Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma? A multicenter retrospective study in Japan


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 interventions examined in the study were two strategies for the optimal examination of patients with prostate cancer for preoperative staging and subsequent management: serum prostate specific antigen (PSA) and PSA plus baseline bone scan.

Type of intervention
Preoperative diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised untreated patients with newly diagnosed prostate carcinoma.

Setting
The setting was hospital. The economic study was carried out in Japan.

Dates to which data relate
The bulk of the effectiveness evidence and resource use data was collected between April 1988 and June 2000. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was mainly derived from a single study. Estimates of effectiveness based on a review of published data plus authors' opinions were also used to support the effectiveness analysis.

Link between effectiveness and cost data
The costing was undertaken retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not reported. A sample of 1,294 patients with newly diagnosed, untreated prostate cancer, seen at the study institutions between April 1988 and June 2000 were selected. The mean age of the sample was 70.7 years (range: 42 - 93 years). Every patient underwent baseline bone scan, serum PSA measurement, and core needle biopsy of the prostate, as routine procedures.
Study design
This was a retrospective study based on a single cohort of patients who underwent both interventions. The study was carried out in five hospitals: Cancer Institute Hospital at Tokyo, Chiba University Hospital at Chiba, Keio University Hospital at Tokyo, National Defense Medical College Hospital at Tokorozawa, and Tokyo Medical College Hospital at Tokyo. Patients were generally not followed up after the interventions. Five different kits were used for the measurement of serum PSA levels, but a conversion formula was then used to standardise the results.

Analysis of effectiveness
It appears that all patients included in the study were accounted for in the analysis (in effect intention to treat). The health outcomes assessed were stage probabilities in patients with PSA levels less than or equal to 10 ng/mL and in patients with negative or positive bone scan, coefficients of correlation of the PSA values measured with different assays kits, receiver operating characteristic (ROC) analysis for the detection of a positive bone scan based on the serum PSA values, and proportion of positive bone scans in each Gleason Grade group. No information regarding the comparability of groups was required since the same cohort of patients was used for both interventions.

Effectiveness results
The effectiveness results were as follows:

The stage probabilities in patients with PSA levels less than or equal to 10 ng/mL were 2% in Stage A, 60.1% in Stage B, 20.8% in Stage C, and 7.1% in Stage D.

The stage probabilities in patients with negative baseline bone scan were 5.3% in Stage A, 46.6% in Stage B, 34.4% in Stage C, and 13.8% in Stage D.

The stage probabilities in patients with positive baseline bone scan were 34.1% in EOD I, 30.7% in EOD II, 24.7% in EOD III, and 10.5% in EOD IV.

The coefficients of correlation of the PSA values measured with different assays kits were high (0.996 - 0.999; 95% CI: 0.978 - 0.999).

ROC analysis indicated that sensitivity and specificity curves of the serum PSA levels for the detection of bone metastasis crossed at a serum PSA value of approximately 60 ng/mL.

The area under the ROC curve was 0.870.

The proportion of positive bone scans was 32.3% in patients with Gleason Grade 5 tumour, 23.7% in patients with Gleason Grade 3 and 4 tumours, and 7.24% in patients with Gleason Grade 1 and 2 tumours.

Of the 300 patients with serum PSA levels less than or equal to 10 ng/mL, the proportion of positive bone scans was 1.33% (5 patients with Gleason Grade 5 tumour).

Clinical conclusions
The effectiveness analysis showed that positive bone scans were quite rare in patients with serum PSA levels less than or equal to 10 ng/mL, especially those patients with a tumour of Gleason Grade less than or equal to 2.

Modelling
A decision tree model was constructed in order to simulate the natural history and clinical management (mainly based on monitoring) of a cohort of patients with newly diagnosed prostate cancer. Cumulative costs and expected disease-specific survival rates were calculated over a time horizon of 10 years. The main arms of the tree referred to the two interventions: PSA alone and PSA plus baseline bone scan. In the PSA alone branch, only patients with serum PSA levels greater than or equal to 10 ng/mL underwent baseline bone scan, while patients with serum PSA levels less than 10 ng/mL underwent magnetic resonance imaging (MRI) studies of both the pelvis and the spine. In the PSA plus
baseline bone scan branch, all patients underwent both interventions, and patients with a negative bone scan underwent MRI studies of the pelvis. Data derived from the single study and the literature (plus authors' assumptions) were used to populate the decision model.

**Outcomes assessed in the review**
The outcome measures assessed from the literature and used as inputs in the model were the 10-year disease specific survival rates for patients with Stage A-D disease and the 10-year disease specific survival rates in patients with extent of disease (EOD) I, II, III, and IV.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Three primary studies (published between 1988 and 1996) were used as sources of the effectiveness evidence.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
Ten-year disease-specific survival rates were 84.2% for patients in Stage A, 70.4% for patients in Stage B, 43% for patients in Stage C, and 30% for patients in Stage D.

Ten-year disease-specific survival rates were 78.2% for patients with EOD I, 22.2% for patients with EOD II, 14.5% for patients with EOD III, and 1% for patients with EOD IV.

**Methods used to derive estimates of effectiveness**
The authors also made some assumptions to support the data used in the decision model.

**Estimates of effectiveness and key assumptions**
Patients with Stage A disease were assumed to be candidates for prostatectomy.

The age of patients was assumed to range between 55 and 75 years and a minimum life expectancy of 10 years was
assumed for patients whose carcinoma was cured.

Hormonal therapy was administered continuously for the rest of the patients' lives.

The sensitivity and specificity of bone scan was set at 100%.

