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Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer (Review)

Ma C, Xie J, Liu W, Wang G, Zuo S, Wang X, Wu F

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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 4
METHODS . . . 4
Figure 1. . . . 6
RESULTS . . . 7
Figure 2. . . . 8
Figure 3. . . . 9
DISCUSSION . . . 10
AUTHORS' CONCLUSIONS . . . 12
ACKNOWLEDGEMENTS . . . 12
REFERENCES . . . 13
CHARACTERISTICS OF STUDIES . . . 18
DATA AND ANALYSES . . . 29
Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Successful ablation rate. . . . 30
Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Ablation by 1850 MBq vs 3700 MBq iodine-131 under rhTSH stimulation. . . . 30
Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Health-related quality of life. . . . 31
Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Radiation exposure to blood and bone marrow. . . . 32
Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Adverse events. . . . 33
ADDITIONAL TABLES . . . 33
APPENDICES . . . 35
CONTRIBUTIONS OF AUTHORS . . . 39
DECLARATIONS OF INTEREST . . . 40
SOURCES OF SUPPORT . . . 40
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 40
INDEX TERMS . . . 40

[Intervention Review]

Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

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ABSTRACT

Background

For patients with differentiated thyroid cancer (DTC) following thyroidectomy, thyroid hormone withdrawal (THW) for four to six weeks has been used for decades to increase serum thyroid-stimulating hormone (TSH) concentrations in order to enhance iodine-131 uptake by normal thyroid cells and differentiated thyroid tumour cells. Exogenous stimulation with recombinant human thyroid-stimulating hormone (rhTSH) offers an alternative to THW while avoiding the morbidity of hypothyroidism. However, the efficacy of rhTSH-aided iodine-131 treatment for residual or metastatic DTC has not been prospectively assessed.

Objectives

To assess the effects of rhTSH-aided radioiodine treatment for normal residual or metastatic DTC.

Search methods

We obtained studies from computerised searches of MEDLINE, EMBASE and *The Cochrane Library* (all until November 2009), and paper collections of conferences held in Chinese.

Selection criteria

Randomised controlled clinical trials and quasi-randomised controlled clinical trials comparing the effects of rhTSH with THW on iodine-131 treatment for residual or metastatic differentiated thyroid cancer with at least six months of follow up.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data.

Main results

Altogether 223 patients with DTC participated in four trials. Overall, studies had a high risk of bias. We found no statistically significant differences between rhTSH and THW treatment in terms of successful ablation rate but significant benefits in radiation exposure to blood and bone marrow. One trial reported on benefits in some domains of health-related quality of life. There were no deaths and no

serious adverse effects in DTC patients treated with either rhTSH or THW. Maximum follow up was 12 months. None of the included trials investigated complete or partial remission of metastatic tumour, secondary malignancies or economic outcomes. We did not find sufficient data comparing rhTSH with THW-aided radioiodine treatment for metastatic DTC.

Authors' conclusions

Results from four randomised controlled clinical trials suggest that rhTSH is as effective as THW on iodine-131 thyroid remnant ablation, with limited data on significant benefits in decreased whole body radiation exposure and health-related quality of life. It is still uncertain whether lower iodine-131 doses (1110 MBq or 1850 MBq versus 3700 MBq) are equally effective for remnant ablation under rhTSH stimulation. Randomised controlled clinical trials are needed to guide treatment selection for metastatic differentiated thyroid cancer.

PLAIN LANGUAGE SUMMARY

Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

After the removal of the thyroid gland (thyroidectomy) thyroid hormones have to be substituted to attain a normal way of life. Thyroid hormone withdrawal for four to six weeks has been used for more than 50 years for the treatment of metastatic differentiated thyroid cancer after thyroidectomy because residual cancer cells may then be better destroyed by radiation therapy using radioiodine. Another therapeutic approach to prepare for radiation uses injections of technologically created (recombinant) human thyroid-stimulating hormone (thyrotropin, TSH) to avoid the symptoms of a malfunctioning thyroid gland (hypothyroidism), which are caused by thyroid hormone withdrawal. This technique has been approved for use in the diagnosis of recurrent and metastatic differentiated thyroid cancer and in the preparation of patients for elimination of normal thyroid remnants after thyroid surgery, but not for treatment of known locally recurrent or metastatic disease.

Overall 223 patients with differentiated thyroid cancer participated in four studies. The duration of the intervention (injections of recombinant human thyrotropin) was two days in all trials. Studies were of rather low quality. We found no statistically significant differences between recombinant human thyrotropin and thyroid hormone withdrawal treatment in terms of successful reduction of thyroid remnants or cancer cells but significant benefits in radiation exposure to blood and bone marrow. One trial reported on benefits in some domains of health-related quality of life. There were no deaths and no serious adverse effects observed, however maximum follow up was only 12 months. None of the included trials investigated complete or partial remission of metastatic tumour, secondary malignancies or economic outcomes. We did not find sufficient data comparing recombinant human thyrotropin with thyroid hormone withdrawal-aided radioiodine treatment for metastatic differentiated cancer.

BACKGROUND

Description of the condition

Thyroid cancer is the most common endocrine malignancy (Kinder 2002; Wartofsky 2002). The most frequent histologic subtype of thyroid carcinoma is papillary, followed by follicular carcinoma. Together these are commonly referred to as differentiated thyroid cancer (DTC) (Sawka 2004). The prognosis of DTC generally is considered favourable, with overall survival rates of 80% to 95% at 10 years for middle-aged adults (Hundahl 1998). Local recurrences and distant metastases are seen frequently, particularly during the initial years of follow up, but sometimes they occur many years later. Overall survival rates decline to 40% when distant metastases are present (Degrossi 1991; Schlumberger 1998), therefore early detection and treatment of DTC recurrences and metastases is essential throughout the patient's life. Radioactive iodine plays an important role in the management of DTC patients (Chao 2005).

Description of the intervention

Iodine-131 for residual or metastatic differentiated thyroid cancer

Radioactive iodine (iodine-131, ^{131}I) is a β-/γ-emitting radionuclide with a physical half-life of 8.1 days. It has a principal γ-ray of 364 keV and a principal β-particle with a maximum energy of 0.61 MeV, giving an average energy of 0.192 MeV and a range in tissue of 0.8 mm.

In many centres iodine-131 is used following thyroidectomy for the ablation of remnant thyroid tissue (Bohuslavizki 1999; Haugen 2004; Mazzaferri 1997; Mazzaferri 2003; Sawka 2004; Schlumberger 2004) and metastatic disease in DTC (Bohuslavizki 1999; Schlumberger 1998). Iodine-131 ablation is performed in patients with DTC who have undergone total or subtotal thyroidectomy, in order to destroy the remaining thyroid tissue that may have residual microscopic cancer. Post-ablation scans may detect metastatic disease (Van Nostrand 2007; Zidan 2004). A systematic review suggested that iodine-131 ablation may be beneficial in decreasing the recurrence of DTC (Jarzab 2003). In the treatment of residual or metastatic DTC patients, increased thyroid-stimulating hormone (TSH) or thyrotropin levels are necessary to maximise selective radioiodine uptake by normal thyroid or neoplastic cells. The retention of iodine-131 by functioning thyroid tissue is believed to be optimised when serum TSH concentrations are high (30 to 50 μU/mL or more, McDougall 2001), which can be obtained either by withdrawing levothyroxine (L-T_4) or the administration of recombinant human thyroid-stimulating hormone (rhTSH).

Withdrawal of thyroid hormones to increase TSH before iodine-131 treatment

Traditionally, withdrawal of thyroid hormones for four to six weeks has been used to attain the increase in serum TSH concentrations necessary to optimise the trapping and retention of radioiodine for diagnostic procedures, thyroid remnant ablation and treatment of patients with DTC. Thyroid hormone withdrawal (THW) typically induces symptoms of hypothyroidism that often physically and psychologically constrain active people for prolonged periods of time (Dow 1997). Symptoms including cognitive impairment, emotional dysfunction and physical discomfort may significantly disrupt patients' lives, especially as a large proportion of patients are young or middle-aged and in good general health (Brans 2001; Dow 1997; Mazzaferri 2000). In the elderly, muscle weakness and cerebellar ataxia as a result of hypothyroidism can impair motion, increasing the risk of trauma (Brans 2001). Thyroid hormone withdrawal also may pose a danger of cardiac, cerebrovascular, pulmonary or neurological complications, especially in patients with co-existing disorders or metastatic involvement of these organ systems, or in frail or elderly individuals. A documented potential risk of THW is stimulation of cancer progression in tumours generally exposed to increased TSH concentrations for several weeks, both during THW and while TSH concentrations return to baseline after the resumption of thyroid hormone suppressive therapy (Jarzab 2000a; Robbins 2001; Rudavsky 1998; Vargas 1999). Indeed, this contraindication has precluded the use of iodine-131 therapy in some patients with the greatest need for such treatment (Berg 2002; Mazzaferri 2000). In addition, THW is not always effective. Even after weeks of withdrawal, TSH concentrations may not increase sufficiently in cases of persistent thyroid hormone production by large thyroid remnants or functionally active metastases, hypothalamic or pituitary dysfunction, long-term steroid administration as prophylaxis against tumour compression of key anatomical structures, or of unusually slow response, particularly in the elderly (Adler 1998; Jarzab 2003; Luster 2000a; Perros 1999).

