Cost-effectiveness of using recombinant human TSH prior to radioiodine ablation for thyroid cancer, compared with treating patients in a hypothyroid state: the German perspective
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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 present study compared the use of a recombinant human thyroid-stimulating hormone (rhTSH) preparation prior to radioiodine remnant ablation with an activity of 3.7 GBq iodine-131 with the standard hypothyroid preparation. Euthyroid patients received exogenous rhTSH (Thyrogen, Genzyme Corporation) while hypothyroid patients underwent a period of thyroid hormone withdrawal to raise serum TSH. Patients in both groups utilised rhTSH prior to the subsequent diagnostic follow-up procedures as this is a common practice in Germany.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The target population for the model was a hypothetical cohort of 100,000 patients with newly diagnosed differentiated papillary or follicular thyroid cancer without metastases, who were considered to be at low risk of recurrence. This reflected the German patient population in the clinical trial upon which the present study was based (Pacini et al. 2006 see ‘Other Publications of Related Interest’ below for bibliographic details). Patients with metastases detected at the time of the post-ablation scan were not included in the model.

Setting
The setting was tertiary care. The economic study was carried out in Germany.

Dates to which data relate
The studies providing the effectiveness evidence dated from 1995 to 2006. For resource use and cost data, the date range was 1996 to 2005. The price year was not reported.

Source of effectiveness data
The evidence was derived from a review or synthesis of studies, estimates based on authors’ assumptions, and expert opinion.

Modelling
An age- and gender-specific Markov (state transition) decision model was used to simulate the costs and outcomes for a cohort of low-risk thyroid cancer patients with a lifetime horizon. The model was based on a multi-centre, randomised controlled trial (Pacini et al. 2006). Patients entered the model at age 44 years, after their initial thyroidectomy while
preparing for follow-up ablation, and they cycled through the model until death, either from secondary malignancies or other causes. The cycle length was 1 week. Ten separate health states were modelled. These were pre-ablation, ablation, post-ablation, well, follow-up scanning, surgery for recurrence, diagnosed with salivary gland cancer, diagnosed with bone/soft-tissue cancer, diagnosed with colorectal cancer and death. The model terminated when the cohort reached the age of 66.

Outcomes assessed in the review
The parameters used in the model included:

- transition probabilities for disease state progression,
- age- and gender-specific incidence,
- radiation dose,
- prevalence, and
- mortality rates.

Study designs and other criteria for inclusion in the review
Although the evaluation was based mainly on a multi-centre randomised control trial (Pacini et al 2006), the authors also reported effectiveness data derived from scientific literature, statistical material and expert interviews. No inclusion criteria were 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
The validity of the primary studies does not appear to have been assessed.

Number of primary studies included
Twenty-seven studies were included as effectiveness sources.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The annual probability for the first 10 years of thyroid cancer recurrence was 0.026220 for both groups.

The annual probability beyond 10 years was 0.004127 for both groups.
The radiation dose was 0.167 mGy/MBq for the hypothyroid group and 0.109 mGy/MBq for the rhTSH group.

The annual probabilities of secondary cancer for the hypothyroid and rhTSH groups were, respectively:

for colorectal cancer, 0.0000850 and 0.0000553;
for bone/soft-tissue cancer, 0.00018015 and 0.00011710; and
for salivary gland cancer, 0.00017291 and 0.00011239.

**Methods used to derive estimates of effectiveness**

This analysis was based on published data, authors’ assumptions and expert opinion.

**Estimates of effectiveness and key assumptions**

The assumptions were as follows.

The probability of developing secondary malignancies was thought to be dependent upon the cumulative exposure to radiation, including that arising from the treatment and the monitoring of thyroid cancer.

A linear relationship between cumulative 131-I exposure and the development of colorectal cancer, salivary gland, and bone and soft-tissue cancers was assumed to hold over a broad range of cumulative exposures, including that equivalent to a single radioiodine ablation (3.7 GBq).

