for secondary outcome measures. Thus, a sample of 332 patients was enrolled but the method of sample selection was not described and it was not clear whether some patients were excluded from the initial study sample for any reasons or whether any refused to participate. There were 166 patients (mean age: 62 +/-11 years; 70% men) in the radiation group and 166 patients (mean age: 62 +/-11 years; 73% men) in the PCI alone group. However, in the present study, only the subgroup of US patients was considered, thus the final sample for the purpose of this study included 283 patients: 143 (mean age: 62.7 +/-10.9 years; 67.8% men) in the radiotherapy group and 140 (mean age: 60.8 +/-10.7 years; 69.3% men) in the PCI alone group.

Study design
This was a prospective, randomised, clinical trial, which was conducted in 24 study regions (18 in the USA and 6 in Europe). Randomisation was performed using envelopes that were opened by the radiation oncologist or physicist after the patient was judged eligible for the study. Randomisation was carried out after angioplasty intervention, which was an entry criterion. An independent committee, the members of which were unaware of the treatment allocation, evaluated all study events. Patients were followed for 9 months and no loss to follow-up was observed in the US group.

Analysis of effectiveness
The basis of the analysis of the clinical study was intention to treat. In the primary study several aggregate outcome measures were estimated, such as the primary safety endpoint of death, myocardial infarction, or repeat target-lesion revascularisation (MACE). However, for the purpose of the present study, only the rate of target lesion revascularisation (TLR) will be reported. Multivariate logistic regression analysis and Cox's proportional models were used to evaluate the possible impact of confounding factors in the primary study. The study groups were comparable at baseline with respect to demographic and clinical characteristics, such as risk factors.

Effectiveness results
The rate of TLR per patient was 0.13% in the radiotherapy group and 0.30 in the PCI alone group, (p=0.001).

Clinical conclusions
The effectiveness analysis showed that, over a period of 9 months, radiation therapy reduced the rate of TLR in comparison with in-stent restenosis. It is worth noting that, in the primary study, the estimated MACE rate in the whole group of US and European patients was 15% in the radiation group and 31% in the PCI alone group, (p=0.0006).

Measure of benefits used in the economic analysis
The main benefit measure used in the economic analysis was the rate of TLR per patient, observed with the two strategies under evaluation. The benefit measure was estimated from the effectiveness study.

Direct costs
Discounting was not relevant as costs were incurred over a period of 290 days. Quantities of resources used were reported but unit costs were not provided. The health services included in the economic evaluation were hospitalisations due to initial procedure or subsequent procedures (PCI, radiation, revascularisation, diagnostic tests, transfusion, thrombolytic treatment, hospital stay, and coronary artery bypass grafting (CABG)), outpatient care (visits and diagnostic tests), and antiplatelet medication. Costs incurred before inclusion in the study were not taken into account. The cost/resource boundary of the study was that of a commercial health plan or centralised payer. The estimation of resource use was based on actual data evaluated alongside the INHIBIT study and referred to 18 participating US sites. Unit costs were estimated from Medicare reimbursement rates whenever possible. The cost of radiotherapy came from the producer. Professional services associated with hospitalisations and outpatient visits were estimated through Current Procedural Terminology codes. The corresponding resource-based relative value scale units were then converted into professional payments with Medicare’s national conversion factor. The costs of antiplatelet drugs were estimated from average wholesale prices discounted by 20%. Compliance with antiplatelet medication was based on authors’ assumptions. Finally, outpatient facility payments were estimated from Ambulatory Payment Classification system. The
price year was 2001.

**Statistical analysis of costs**
Costs were treated deterministically but statistical tests were conducted on resources used.

**Indirect Costs**
Indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted to evaluate the robustness of the conclusions of the analysis to variations in the main endpoint of the interventions. Secondary analyses used two alternative benefit measures: the rate of TLR and adjacent to target lesion revascularisation (TLR + AR), defined as revascularisations within the length between the markers on the centring catheter plus 5mm on each end; and II target vessel revascularisation (TVR), defined as revascularisations within the target vessel. These alternative measures were used to make a distinction based on the revascularisation location. A bootstrap procedure was conducted by drawing 2,000 random samples (with replacement) and 1,000 cost-effectiveness ratios were calculated. Subsequently, the probability that the cost-effectiveness ratio fell within the benchmark of $16,852 (the mean cost of services associated with the treatment of restenosis that involved either a PCI or CABG procedures) was calculated.