Recombinant human thyrotropin (rhTSH) aided iodine-131 treatment

Exogenous stimulation with bovine TSH was first introduced as an alternative to withdrawal of thyroid hormones but because of frequent adverse reactions and the development of neutralising antibodies it has fallen into disuse (Schlumberger 2003). Recombinant human TSH contributes substantially to the diagnostic and therapeutic approaches to thyroid cancer, offering an alternative to THW by avoiding the morbidity of hypothyroidism. Clinical studies have shown that administration of rhTSH promotes radioiodine uptake and thyroglobulin production by thyroid cells, as achieved by THW, for diagnosing residual or recurrent cancer (Haugen 1999; Ladenson 1997; Meier 1994). In the USA and Europe, rhTSH is approved for use before thyroglobulin testing or diagnostic radioactive iodine scintigraphy in patients on thyroid hormone suppressive therapy (de Keizer 2004).

Differences in the iodine kinetics have been found in remnant ablation therapy in groups of patients with DTC after endogenous TSH stimulation by THW or after application of rhTSH (Pacini 2006). Stimulation with rhTSH not only increases iodine-131 uptake but also significantly enhances the absorbed thyroid dose. When rhTSH is used to prepare euthyroid patients, a significant lower mean residence time of radioiodine in the whole body and blood (Luster 2003; Sisson 2003) and a significantly longer half-time in the remnant thyroid tissue were observed compared to those patients who underwent THW (Pacini 2006). In studies of rhTSH-aided therapy (Barbaro 2003; Berg 2002; de Keizer 2003; Kovatcheva 2004; Jarzab 2003; Lippi 2001; Luster 2000a; Mariani 2000; Pacini 2002; Pellegriti 2001; Robbins 2002) peak serum TSH concentrations after the administration of rhTSH ranged from 42 to 400 μU/mL in euthyroid patients and from 124 to 582 μU/mL in hypothyroid patients. Limited reports show generally minimal effects of the administration of rhTSH on serum free triiodothyronine and free L-T_4 concentrations in patients with DTC and total thyroidectomy (Jarzab 2003; Luster 2000a).

Currently, rhTSH is not licensed as an adjunct to iodine-131 remnant ablation. There is a trend for widening the use of rhTSH

for residual (Barbaro 2003; Pacini 2002; Pacini 2006; Pilli 2007; Robbins 2001) or metastatic differentiated thyroid cancer (Berg 2002; de Keizer 2003; Goffman 2003; Jarzab 2000b; McDougall 2001; Muller 2002; Pellegriti 2001; Robeson 2002). This would be particularly useful in patients with insufficient or unusually slow endogenous TSH production after THW (Checrallah 2001; Colleran 1999; Luster 2000a; Masiukiewicz 1999). Recombinant human thyrotropin is also used in patients with risk of progressive disease or potentiation of tumour compression symptoms (Adler 1998; Aslam 2001; Chiu 1997; Luster 2000a; Menzel 2003; Robbins 2000; Rudavsky 1998), life-threatening or debilitating exacerbation or appearance of concomitant illness (Kovatcheva 2004; Luster 2000a; Taeb 2004) and aggravation by THW. In addition, rhTSH has been applied to patients with hyperlipidaemia (Jarzab 2003), to patients in need of very frequent treatment in order to avoid quality of life impairment of nearly unremitting hypothyroidism secondary to withdrawals (Driedger 2004), and to patients refusing to withdraw thyroid hormones (Luster 2005; Mazzaferri 2000). However, rhTSH is a particularly costly drug.

Adverse effects of the intervention

The common adverse effects of rhTSH include nausea, headache, weakness, vomiting, dizziness, tingling sensation, chills and fever. Less common adverse effects are allergic reactions including urticaria, rash, pruritus, flushing, and respiratory signs and symptoms. Moreover, mild extremity paraesthesia, pathological spine fracture (Jarzab 2003), neck tumour oedema (Berg 2002; Braga 2001; Goffman 2003; Robbins 2000; Vargas 1999), transient, moderate to severe exacerbations of bone pain in patients with bone metastases (Berg 2002; Jarzab 2003; Lippi 2001), clinical thyrotoxicosis (Jarzab 2003) and pneumonia (Rudavsky 1998) have been reported.

How the intervention might work

Radioactive iodine uptake by thyroid cells is mediated by a glycoprotein located on the cell membrane: the Na^+/ I^-symporter (NIS). The persistence of NIS expression in DTC is the rationale for the use of iodine-131 as a therapeutic agent. NIS expression, as well as thyroglobulin production and iodine uptake, are TSH-dependent. Recombinant human TSH is a heterodimeric glycoprotein produced by recombinant DNA technology. It is obtained following transfection of a microorganism with genes encoding human TSH α and β subunits; rhTSH is then purified. The amino acid sequence is identical to that of human pituitary TSH and shares some of its biochemical properties. Recombinant human TSH has been shown to stimulate thyroglobulin production and thyroid cell proliferation as well as radioactive iodine uptake by thyroid cells (Haugen 1999; Ladenson 1997; Thotakura 1991; Torres 2001; Zanotti-Fregonara 2008).

Why it is important to do this review

Recombinant human thyrotropin has the advantage of avoiding both the clinical consequences of hypothyroidism, with potential positive impacts on quality of life and work productivity, and the risk of cancer growth due to the long-lasting endogenous TSH stimulation. Unfortunately, studies which address the effects of rhTSH in DTC residual and metastatic disease treatment are still scarce and the opportunity of its clinical application remains controversial. There are currently no systematic reviews of randomised studies of rhTSH-aided iodine-131 treatment for residual or metastatic differentiated thyroid cancer.

OBJECTIVES

To assess the effects of recombinant human thyroid-stimulating hormone (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled clinical trials.

Types of participants

Patients with differentiated thyroid cancer (DTC) after total or near total thyroidectomy followed by recombinant human thyroid-stimulating hormone (rhTSH) aided iodine-131 treatment for normal remnants or metastatic DTC. The DTC diagnosis had to be pathologically established.

Types of interventions

Intervention

Recombinant human thyroid-stimulating hormone (rhTSH) aided iodine-131 treatment.

Control

Thyroid hormone withdrawal (THW) aided iodine-131 treatment.

Types of outcome measures

Primary outcomes

- ablation rate of post surgical thyroid residues;
- complete and partial remission of metastatic tumour;
- death from any cause.

Secondary outcomes

- health-related quality of life;
- radiation exposure to blood and bone marrow;
- adverse effects;
- secondary malignancy;
- thyroglobulin levels;
- costs.

Covariates, effect modifiers, confounders

- age;
- gender;
- dose of iodine-131.

Timing of outcome measurement

The follow up for ablation rate of thyroid remnants should be at least six months after administration of TSH-stimulated iodine-131 treatments.

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (Issue 2, 2009);
- MEDLINE (until November 2009); and
- EMBASE (until November 2009).

We also searched databases of ongoing trials: 'Current Controlled Trials' (www.controlled-trials.com - with links to other databases of ongoing trials). For detailed search strategies please see Appendix 1. Additional key words of relevance could have been detected during any of the electronic or other searches. If this was the case, we would have modified the electronic search strategies to incorporate these terms. Studies published in any language were included.