The risk reduction for patients who received rhTSH was calculated on the assumption that a 35% reduction in mean radiation dose to the blood would equate to a 35% reduction in the risk of one of the above secondary cancers.

The model was run both with and without this assumed relationship. The authors stated that when published estimates were not available, data were sourced from local clinicians using a structured questionnaire.

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

The measure of benefits was the quality-adjusted life-years (QALY). Preference values for the pre- and post-ablation health states that differed between groups were obtained from the parent study (Pacini et al. 2006), with utilities derived from the SF-36 and using the SF-6D method. Other utility weights not different between groups were taken from published literature, assumptions and convention. The health benefits were discounted at an annual rate of 5%.

**Direct costs**

The direct health care costs included were costs for thyroidectomy, radioiodine (131-I) ablation, rhTSH (Thyrogen), inpatient services, visits to general practitioner and specialist, laboratory tests, drugs and the lifetime costs of secondary cancers. With the exception of the lifetime costs of secondary cancers, which were discounted at a conservative rate of 3%, all costs were discounted at an annual rate of 5%. Reflation from the original date was not reported. The estimations of the quantities and total costs were derived through modelling. Resource use and cost data were reported separately with the corresponding unit cost for each health state and group. The authors adequately referenced the base-case value and sources for all cost items. The price year was not reported.

**Statistical analysis of costs**

No statistical analysis of the costs was reported.

**Indirect Costs**

The authors reported a societal perspective, therefore the indirect costs were appropriately included. The model adopted the friction-cost method for calculating productivity losses. The authors reported the average daily wage, the current
unemployment rate and the current labour-force participation rate. Since the costs were incurred during more than 2 years, they were appropriately discounted at an annual rate of 5%. The authors adequately referenced the base-case value and sources for all cost items. The quantities and the costs were analysed separately. The estimations of the quantities and costs were derived through modelling. The price year was not reported.

**Currency**
Euros (EUR).

**Sensitivity analysis**
A Monte Carlo simulation was used to simulate patients progressing through the various health states at the individual level in order to take appropriate account of first-order uncertainty. Second-order uncertainty was not addressed. One- and two-way sensitivity analyses and threshold analyses were conducted. The parameters investigated were a wide range of plausible estimates of quality of life scores, probabilities, costs and productivity losses.

**Estimated benefits used in the economic analysis**
In the base-case analysis, the average total QALY per patient over the course of the model was 14.0903 for the rhTSH group and 14.0408 for the hypothyroid group.

**Cost results**
In the base-case analysis, the average cost accrued per patient was EUR 10,600.43 for the rhTSH group and EUR 10,552.97 for the hypothyroid group.

**Synthesis of costs and benefits**
The rhTSH used in preparation for radioiodine ablation had an incremental societal cost of EUR 47 per patient. The incremental benefit in QALY terms was 0.0495 and the incremental cost-effectiveness ratio (ICER) was EUR 958/QALY.

Sensitivity analyses showed that the model inputs had only a modest impact upon the ICER results in absolute terms. Even when the differences in hospital stay and workdays were the major drivers of the model's result, one-way sensitivity analyses showed that the ICER remained under EUR 15,000/QALY. Also, two-way sensitivity analyses showed that the effect of assuming no difference in either secondary cancers or productivity loss resulted in EUR 21,000/QALY.

**Authors' conclusions**
The present study indicated that the use of recombinant human thyroid-stimulating hormone (rhTSH) in preparation for radioiodine remnant ablation represented good value-for-money from a societal perspective. As new health care interventions are typically considered cost-effective if the incremental cost-effectiveness ratio (ICER) is below EUR 45,000, the use of rhTSH represented a highly cost-effective technology.

**CRD COMMENTARY - Selection of comparators**
The authors gave a justification for the comparators. The model was based upon typical treatment practice for thyroid cancer patients in Germany. Nevertheless, the structure of the model should be broadly applicable to many other international settings. You should judge whether these preparation and drug strategies are relevant in your own setting, or whether other comparators could have been relevant as well.