The death rate due to radical prostatectomy was assumed to be 0.5%.

Finally, sensitivity and specificity of both transrectal ultrasound (TRUS) and pelvic and spinal MRI were set at 100%.

**Measure of benefits used in the economic analysis**

The benefit measure adopted in the analysis was the 10-year disease specific survival rate, obtained from the decision tree model. It was not clear whether a discount rate was used for future benefits.

**Direct costs**

A 5% discount rate was appropriately used to calculate future costs since the time horizon used in the model was 10 years. The cost/resource boundary adopted was not reported. Unit costs were reported, but quantities of resources were not. The health service costs included in the costing were PSA measurement, bone scan, radical prostatectomy, hormonal therapy, and radiotherapy. Depreciation of gamma cameras, personnel expenses, and overhead costs were not included in the analysis. The estimation of cost data was based on actual data derived from the inpatient and outpatient bills for those patients included in the sample. Ten-year costs were calculated through the decision model. Quantities of resources used were collected during the study period (April 1988 - June 2000). The price year was not reported.

**Statistical analysis of costs**

Statistical analyses of costs were not conducted.

**Indirect Costs**

Indirect costs were not included.

**Currency**

US dollars ($) and Japanese Yen (Y). The exchange rate of Japanese Yen into US dollars was as follows: Y105 = $1.

**Sensitivity analysis**

A sensitivity analysis was carried out by observing the impact of variations of values of serum PSA levels on cost savings associated with the interventions.

**Estimated benefits used in the economic analysis**

The ten-year survival rate was 51.8% for both the PSA alone strategy and the PSA plus bone scan strategy.

**Cost results**

Cost of examinations and therapies per patient were $527 and $42,422 for the PSA alone strategy, and $543 and $42,422 for the PSA plus bone scan strategy.

The net cost per patient was $42,949 for the PSA alone strategy and $42,965 for the PSA plus bone scan strategy.

The incremental saving of the PSA alone strategy over the PSA plus bone scan strategy was $16.

The cost-saving associated with the strategy of PSA alone was sensitive to the variations in serum PSA levels: cost-
savings gradually declined as serum PSA levels decreased.

Synthesis of costs and benefits
Costs and benefits were not combined as a cost-minimisation analysis was conducted (although this was not explicitly stated in the study), due to the fact that 10-year survival rates were equal for both interventions.

Authors’ conclusions
The authors concluded that a strategy based on serum PSA and baseline bone scan was as effective as a strategy based on PSA only, in terms of long-term survival, but was slightly more expensive. As a result, baseline bone scan could be eliminated in patients who have PSA levels less than or equal to 10 ng/mL or, in particular, in patients with tumours of Gleason Grade less than or equal to 2 or with a Gleason score less than or equal to 6, since these patients have a very low probability of a positive bone scan.

CRD COMMENTARY - Selection of comparators
The authors justified the rationale for the choice of the comparators. Both bone scintigraphy and serum PSA measurements were routinely performed in patients with newly diagnosed prostate cancer in Japan. You, as a user of this database, should assess whether they represent widely used health interventions in your own setting.

Validity of estimate of measure of effectiveness
The analysis of the effectiveness was conducted by combining effectiveness evidence from different sources. Data derived from the retrospective multicentre study were obtained from a large sample of unselected patients who underwent both interventions, therefore limiting the potential for bias and confounding factors. However, data derived from published studies were not obtained from a systematic review of the literature and some of them were relevant to the US setting, which appeared quite different from the Japanese setting, especially in the case of prostate cancer that, as noted by the authors, was quite race-related. As a consequence the effectiveness data will have limitations in terms of its applicability to the Japanese patient population. Finally, the numerous assumptions made in the decision model were based on authors’ opinion rather than on a formal panel of experts (such as a Delphi panel). These issues could have limited the internal validity of the analysis.

Validity of estimate of measure of benefit
The benefit measure adopted in the analysis (10-year survival rate) was obtained through the decision model. It would have been interesting to have assessed not only length of survival, but also quality of life (i.e. through quality-adjusted life-years (QALYs)). However, the benefit measure was not found to differ between the interventions, therefore costs and benefits were not combined.

Validity of estimate of costs
The perspective of the study was not clearly reported, therefore it was not possible to assess whether all relevant categories of costs were included in the analysis. Some cost items, such as depreciation of gamma cameras, personnel expenses, and overhead costs were not taken into account. The estimation of costs appears to have been somewhat specific to the study setting, especially as costs were treated deterministically and no statistical analyses were conducted on resources. The price year was not reported. However, appropriate currency conversions were conducted.

Other issues
The authors compared their findings with those from a few studies conducted in the USA. The issue of the generalisability of the study to other settings was not addressed and sensitivity analyses were conducted only on serum PSA levels. Therefore, the external validity of the study could be low. The authors reported some limitations of the analysis, mainly arising from the use of different kits for measuring serum PSA and the use of data from the USA.
Implications of the study
Although the study suggests that a strategy based on serum PSA alone in patients with PSA levels less than or equal to 10 ng/mL was cost-effective, the authors noted that avoiding a baseline bone scan “may not be a favourable policy, and we still hesitate to change our conventional algorithm for the work-up of these newly diagnosed patients on the basis of their serum PSA levels”. The reasons for this practical decision were as follows: low cost savings associated with the strategy based on PSA alone; importance of bone scan for the prognosis suggested by the EOD and relevance of bone scans as standard diagnostic component for patients who underwent radical prostatectomy; and increase in health care costs as a result of use of alternative diagnostic modalities.

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