Searching other resources

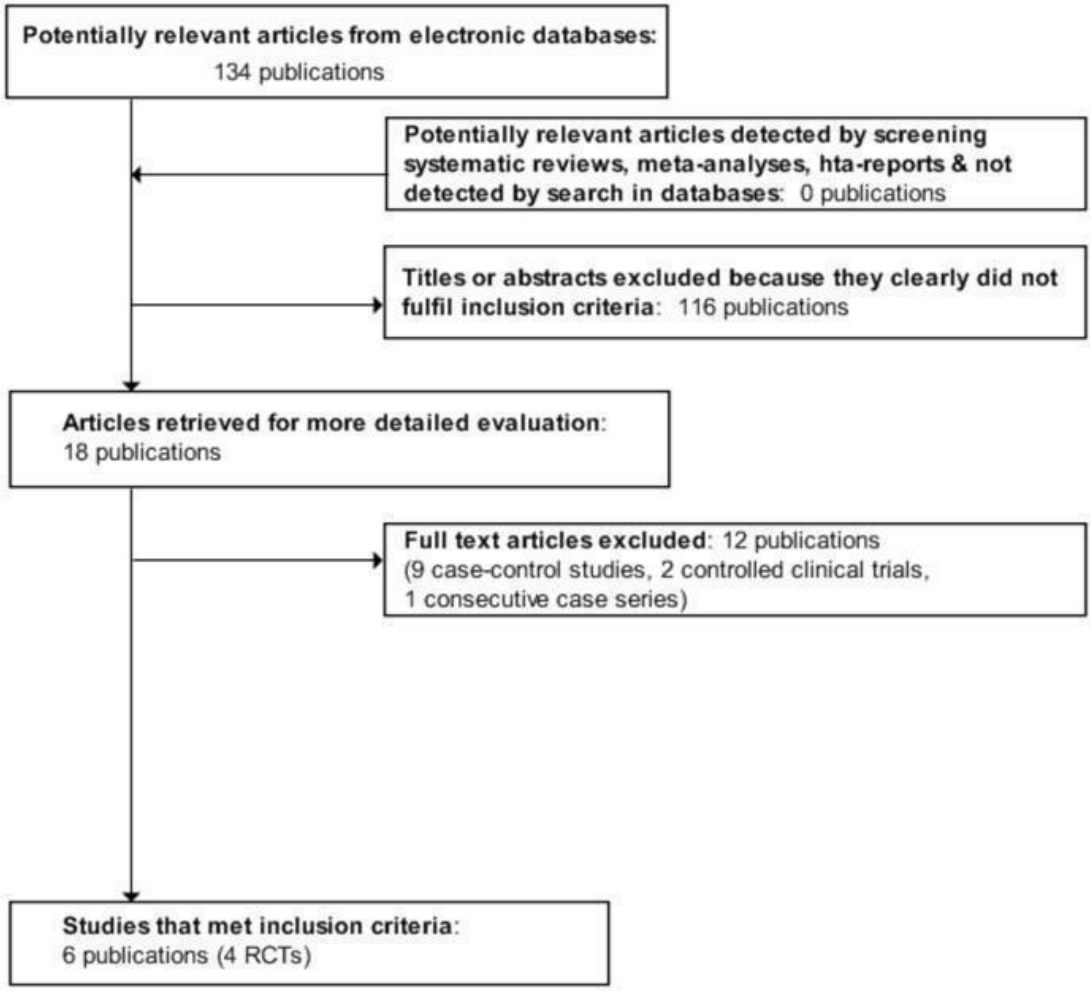
We also searched the reference lists of included trials and systematic reviews, meta-analyses and health technology assessment reports.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (MC and XJW) independently scanned the abstract, titles or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Differences were marked and if these studies were later included, we planned to subject the influence of the primary choice to a sensitivity analysis. If resolution was not possible, we added the article to those 'awaiting assessment' and contacted the authors for clarification. An adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection is attached (Figure 1; Liberati 2009).

Figure 1. Adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection



Data extraction and management

For studies that fulfilled our inclusion criteria, two authors (MC and XJW) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see 'Characteristics of included studies', Table 1 and Appendix 2) with any disagreements to be resolved by discussion, or if required by a third party. We sought any relevant missing information on the trial from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

Two authors (MC and XJW) assessed each trial independently. Possible disagreements were resolved by consensus, or with consultation of a third party in case of disagreement. We explored the influence of individual bias criteria in a sensitivity analysis (see under 'Sensitivity analysis') using the Cochrane Collaboration's 'Risk of bias' tool. In cases of disagreement, the rest of the group was consulted and a judgement was made based on consensus.

Measures of treatment effect

Dichotomous data

For dichotomous data (for example, successful ablation rate and adverse effects), we extracted the number of participants experiencing the event and the total number of participants in each arm of the trial. We used odds ratios.

Continuous data

For continuous data (for example, irradiation effects to patients), we extracted the arithmetic means and standard deviations for each group. We used mean differences.

Unit of analysis issues

We planned to describe special issues in the analysis of studies with non-standard designs, such as cluster-randomised trials.

Dealing with missing data

We obtained relevant missing data from authors, if possible. We carefully performed valuation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT) and per-protocol (PP) population. We investigated attrition rates, for example drop-outs, losses to follow up and withdrawals. We critically appraised issues of missing data and techniques used to handle these (for example, last observation carried forward (LOCF)).

Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, we did not combine study results by means of meta-analysis. We identified heterogeneity by visual inspection of the forest plots, by using a standard Chi^2 test and a significance level of α = 0.1, in view of the low power of such tests. We specifically examined heterogeneity with the I^2 statistic, where I^2 values of 30% to 60% are considered as moderate, 50% to 90% as substantial and 75% to 100% as considerable (Higgins 2008). When heterogeneity was found, we attempted to determine potential reasons by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases

We used funnel plots to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001). Therefore, we planned to interpret results carefully (Lau 2006).

Data synthesis

We summarised data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analysis according to the statistical guidelines referenced in the current version of the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2008).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

- age;
- gender;
- dose of radioiodine;
- dose of human recombinant TSH.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We planned to test the robustness of the results by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed-effect and random-effects models).

RESULTS

Description of studies

Results of the search

The electronic searches identified 134 studies. After reading the titles and abstracts, we retrieved 18 potentially relevant clinical trials for further assessment; we excluded 116 citations. Four randomised controlled clinical trials (Chianelli 2009; Pacini 2006; Pilli 2007; Vaiano 2007) were included. Duration of intervention was two days in all trials. Summary details of these trials are given in the 'Characteristics of included studies section'. We excluded 12 studies (see 'Excluded studies'). For an overview (Figure 1), please see the adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection (Liberati 2009).

Included studies

Altogether 223 patients with differentiated thyroid cancer (DTC) participated in four trials. Seventy-one patients were randomised to intervention and 80 patients to control for iodine-131 thyroid remnant ablation; 36 patients were randomised to 1850 MBq and 36 patients to 3700 MBq iodine-131 treatment, respectively. Investigators recruited 63 participants in Germany, USA, Italy and France (Pacini 2006) and 160 patients in Italy (Chianelli 2009; Pilli 2007; Vaiano 2007). Age ranged from 17 to 76 years. Inclusion and exclusion criteria were described in all trials. Three patients were lost to follow up due to the discovery of metastases on the post therapy scans and un-interpretable neck scans (Pacini 2006). According to the results mentioned in the other included trials, there were no losses to follow up (Chianelli 2009; Pilli 2007; Vaiano 2007). Apart from L-T_4 (thyroxine) replacement, co-medications and co-morbidities were not mentioned in any of the included trials.

Excluded studies

We excluded 12 studies, including nine case-control studies (Barbaro 2006; Borget 2008; Duntas 2007; Luster 2005; Montesano 2007; Pacini 2002; Robbins 2002; Tuttle 2008; Wong 2009), two non-randomised prospective controlled clinical trials (Papadimitriou 2006; Rosario 2008) and consecutive series of patients (Jarzab 2003).

Risk of bias in included studies

Four randomised controlled clinical trials were included. Three patients were lost to follow up. Details of the risk of bias evaluation are provided in the 'Risk of bias in included studies' table as well as in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