**Validity of estimate of measure of effectiveness**
The model was based mainly on a multi-centre randomised controlled trial (Pacini et al. 2006). It was adjusted for age.
and gender to simulate the population of the parent study. Other effectiveness evidence was derived from scientific literature and international data. Whilst these represent adequate sources, it was unclear if a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. The authors used data from the available studies selectively. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, their own assumptions and expert opinion. They justified their assumptions with reference to the published literature. The estimates were investigated by sensitivity analyses, but no specific details were given to justify the ranges used.

**Validity of estimate of measure of benefit**

The authors used QALYs as the measure of benefits. This enables cross health technology comparisons. Quality adjustment utility weights that differed for each group were estimated using the SF-36 data from the parent study through the SF-6D method. Other utility weights, which did not differ between groups, were taken from published literature and assumptions.

**Validity of estimate of costs**

The authors reported that the study had been conducted from a societal perspective. Both the direct and indirect costs were appropriately included and reported in sufficient detail. The resource quantities and the costs were reported separately for each group and health state, which will enhance the generalisability of the authors' results. The unit costs were taken from published sources. A statistical analysis of the costs was not undertaken. Sensitivity analyses of cost variables were conducted and were reported to have assessed the robustness of the estimates used. The costs were appropriately discounted as they were incurred during more than 2 years. The estimations of the quantities and costs were derived through modelling. Since the price year and revaluation of costs were not reported this will hinder any future reflation exercise. As the authors reported, the inclusion of both QALYs in the numerator and time costs in the denominator might have led to some double-counting of this aspect, as the SF-36 included two dimensions related to the impacts upon professional life and the QALYs estimates used in the model may already have captured some of the productivity loss.

**Other issues**

The authors compared their findings with those from other studies. They also addressed the issue of generalisability of the results to other settings. The conclusions reflected the scope of the analysis. The authors recognised certain limitations. First, the model only related to the treatment of low-risk thyroid cancer patients and, therefore, was not relevant for patients with metastatic disease. Second, the model relied upon several assumptions concerning the possible reduction in secondary malignancy due to reduced radiation exposure as there were only retrospective data. Finally, the model was unable to quantify and cost the more salient clinical differences between hypothyroid and rhTSH preparation for ablation.

**Implications of the study**

The model related to the ablation setting and, therefore, differs from previous models examining its use in a diagnostic setting. However, both settings are similar in that patients prepared with rhTSH avoid the quality of life impairment and disutility associated with hypothyroidism to a similar extent. Also, the use of rhTSH provides the patient and the clinician with more flexibility with regard to scheduling radioiodine ablation as, theoretically, this can occur soon after thyroidectomy and be arranged at reasonably short notice.

**Source of funding**

Funded by Genzyme Corporation, Cambridge (MA), USA.

**Bibliographic details**

Mernagh P, Campbell S, Dietlein M, Luster M, Mazzaferri E, Weston A R. Cost-effectiveness of using recombinant human TSH prior to radioiodine ablation for thyroid cancer, compared with treating patients in a hypothyroid state: the
German perspective. European Journal of Endocrinology 2006; 155(3): 405-414

**PubMedID**
16914594

**DOI**
10.1530/eje.1.02223

**Other publications of related interest**
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Combined Modality Therapy; Cost-Benefit Analysis; Efficiency; Germany; Health Status; Humans; Hypothyroidism /economics; Iodine Radioisotopes /therapeutic use; Markov Chains; Models, Economic; Models, Statistical; Monte Carlo Method; Quality of Life; Quality-Adjusted Life Years; Recombinant Proteins /therapeutic use; Thyroid Neoplasms /economics /therapy; Thyroidectomy; Thyrotropin /therapeutic use

**AccessionNumber**
22006002130

**Date bibliographic record published**
28/02/2007

**Date abstract record published**
28/02/2007