**Estimated benefits used in the economic analysis**
The rate of TLR was 0.13 with radiotherapy and 0.30 with PCI alone, (p=0001).

The rate of TLR + AR was 0.22 with radiotherapy and 0.35 with PCI alone, (p=0.037).

The rate of all TVR was 0.27 with radiotherapy and 0.37 with PCI alone, (p=0.073).

**Cost results**
The estimated mean 290-day costs per patient were $19,286 with radiotherapy and $18,349 with PCI alone when only TLR were considered; $20,535 with radiotherapy and $19,141 with PCI alone when TLR + AR were considered; and $21,483 with radiotherapy and $19,469 with PCI alone when all TVR were considered.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio (ICER) was calculated to combine costs and benefits of radiotherapy relative to PCI alone.

The ICER was $5,512 when only TLR were considered, $10,723 when TLR + AR were considered, and $20,140 when all TVR were considered.

The bootstrap analysis suggested that the probability that the ICER fell within the threshold of $16,852 was 82.7% when TLR was used, 64.5% when TLR + AR was used, and 46.2% when all TVR were considered.

**Authors' conclusions**
The authors concluded that the use of beta-radiation therapy as an adjunct to PCI for the treatment of in-stent restenosis was cost-effective from the perspective of the payer in the USA. Despite the initial increase in costs due to the addition
of radiotherapy, fewer episodes of revascularisation were associated with radiotherapy treatment during the follow-up period. On average, the payer would need to pay an additional $5,512 relative to the cost of PCI alone and this figure compared favourably with the observed mean cost of $16,852 for the treatment of restenosis.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. PCI represented the standard procedure offered to patients who presented with in-stent restenosis. The use of radiation (both beta or gamma-radiation) is a newly available technique that has already proved its efficacy, but the economic implications of its use were not clear. You should decide whether PCI is a widely used procedure for patients with in-stent restenosis and whether radiotherapy represents a feasible intervention as adjunct to PCI in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a randomised clinical trial, which was appropriate for the study question. The method of randomisation was described and power calculations were conducted. The analysis of the clinical study was based on intention to treat and study groups were comparable at baseline. These issues tend to enhance the internal validity of the analysis. However, the present analysis used a subgroup of patients involved in the primary study, namely US patients. The main clinical outcome used in the economic evaluation was a secondary measure of effectiveness in the original effectiveness study and the authors did not state why the composite measure (MACE) was not used. It was not clear whether the study sample was representative of the study population as the authors acknowledged that outside the setting of the clinical trial, patients might be monitored and followed less. The authors also noted that the time horizon of the study was too short to assess the long-term impact of beta radiations.

Validity of estimate of measure of benefit
The summary benefit measure was derived from the effectiveness study and represented a disease-specific measure. On the one hand, this limits the comparability of such a measure with the benefits of other health care interventions, but, on the other hand, TLR (or TVR) is a widely used endpoint in studies estimating treatments for restenosis. Indeed, the use of (quality-adjusted) life year is not common for the disease under evaluation, although aggregate measures, such as MACEs, are usually employed. However, it is worth noting that, when a more complex benefit measure was used (such as TVRs), the cost-effectiveness of radiation was no longer favourable. Thus, as the authors noted, the choice of the endpoint represented a critical issue.

Validity of estimate of costs
The perspective adopted in the study was explicitly reported and it appears that all relevant categories of costs were included in the economic analysis. A detailed breakdown of costs was provided but unit costs were not reported. Average resource use per patient was described and statistical tests were conducted (in the INHIBIT study) and reported in the present study to show which categories of costs were significantly lower in the radiotherapy group. The price year was reported, thus facilitating reflation exercises in other settings. Cost estimates were specific to the study setting and were not varied in the sensitivity analysis. The source of each cost category was reported.

Other issues
The authors made some comparisons of their findings with those from other studies evaluating beta- and gamma-radiation therapies. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were conducted only to take into account alternative benefit measures. Thus the overall external validity of the analysis was low. The authors noted some limitations of the analysis, which have been reported above.

Implications of the study
The study results suggest that, in the short-term, beta-radiation may represent an efficient alternative to PCI alone in patients with restenosis from the perspective of a US health plan or payer. Future studies should evaluate the long-term clinical and economic implications of the use of beta-radiation.
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None stated.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
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