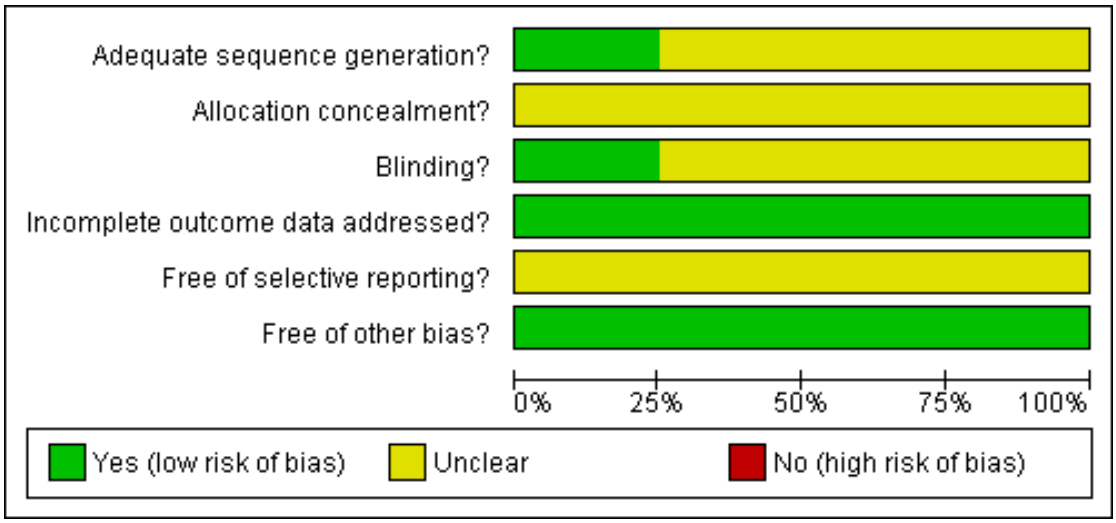
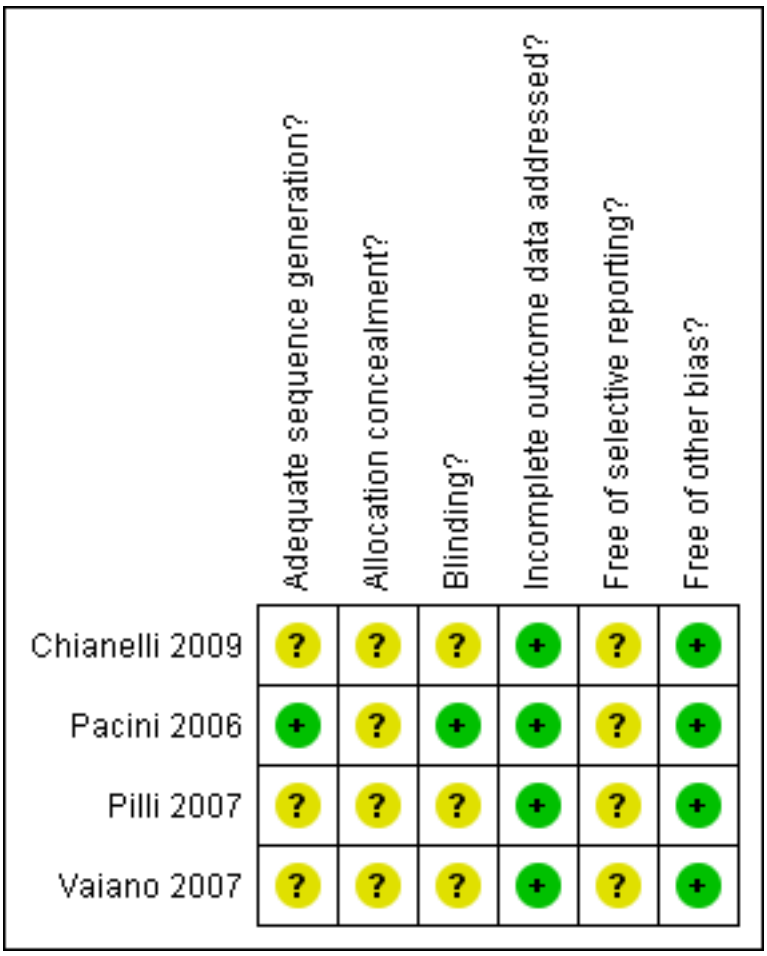


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Only one study provided details on randomisation procedures (Pacini 2006) and no study on concealment of allocation.

Blinding

Only one trial (Pacini 2006) reported blinding conditions (outcome assessors).

Incomplete outcome data

Outcome data were available for all randomised patients.

Selective reporting

Selective reporting was unclear due to non-availability of study protocols.

Other potential sources of bias

Summary data on age, gender, tumour pathology and staging were reported for all participants. No relevant differences were found between comparison groups at baseline.

Effects of interventions

Primary outcomes

Ablation rate of post surgical thyroid residues

Recombinant human thyrotropin (rhTSH) versus thyroid hormone withdrawal (THW) therapy showed no statistically significant difference in successful thyroid remnant ablation rate: 102 patients, two trials, P = 0.56 (Analysis 1.1).
In one trial, 1850 MBq iodine-131 versus 3700 MBq iodine-131 under rhTSH stimulation showed no significant difference in the thyroid remnant ablation rate: 72 patients, P = 1.0 (Analysis 1.2).

Complete and partial remission of metastatic tumour

No study compared rhTSH with THW on iodine-131 treatment for differentiated thyroid cancer (DTC) metastases.

Death from any cause

No deaths were reported in the included studies. No study reported all-cause mortality as an outcome criterion.

Secondary outcomes

Health-related quality of life

Individuals under rhTSH treatment as compared to THW therapy showed lower pretreatment scores on the Billewicz scale (Appendix 3) for hypothyroid signs and symptoms and higher Short form-36 health assessment (Appendix 4) change from baseline scores in five of eight categories (physical functioning and role, vitality, social functioning, mental health): 63 patients, one trial (Analysis 2.1).

Radiation exposure to blood and bone marrow

Recombinant human thyrotropin versus THW treatment showed statistically significant benefits on absorbed dose to blood and blood retention, red marrow dose and whole body residence time of radioiodine: 109 patients, two trials (Analysis 2.2).

Adverse effects

Recombinant human thyrotropin versus THW therapy showed no statistically significant differences in symptoms around the time of iodine-131 ablation: 63 patients, one trial (Analysis 2.3).

Secondary malignancy

No study provided data on secondary malignancies.

Thyroglobulin levels

No study reported thyroglobulin levels.

Costs

No study recorded economic data.

Compliance

A dose of 0.9 mg recombinant human thyroid-stimulating hormone (rhTSH) was injected intramuscularly on two consecutive days followed by oral administration of iodine-131 for thyroid remnant ablation. Compliance was satisfactory in the four trials.

Subgroup analyses

Subgroup analyses were not feasible due to the low number of studies.

Sensitivity analyses

Sensitivity analyses were not feasible due to the low number of studies.

Reporting bias

We did not investigate reporting bias due to the low number of studies.

DISCUSSION

Summary of main results

We included four randomised controlled clinical trials involving 223 patients. Seventy-one patients were randomised to recombinant human thyroid-stimulating hormone (rhTSH) and 80 patients to thyroid hormone withdrawal (THW) intervention; 36 patients were randomised to 1850 MBq and 36 patients to 3700 MBq radioiodine treatment, respectively. Three patients were lost to follow up and the reasons for withdrawal were reported (Pacini 2006).
We found no significant differences in successful ablation rates between rhTSH and THW-aided iodine-131 for patients with differentiated thyroid cancer (DTC). There was no death from any cause in DTC patients treated with rhTSH and THW. Recombinant human thyrotropin-aided radioiodine treatment resulted in significant benefits in some domains of health-related quality of life scales and radiation exposure to blood and bone marrow. No serious adverse events were observed in the included trials, no data on costs and secondary malignancies were reported.

Overall completeness and applicability of evidence

The four included randomised controlled clinical trials were similar at baseline regarding age, gender and tumour pathology by tumour staging. One trial studied patients with T1 staging (Chianelli 2009). Patients with T2 and T3 staging were included in one trial (Pacini 2006). The pathological staging was not mentioned in two trials (Pilli 2007; Vaiano 2007). Investigators used different dosages of iodine-131, such as 1850 MBq and 3700 MBq (Pilli 2007), 1998 MBq (Chianelli 2009) and 3700 MBq (Pacini 2006), which may lead to different therapeutic effects. The diagnostic criteria of successful thyroid remnant ablation varied in duration of follow up, the dose of diagnostic iodine-131, thyroid-stimulating hormone (TSH) stimulation and thyroglobulin (Tg) concentrations. However, there is currently no accepted standard of diagnostic criteria for successful thyroid remnant ablation. Inclusion and exclusion criteria were described in all included trials. Apart from thyroxine (L-T4) replacement, co-medications and co-morbidities were not mentioned in any of the included studies. There was no information about secondary malignancy or economic outcomes. However, decades of observation may be needed to evaluate this endpoint.

Quality of the evidence

Overall the four included studies did not provide sufficient information about some key risk of bias elements such as adequate sequence generation, allocation concealment and blinding. Outcome assessment could have been blinded but three trials did not report this blinding method (Chianelli 2009; Pilli 2007; Vaiano 2007). Calculation of sample size was not reported in one trial (Chianelli 2009). Inclusion and exclusion criteria were described in all included trials.

Potential biases in the review process

The sparse data on adverse events, health-related quality of life and different doses of iodine-131 give reason to interpret the results of this systematic review carefully.

