Using recombinant human thyroid-stimulating hormone for the diagnosis of recurrent thyroid cancer

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CRD summary
The review compared two methods of thyroglobulin stimulation testing for assessing the recurrence of thyroid cancer. The results were used to develop a cost-effectiveness model; this was the primary aim. The review concluded that recombinant human thyroid-stimulating hormone seems a safe diagnostic agent but is less accurate than thyroid hormone withdrawal. However, since the data were sparse and incompletely reported, this conclusion should be treated with caution.

Authors' objectives
To assess the safety, efficacy and cost-effectiveness of using recombinant human thyroid-stimulating hormone (rhTSH) in thyroglobulin (Tg) stimulation testing to diagnose recurrent thyroid cancer.

Searching
A literature search was conducted to identify relevant studies for the period 1980 to 2002. The following databases were searched: MEDLINE (from 1966), EMBASE (from 1980), Cancerlit (from 1975), EconLit (from 1969) and HealthSTAR (from 1975); the search terms were reported in full. Sixteen databases of secondary research were also searched.

Study selection
Study designs of evaluations included in the review
The included studies (other than adverse events reports) were required to report on more than 20 patients. All included studies were comparative, either prospective or retrospective in design.

Specific interventions included in the review
Studies assessing the diagnostic performance of rhTSH testing, where rhTSH is used at the correct dose, in detecting recurrent thyroid cancer or thyroid remnants were eligible for inclusion. Studies of the therapeutic or ablative use of rhTSH were excluded.

The included studies also evaluated concurrent use of whole body radioiodine scan (WBS) and stimulated thyroglobulin (Tg) testing. A positive diagnosis was defined as a Tg level of 2 or 5 ng/mL and/or a positive WBS. In addition, data on the diagnostic performance of Tg level on withdrawal of thyroid hormone therapy (THT) were also reported, although this test formed part of the reference standard.

Reference standard test against which the new test was compared
Studies reporting comparison with an appropriate reference standard were eligible for inclusion. The included studies used combinations of Tg level on withdrawal of THT and WBS, or a composite of all clinical information, as the reference standard. The positive reference standard threshold was defined as either a Tg level of 2 ng/mL on withdrawal of THT or a positive WBS, which was a proxy reference standard as it was not possible to establish the exact disease status of a patient.

Participants included in the review
The included studies were of patients with differentiated thyroid cancer, post-thyroidectomy, who had a previous negative WBS after THT withdrawal.

Outcomes assessed in the review
No inclusion criteria for the outcome measures were reported. The primary outcome measures reported in the review were the sensitivity, specificity, accuracy, positive and negative predictive values, and adverse events associated with...
rhTSH stimulation.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The included studies were assigned a level of evidence on a scale of 1 to 5, specific to studies of diagnostic tests. The scale considered appropriateness and selection of the study population, independence of the reference standard, completeness of application of reference standard, and blinded interpretation.

A quality score ranging from 0 (poor) to 16 (excellent) was also presented, but no further explanation of this was given.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Incomplete results of individual included studies were tabulated and summarised. The results of the review were used as the basis for a cost-effectiveness model.

How were differences between studies investigated?
Differences between the studies were discussed in the text.

Results of the review
Six studies were included in the review with five (n=743) included in the efficacy review of diagnostic accuracy and a further study (numbers unclear) reporting on adverse events only.

Studies for which the level of evidence was reported were classified as level two or level four. The quality scores for the included studies ranged from 0 to 9.

Diagnostic accuracy results for rhTSH were only presented for one of the five studies. This reported Tg and WBS results after both administration of rhTSH and THT withdrawal. For rhTSH stimulation, using a Tg threshold of 2 ng/mL, this study found a sensitivity of 87%, a specificity of 95% and an accuracy of 89%. The corresponding values for a Tg threshold of 5 ng/mL were 81%, 95% and 85%, respectively. Another study assessed the adequacy of Tg level on withdrawal of THT and WBS as a reference standard by comparing it with clinical diagnosis based on all available information. This study found a sensitivity and specificity for THT withdrawal of 98% and 81%, respectively.

Three studies reported adverse events; the most common events associated with rhTSH were headache (3.5 to 11.1%) and nausea (7.7 to 17%).

Cost information
The average cost of using rhTSH in diagnostic follow-up of athyroid cancer patient over 5 years was Aus$6,761.10. The corresponding cost using THT withdrawal was Aus$2,308.90. For a full discussion of the economic aspects of this study see NHS EED record 22005000471.

Authors' conclusions
The use of rhTSH as a diagnostic agent seemed safe, but less accurate, than THT withdrawal when used to follow up
thyroid cancer patients who have had a previous negative radioiodine scan after THT withdrawal. The use of rhTSH as a diagnostic agent, particularly for initial post-thyroidectomy scan and treatment, requires further evaluation.

**CRD commentary**

The review aimed to compare two methods of thyroglobulin stimulation testing for the assessment of recurrence of thyroid cancer. It should be noted that the authors’ stated reason for conducting the review was as the basis for a cost-utility, decision-analytic model. A thorough search of the published literature was reported, though this was somewhat out of date at the time of publication (it covered only the period up to 2002). No specific attempt to identify unpublished literature or an assessment of publication bias were reported.

The available literature was sparse and one study was not sufficient to fully address the question of comparative accuracy. Furthermore, diagnostic accuracy might have been overestimated in this study given the apparent possibility of incorporation bias. Interpretation was further hindered by incomplete reporting of the results of the included studies. The review methods were poorly reported, and it was therefore not possible to determine whether measures were taken to minimise the introduction of error and bias during the review process. Given the methodological limitations outlined, and the fact that a review of diagnostic accuracy was not the primary aim of the study, the conclusions regarding diagnostic accuracy should be treated with caution.

**Implications of the review for practice and research**

Practice: The authors did not make any recommendations for practice.

Research: The authors stated that the use of rhTSH as a diagnostic agent, particularly for initial post-thyroidectomy scan and treatment, requires further evaluation.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.