Agreements and disagreements with other studies or reviews

The dose of iodine-131 under rhTSH stimulation for thyroid remnant ablation

The completeness of thyroid remnant ablation depends on the amount of thyroid tissue residue and the delivered radiation dose. Therefore, patients with DTC after total thyroidectomy, ideally by the same surgeons in a centre (Vaiano 2007), should be included. Uncertainty exists concerning the iodine-131 dose required to ablate post surgical remnants. Higher activities may achieve higher ablation rates (Doi 2000; Hackshaw 2007). According to the American Thyroid Association Guidelines in 2009, a dose of 1110 to 3700 MBq is recommended for low-risk patients and 3700 to 7400 MBq for high-risk patients for the first remnant ablation attempt (Cooper 2009). A dose of approximately 1850 MBq iodine-131 was used in DTC patients at low risk of recurrence (Chianelli 2009) and 3700 MBq iodine-131 in patients at high risk of recurrence (Pacini 2006). A dose of 1110 MBq iodine-131 could not achieve a satisfactory thyroid ablation rate (54%) under rhTSH in one excluded trial (Pacini 2002). A low dose of 1110 MBq was an effective remnant-ablative dose for THW patients but 3700 MBq was required to achieve this with rhTSH stimulation (Pacini 2002). However, an 81% ablation rate was observed by using 1110 MBq iodine-131 in patients at low risk with rhTSH preparation (Barbaro 2003). The minimal necessary activity of iodine-131 under rhTSH stimulation for complete ablation is higher than that under THW. In 2004, the European Agency licensed rhTSH for use in thyroid remnant ablation with 3700 MBq iodine-131. Recombinant human thyrotropin versus THW-aided 3700 MBq iodine-131 treatment in one included trial (Pacini 2006) also achieved equally satisfactory remnant ablation rates. Currently, similar successful thyroid remnant ablation rates by rhTSH (91%) versus THW (95%) stimulation were achieved by a dose of 1850 MBq iodine-131 (Chianelli 2009). A recent randomised study found no significant difference in the remnant ablation rate using 1110 or 3700 MBq iodine-131 with THW preparation (Maenpaa 2008). However, whether the low iodine-131 activity of 1850 MBq or even the lower activity of 1110 MBq should be used for thyroid remnant ablation under rhTSH stimulation remains unclear. In addition, the optimal dose of iodine-131 depends on many local factors, such as the experience of surgeons to perform total thyroidectomies, patient size and dietary iodine intake.

Recombinant human thyrotropin-aided iodine-131 treatment for thyroid remnant ablation

Two of the included trials (Chianelli 2009; Pacini 2006) in this review showed no significant differences between rhTSH and THW-aided low (1850 MBq) and high (3700 MBq) activity of iodine-131 for patients with DTC in terms of the ablation rate; this is in concordance with the results from other trials (Ladenson 1997; Luster 2005). Significant benefits on quality of life were also observed in patients prepared with rhTSH stimulation compared to THW (Ladenson 2002; Schroeder 2006). With only one included trial, the benefits on health-related quality of life under rhTSH-aided iodine-131 thyroid remnant ablation were not well documented. However, the Billewicz Scale for hypothyroid signs and symptoms, in which a higher positive score indicates a greater de-

gree of clinical hypothyroidism and Short Form-36 Health Assessment Scale (SF-36) scores, are independently validated morbidity measures. Both methods showed significantly improved quality of life in patients prepared with rhTSH. In addition to the avoidance of hypothyroidism, rhTSH-stimulated iodine-131 thyroid remnant ablation reduces average sick leave time (Emmanouilidis 2009). Similarly, a systematic review (Yoo 2009) of four studies (Barbaro 2006; Pacini 2002; Pacini 2006; Robbins 2002) revealed that rhTSH preparation is not different from THW, with a better quality of life and cost-effectiveness. Short-term recurrence rates have been found to be similar in patients prepared with THW or rhTSH (Tuttle 2008). rhTSH is approved for remnant ablation in the United States, Europe and many other countries around the world (Cooper 2009; Wartofsky 2009). The significant lower radiation effects of rhTSH than THW (Pacini 2006; Vaiano 2007) have been confirmed by two other studies (Remy 2008; Rosario 2008). Therefore, rhTSH may be recommended for thyroid remnant ablation after thyroidectomy, and it is particularly useful in patients with insufficient or unusually slow endogenous TSH production after THW (Checrallah 2001; Luster 2000a), patients with risk of progressive disease or potential of tumour compression symptoms while becoming hypothyroid (Aslam 2001; Menzel 2003) and life-threatening or debilitating exacerbation or appearance of concomitant illness (Kovatcheva 2004), and patients with hyperlipidaemia (Jarzab 2003).

Recombinant human thyrotropin-aided iodine-131 treatment for metastatic DTC

No randomised clinical controlled trials were found that compared rhTSH versus THW-aided iodine-131 treatment for metastatic differentiated thyroid cancer. Recombinant human thyrotropin-aided iodine-131 treatment for metastatic DTC has been used on a 'compassionate programme', and therapeutic effects were achieved (Jarzab 2003; Lippi 2001; Luster 2000; Robbins 2006). Recombinant human thyrotropin avoids the drawbacks of hypothyroidism at roughly equivalent societal cost to that of THW (Luster 2005). One non-randomised prospective within-patient comparison of short-term outcomes of rhTSH versus THW therapy suggested that rhTSH safely and effectively aids iodine-131 treatment for metastatic DTC (Jarzab 2003). The results of this study were biased by the introduction of re-differentiating retinoic acid therapy in some patients. A retrospective, non-randomised uncontrolled trial studied 115 patients with metastatic DTC who were either unable to elevate endogenous TSH during THW, or in whom THW was contraindicated for medical reasons (Robbins 2006). The post therapy scans under rhTSH stimulation displayed iodine-131 uptakes in 105 of the 115 patients. Recombinant human thyrotropin-aided iodine-131 treatment for metastatic DTC decreased serum Tg levels in 73% of patients. Cancer-related symptoms were improved in approximately 25%. Two patients had serious rhTSH-related adverse events. However, the results are difficult to interpret due to several potential biases, including late- or end-stage status of most of the patients enrolled, heterogeneity of patient selection, and number of consecutive treatments delivered. Therefore, the data are too limited to establish the effects of rhTSH-aided iodine-131 treatment on metastatic DTC (Pacini 2008). Hopefully, future prospective controlled studies will be carried out to establish the effects of rhTSH on iodine-131 treatment for metastatic DTC.

AUTHORS' CONCLUSIONS

Implications for practice

Results from four randomised controlled clinical trials show that recombinant human thyroid-stimulating hormone (rhTSH) is as effective as thyroid hormone withdrawal (THW) on iodine-131 thyroid remnant ablation with significant benefits in decreased whole body radiation exposure and health-related quality of life. Iodine-131 under rhTSH stimulation is recommended for thyroid remnant ablation after total or near total thyroidectomy. Further evidence is needed to confirm benefits on lower radiation dose of iodine-131 for thyroid remnant ablation.

Implications for research

High-quality randomised controlled clinical trials comparing rhTSH with THW for metastatic differentiated thyroid cancer and comparing 1110 MBq with 1850 MBq as well as 1850 MBq with 3700 MBq radioiodine therapy for thyroid remnant ablation are required. Further evidence is needed to confirm the limited data on improved health-related quality of life. The diagnostic criteria of successful thyroid remnant ablation should be based on the same diagnostic criteria in terms of duration of follow up, dose of iodine-131, thyroid-stimulating hormone stimulations, thyroglobulin concentration and measurement. In addition to the cost of rhTSH, future trials should consider other costs, such as patients' related costs, loss of work income, injections of rhTSH at home or in the hospital, transport costs or lodging expenses.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chianelli 2009

Methods	RANDOMISED CONTROLLED CLINICAL PARALLEL TRIAL RANDOMISATION RATIO: 1:1 SUPERIORITY DESIGN
Participants	WHO PARTICIPATED: Patients with PTC or minimally invasive follicular cancer, pT1 at low risk of recurrence, stage I, no positive cervical lymph nodes at the time of treatment as evaluated by ultrasound SEX (female% / male%): I: 81%/19%; C: 76%/24% AGE (mean years (SD)): I: 46.1 ± 12.3; C: 48 ± 9.9 ETHNIC GROUPS (%): Not reported DURATION OF DISEASE (mean years (SD)): Not reported INCLUSION CRITERIA: Patients with PTC or minimally invasive follicular cancer, pT1 at low risk of recurrence, stage I, no positive cervical lymph nodes at the time of treatment as evaluated by ultrasound. All patients underwent total thyroidectomy or near-total thyroidectomy and, after surgery, began treatment with a TSH suppressive dose of thyroxine. All patients adhered to a low iodine diet for 2 weeks before receiving iodine-131 EXCLUSION CRITERIA: Patients with positive Tg autoantibodies were excluded DIAGNOSTIC CRITERIA: 6 to 12 months after ablation therapy, the outcome of thyroid ablation was assessed in both groups by conventional ^{131}I scan and serum Tg measurements with THW preparation CO-MORBIDITIES: Not reported CO-MEDICATIONS: Thyroid hormone replacement
Interventions	NUMBER OF STUDY CENTRES: Single centre COUNTRY/ LOCATION: Italy SETTING: In-patients INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): rhTSH (Thyrogen) 0.9 mg i.m. for 2 consecutive days CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Thyroxine was stopped for 37 days. From the 3rd to 22nd day after thyroid hormone withdrawal patients were treated with T3

	TREATMENT BEFORE STUDY: Thyroid hormone replacement TITRATION PERIOD: None
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Ablation rate: the number of patients with no visible uptake in the thyroid bed on 48 hour iodine-131 scans (185 MBq) or thyroglobulin < 1 ng/ml under thyroid hormone withdrawal 6 to 12 months post ablation SECONDARY OUTCOMES (as stated in the publication): Thyroid uptake of iodine-131 at 24 hours ADDITIONAL OUTCOMES: Thyroid uptake of iodine-131 at 24 hours after 6 months treatment
Study details	DURATION OF INTERVENTION: 2 days DURATION OF FOLLOW UP: 6 to 12 months RUN-IN PERIOD: None
Publication details	LANGUAGE OF PUBLICATION: English NON-COMMERCIAL FUNDING PUBLICATION STATUS: peer reviewed journal
Stated aim of study	Quote: "To compare the efficacy of low-activity (2 GBq; 54 mCi) ^{131}I ablation using L-thyroxine withdrawal or rhTSH stimulation, and to assess the influence of thyroid remnants volume on the ablation rate"
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "The rate of ablation was compared in a series of consecutively enrolled patients who gave their written consent and were randomised into two groups"
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data are available for all included patients

Chianelli 2009 (*Continued*)

Free of selective reporting?	Unclear risk	-
Free of other bias?	Low risk	None detected

Pacini 2006

Methods	RANDOMISED CONTROLLED CLINICAL PARALLEL TRIAL RANDOMISATION RATIO: 1: 1 SUPERIORITY DESIGN
Participants	WHO PARTICIPATED: Patients with DTC followed by total or near-total thyroidectomy were treated with 3.7 GBq iodine-131 without preceding diagnostic scanning and after a low-iodine diet for 2 weeks SEX (female% / male%): I: 79%/21%; C: 80%/20% AGE (mean years (SD)): I: 44.5 ± 12.2; C: 43.2 ± 12.5 ETHNIC GROUPS (%): Not reported DURATION OF DISEASE (mean years (SD)): Not reported INCLUSION CRITERIA: Patients who were 18 years or older with newly diagnosed DTC and the sole previous treatment was total or near-total thyroidectomy within 2 weeks before enrolment, had T2 or T4 with minor invasion of the thyroid capsule, N0-N1, and M0 or T0-T1, N1, and M0. Also patients who had no clinically significant abnormalities of haematological or blood chemistry testing for routine analyses including serum creatinine concentration, major concurrent medical disorders including other malignancies within the past 5 years; and a recent history of drugs affecting thyroid or renal function including iodine containing medications or radiocontrast agents EXCLUSION CRITERIA: Patients with significant protocol violations, primarily due to technical problems during the measurements DIAGNOSTIC CRITERIA: Remnant ablation rate based on the diagnostic iodine-131 scan and serum Tg 8 ± 1 months post ablation. Quality of life was assessed by the Billewicz scale and Short Form-36 (SF-36) questionnaire CO-MORBIDITIES: Not reported CO-MEDICATIONS: Thyroid hormone replacement
Interventions	NUMBER OF STUDY CENTRES: 9 centres COUNTRY/ LOCATION: Germany, USA, Italy and France SETTING:

	In-patients INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): rhTSH (Thyrogen) 0.9 mg i.m. for 2 consecutive days CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Withdrawal of thyroid hormone therapy until endogenous serum TSH concentration was 25 mU/L TREATMENT BEFORE STUDY: Thyroid hormone replacement TITRATION PERIOD: None
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): 1. Ablation rate: the number of patients with no visible uptake, or if visible, less than 0.1% uptake, on 48-hour rhTSH iodine-131 WBS performed 8 ± 1 months after therapeutic iodine-131 administration 2. Quality of life SECONDARY OUTCOMES (as stated in the publication): 1. Effective half-life of ^{131}I in the remnant (hour) 2. Absorbed dose of ^{131}I to blood (mGy/MBq) 3. Residence time of ^{131}I in remnant tissue (hour) 4. 48-hour uptake of ^{131}I in remnant tissue (%) 5. Whole-body retention of ^{131}I at 48 hours (%) 6. Whole-body residence time of ^{131}I (hour) ADDITIONAL OUTCOMES: 1. Urinary iodine before ablation 2. Urinary iodine after ablation 3. Remnant uptake of iodine-131 at 48 hours (%).
Study details	DURATION OF INTERVENTION: 2 days DURATION OF FOLLOW UP: 8 ± 1 months after thyroid remnant ablation RUN-IN PERIOD: None
Publication details	LANGUAGE OF PUBLICATION: English NON-COMMERCIAL FUNDING PUBLICATION STATUS: peer reviewed journal
Stated aim of study	Quote "to determine whether thyroid remnant ablation in T4-treated euthyroid patients after preparation with rhTSH results in a comparable ablation rate to treating patients in the hypothyroid state and evaluate the safety profile of rhTSH when used for thyroid remnant ablation. Other objectives were to compare the quality of life in both groups and the uptake and retention of radioiodine in the remnant thyroid tissue as well as radiation exposure to the blood and whole body in both groups."
Notes	-

Pacini 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Patients were randomized in 1:1 ratio into the two treatment arms based on a blocked and stratified randomization scheme, with permuted blocks of 4 and stratification by site to ensure balance between the treatment arms in each site."
Allocation concealment?	Unclear risk	Quote: "A box was provided to each clinical site that contained a batch of sealed randomization envelopes numbered sequentially. On confirmation that a potential patient met all entry criteria, an envelope would be drawn, starting with the lowest number, and opened to reveal the treatment group to which the patient was assigned."
Blinding? All outcomes	Low risk	Quote: "The neck and whole-body scans performed 8 ± 1 months after ablation and 48 h after the administration of the diagnostic activity were evaluated in a blinded manner by three independent readers."
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data are available for all included patients
Free of selective reporting?	Unclear risk	No protocol data are available
Free of other bias?	Low risk	None detected

Pilli 2007

Methods	RANDOMISED CONTROLLED CLINICAL PARALLEL TRIAL RANDOMISATION RATIO: 1: 1 SUPERIORITY DESIGN
Participants	WHO PARTICIPATED: Patients with newly diagnosed DTC, more than 18 years old, recently treated by near total thyroidectomy SEX (female% / male%): I1: 80.5%/19.5%; I2: 86.1%/13.9% AGE (mean years (SD)): I1: 47.9 ± 13.9; I2: 50.5 ± 15.6 ETHNIC GROUPS (%): Not reported

	DURATION OF DISEASE (mean years (SD)): Not reported INCLUSION CRITERIA: Patients with newly diagnosed DTC, more than 18 years old, treated by near total thyroidectomy EXCLUSION CRITERIA: Patients with evidence of distant metastases and/or significant extrathyroidal invasion DIAGNOSTIC CRITERIA: The remnant ablation rate based on diagnostic iodine-131 scan and serum Tg 6 to 8 months post ablation CO-MORBIDITIES: Not reported CO-MEDICATIONS: Thyroid hormone replacement
Interventions	NUMBER OF STUDY CENTRES: Single centre COUNTRY/ LOCATION: Italy SETTING: In-patients INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): rhTSH (Thyrogen) 0.9 mg i.m. for 2 consecutive days TREATMENT BEFORE STUDY: Thyroid hormone replacement TITRATION PERIOD: None
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Ablation rate: the number of patients with no visible uptake in the 6 to 8-month iodine-131 scan under rhTSH stimulation SECONDARY OUTCOMES (as stated in the publication): None ADDITIONAL OUTCOMES: None
Study details	DURATION OF INTERVENTION: 2 days DURATION OF FOLLOW UP: 6 to 8 months after thyroid remnant ablation RUN-IN PERIOD: None
Publication details	LANGUAGE OF PUBLICATION: English NON-COMMERCIAL FUNDING PUBLICATION STATUS: peer reviewed journal

Pilli 2007 (*Continued*)

Stated aim of study	Quote "To compare the efficacy of fixed activities of 1850 vs. 3700 MBq iodine-131 for post surgical thyroid ablation in DTC patients prepared with rhTSH"
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "A total of 72 patients with DTC (66 papillary, six follicular) were enrolled and randomly assigned to receive either 1850 or 3700 MBq ^{131}I. After randomization, 36 patients received 1850 MBq (group A), and 36 received 3700 MBq (group B) ^{131}I."
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data are available for all included patients
Free of selective reporting?	Unclear risk	No protocol data are available
Free of other bias?	Low risk	None detected

Vaiano 2007

Methods	RANDOMISED CONTROLLED CLINICAL PARALLEL TRIAL RANDOMISATION RATIO: 1: 1.7 SUPERIORITY DESIGN
Participants	WHO PARTICIPATED: Patients with DTC submitted to iodine-131 therapy for ablation of thyroid remnant after total thyroidectomy SEX (female% / male%): I: 58.8%/41.2%; C: 86.2%/13.8% AGE (mean years (SD)): I: 52 ± 16; C: 46 ± 13 ETHNIC GROUPS (%): Not reported DURATION OF DISEASE (mean years (SD)): Not reported INCLUSION CRITERIA: Patients with DTC submitted to iodine-131 therapy for ablation of thyroid remnant

	after total thyroidectomy and the surgical procedure was performed by the same surgeon. It was the first iodine-131 treatment after near-total thyroidectomy EXCLUSION CRITERIA: Patients with spread of disease or involvement of red marrow or bone DIAGNOSTIC CRITERIA: Unclear CO-MORBIDITIES: Not reported CO-MEDICATIONS: Thyroid hormone replacement
Interventions	NUMBER OF STUDY CENTRES: Single centre COUNTRY/ LOCATION: Italy SETTING: In-patients INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): rhTSH (Thyrogen) 0.9 mg i.m. for 2 consecutive days CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Withdrawal of thyroid hormone 4 to 6 weeks and low-iodine diet 2 weeks before iodine-131 administration TREATMENT BEFORE STUDY: Thyroid hormone replacement TITRATION PERIOD: None
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): The outcomes were evaluated by irradiation of iodine-131 to patients on the basis of body rentention, absorbed dose in the blood and marrow post ablation, respectively 1.Red-marrow dose of ^{131}I per unit activity (mGy/MBq^{-1}) 2. Red-marrow dose of ^{131}I per unit activity due to the activity distributed in total body (mGy/MBq^{-1}) 3. Red-marrow dose of ^{131}I per unit activity due to the self-irradiation (mGy/MBq^{-1}) 4. Decay constant of radioiodine in total body (hour^{-1}) 5. Maximum radioiodine activity concentration in blood (1 hour after therapy administration) 6. Decay constant of radioiodine in blood: (hour^{-1}) SECONDARY OUTCOMES (as stated in the publication): 1. Cumulated activity per unit activity administered (hour) 2. Time to maximum uptake (hour) 3. Decay constant of radioiodine in post-surgical remnant (hour^{-1}) ADDITIONAL OUTCOMES: None
Study details	DURATION OF INTERVENTION: 2 days DURATION OF FOLLOW-UP: From 3 to 72 hours after iodine-131 ablation RUN-IN PERIOD:

Vaiano 2007 (*Continued*)

	None
Publication details	LANGUAGE OF PUBLICATION: English NON-COMMERCIAL FUNDING PUBLICATION STATUS: peer reviewed journal
Stated aim of study	Quote "To evaluate if the pre-therapy rhTSH and thyroid hormone withdrawal treatments are equivalent from a dosimetric point of view in patients submitted to ^{131}I post-surgical remnant ablation."
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "The patients were randomly divided into two groups."
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data are available for all included patients
Free of selective reporting?	Unclear risk	No protocol data are available
Free of other bias?	Low risk	None detected

C: control (thyroid hormone withdrawal); DTC: differentiated thyroid cancer; I: intervention (rhTSH); I1: 1850 MBq iodine-131; I2: 3700 MBq iodine-131; i.m.: intramuscular; L-T3: triiodothyronine; M0: pathological distant metastasis-negative; N0: pathological lymph node metastasis-negative; N1: pathological lymph node metastasis-positive; pT: pathological classification of the primary tumour; PTC: papillary thyroid cancer; rhTSH: recombinant human thyroid-stimulating hormone; ROI: region of interest; Tg: thyroglobulin; THW: thyroid hormone withdrawal; TSH: thyroid-stimulating hormone; WBS: whole body scan; u: unknown

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barbaro 2006	Case-control trial
Borget 2008	Case-control trial
Duntas 2007	Case-control trial
Jarzab 2003	Consecutive series of patients
Luster 2005	Case-control trial
Montesano 2007	Case-control trial
Pacini 2002	Case-control trial
Papadimitriou 2006	Non-randomised prospective controlled clinical trial
Robbins 2002	Case control trial
Rosario 2008	Non-randomised prospective controlled clinical trial
Tuttle 2008	Case-control trial
Wong 2009	Case-control trial

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Successful ablation rate	2	102	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.68]
2 Ablation by 1850 MBq vs 3700 MBq iodine-131 under rhTSH stimulation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Health-related quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Physical functioning	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Physical functioning role	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Bodily pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 General health	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Vitality	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Social functioning	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Emotional functioning role	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 Mental health	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 Mental component summary	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 Physical component summary	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Radiation exposure to blood and bone marrow	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Absorbed dose to blood (mGy/MBq)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Whole body residence time (h)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 The red marrow dose per unit activity (mGy MBq^{-1})	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Blood retention at 48h	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Red-marrow dose per unit activity due to the activity distributed in total body (mGy MBq^{-1})	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Red-marrow dose per unit activity due to the self-irradiation (mGy MBq^{-1})	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Successful ablation rate.

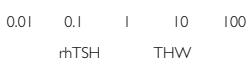
Review: Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

Comparison: 1 Primary outcomes

Outcome: 1 Successful ablation rate

Study or subgroup	rhTSH n/N	THW n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Chianelli 2009	19/21	20/21		100.0 %	0.48 [0.04, 5.68]
Pacini 2006	28/28	32/32			Not estimable
Total (95% CI)	**49**	**53**		**100.0 %**	**0.48 [0.04, 5.68]**

Total events: 47 (rhTSH), 52 (THW)
Heterogeneity: not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



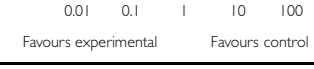
Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Ablation by 1850 MBq vs 3700 MBq iodine-131 under rhTSH stimulation.

Review: Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

Comparison: 1 Primary outcomes

Outcome: 2 Ablation by 1850 MBq vs 3700 MBq iodine-131 under rhTSH stimulation

Study or subgroup	3700 MBq iodine-131 n/N	7400MBq iodine-131 n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Pilli 2007	32/36	32/36			1.00 [0.23, 4.35]



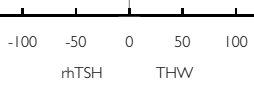
Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Health-related quality of life.

Review: Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

Comparison: 2 Secondary outcomes

Outcome: 1 Health-related quality of life

Study or subgroup	rhTSH N	Mean(SD)	THW N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Physical functioning						
Pacini 2006	33	84.5 (18.3)	30	57.8 (29.4)		26.70 [14.47, 38.93]
2 Physical functioning role						
Pacini 2006	33	58.3 (38.9)	30	22.5 (34.3)		35.80 [17.72, 53.88]
3 Bodily pain						
Pacini 2006	33	67.4 (23.6)	30	55 (22.4)		12.40 [1.04, 23.76]
4 General health						
Pacini 2006	33	66.1 (20.8)	30	61.6 (21.2)		4.50 [-5.89, 14.89]
5 Vitality						
Pacini 2006	33	54.5 (22.5)	30	36.4 (21.3)		18.10 [7.28, 28.92]
6 Social functioning						
Pacini 2006	33	74.2 (21.4)	30	53.3 (28.4)		20.90 [8.39, 33.41]
7 Emotional functioning role						
Pacini 2006	33	57.6 (44.3)	30	31.3 (41)		26.30 [5.24, 47.36]
8 Mental health						
Pacini 2006	33	71 (20.1)	30	58.8 (16.5)		12.20 [3.15, 21.25]
9 Mental component summary						
Pacini 2006	33	45.2 (11.9)	30	38.5 (9.8)		6.70 [1.34, 12.06]
10 Physical component summary						
Pacini 2006	33	47.6 (7.7)	30	40 (9.9)		7.60 [3.19, 12.01]



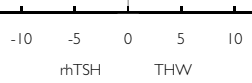
Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Radiation exposure to blood and bone marrow.

Review: Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

Comparison: 2 Secondary outcomes

Outcome: 2 Radiation exposure to blood and bone marrow

Study or subgroup	rhTSH N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Absorbed dose to blood (mGy/MBq)						
Pacini 2006	33	0.109 (0.028)	30	0.17 (0.061)		-0.06 [-0.08, -0.03]
2 Whole body residence time (h)						
Pacini 2006	33	17.3 (3.9)	30	24.1 (7.8)		-6.80 [-9.89, -3.71]
3 The red marrow dose per unit activity (mGy MBq^{-1})						
Vaiano 2007	17	0.06 (0.02)	29	0.09 (0.03)		-0.03 [-0.04, -0.02]
4 Blood retention at 48h						
Pacini 2006	33	0.78 (0.78)	30	1.79 (1.71)		-1.01 [-1.68, -0.34]
5 Red-marrow dose per unit activity due to the activity distributed in total body (mGy MBq^{-1})						
Vaiano 2007	17	0.04 (0.01)	29	0.06 (0.02)		-0.02 [-0.03, -0.01]
6 Red-marrow dose per unit activity due to the self-irradiation (mGy MBq^{-1})						
Vaiano 2007	17	0.022 (0.006)	29	0.03 (0.009)		-0.01 [-0.01, -0.01]

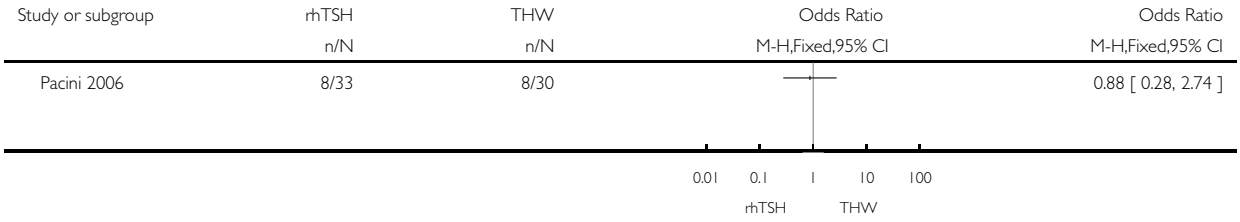


Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Adverse events.

Review: Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer

Comparison: 2 Secondary outcomes

Outcome: 3 Adverse events



ADDITIONAL TABLES

Table 1. Overview of study populations

Study ID	Intervention	[n] Screened	[n] Randomised	[n] Safety	[n] ITT	[n] Finishing study	[%] of randomised participants finishing study	Comments
Pacini 2006	I: recombinant human thyrotropin-aided radioiodine treatment C: thyroid hormone withdrawal	I: 33 C: 30 Total: 63	I: 33 C: 30 Total: 63	I: 33 C: 30 Total: 63	I: 33 C: 30 Total: 63	I: 32 C: 28 Total: 60	I: 97 C: 93 Total: 95	In the hypothyroid group (thyroid hormone withdrawal), 2 patients were excluded from the final analysis: 1 due to discovery of lung metastases on the post therapy whole-body

Table 1. Overview of study populations (*Continued*)

								scan and 1 because the neck scan was un-interpretable due to a positioning error. In the rhTSH group, 1 patient was ineligible for the final analysis due to a mistake in the reconstitution of 1 rhTSH dose in preparation for radioiodine ablation
Pilli 2007	I1: recombinant human thyrotropin-aided 1850 MBq radioiodine treatment I2: recombinant human thyrotropin-aided 3700 MBq radioiodine treatment	I1: 36 I2: 36 Total: 72	I1: 36 I2: 36 Total: 72	I1: 36 I2: 36 Total: 72	I1: 36 I2: 36 Total: 72	I1: 36 I2: 36 Total: 72	I1: 100 I2: 100 Total: 100	-
Vaiano 2007	I: recombinant human thyrotropin-aided radioiodine treatment C: thyroid hormone withdrawal	I: 17 C: 29 Total: 46	I: 17 C: 29 Total: 46	I: 17 C: 29 Total: 46	I: 17 C: 29 Total: 46	I: 17 C: 29 Total: 46	I: 100 C: 100 Total: 100	-

Table 1. Overview of study populations (*Continued*)

Chianelli 2009	I: recombinant human thyrotropin-aided radioiodine treatment C: thyroid hormone withdrawal	I: 21 C: 21 Total: 42	I: 21 C: 21 Total: 42	I: 21 C: 21 Total: 42	I: 21 C: 21 Total: 42	I: 21 C: 21 Total: 42	I: 100 C: 100 Total: 100	-
Total			*I: 143 C: 80 Total: 223*			*I: 142 C: 78 Total: 220*		

C: control; I: intervention; ITT: intention-to-treat; rhTSH: recombinant human thyroid-stimulating hormone

APPENDICES

Appendix 1. Search strategies

Search terms
Unless otherwise stated, search terms are free-text terms; MeSH = Medical subject heading (MEDLINE medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent
The Cochrane Library
#1 MeSH descriptor Thyroid Neoplasms explode all trees
#2 (thyroid in All Text near/6 cancer in All Text)
#3 (thyroid in All Text near/6 carcinom* in All Text)
#4 (thyroid in All Text near/6 tumo?r* in All Text)
#5 (thyroid in All Text near/6 neoplasm* in All Text)
#6 (thyroid in All Text near/6 metastas* in All Text)
#7 DTC in All Text
#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9 (recombinant in All Text and human in All Text and thyreotropin* in All Text)
#10 rhTSH in All Text
#11 (#9 or #10)
#12 (radioiodin* in All Text near/6 treatment* in All Text)
#13 (radioiodin* in All Text near/6 therap* in All Text)
#14 (radioiodin* in All Text near/6 intervention* in All Text)

(*Continued*)

#15 (131J in All Text or (131 in All Text and J in All Text) or 131I in All Text or (131 in All Text and I in All Text))
#16 MeSH descriptor Iodine Radioisotopes explode all trees with qualifiers: TU
#17 MeSH descriptor Radiopharmaceuticals explode all trees with qualifiers: TU
#18 MeSH descriptor Thyroidectomy explode all trees
#19 MeSH descriptor Thyrotropin explode all trees
#20 (thyroidectom* in All Text or TSH in All Text or thyreotrop?in* in All Text)
#21 (#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#22 (#8 and #11 and #21)

MEDLINE
1. exp Thyroid Neoplasms/
2. (thyroid adj6 (cancer or carcinom$ or tumo?r$ or neoplasm$ or metastas$)).ab,ti,ot.
3. DTC.ab,ti,ot.
4. or/1-3
5. recombinant human thyrotrop?in.ab,ti,ot.
6. rhTSH.ab,ti,ot.
7. 5 or 6
8. (radioiodine adj6 (treatment$ or therap$ or intervention$)).ab,ti,ot.
9. (131J or J131 or I131 or 131I).ab,ti,ot
10. exp Iodine Radioisotopes/tu [Therapeutic Use]
11. exp Radiopharmaceuticals/ [Therapeutic Use]
12. exp Thyroidectomy/
13. exp Thyrotropin/
14. (thyroidectom$ or TSH or thyreotrop?in$ or thyrotrop?in$).ab,ti,ot.
15. or/8-14
16. 7 and 15
17. 4 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. Meta-analysis.pt.
28. exp Technology Assessment, Biomedical/
29. exp Meta-analysis/
30. exp Meta-analysis as topic/
31. hta.tw,ot.
32. (health technology adj6 assessment$).tw,ot.
33. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
34. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot.
35. or/27-34
36. (comment or editorial or historical-article).pt.
37. 35 not 36
38. 26 or 37

(*Continued*)

39. 17 and 38

EMBASE
1. exp Thyroid Tumor/
2. (thyroid adj6 (cancer or tumo?r$ or neoplasm$ or metastas$)).ab,ti,ot.
3. DTC.ab,ti,ot.
4. or/1-3
5. (recombinant human adj6 (thyrotropin$ or thyreotropin$)).ab,ti,ot.
6. rhTSH.ab,ti,ot.
7. 5 or 6
8. (radioiodine adj6 (treatment$ or therap$ or intervention$)).ab,ti,ot.
9. (131J or J131 or I131 or 131I).ab,ti,ot.
10. exp Radioactive Iodine/
11. exp Radiopharmaceutical Agent/dt [Drug Therapy]
12. exp Radiopharmaceutical Agent/
13. exp Thyroidectomy/ or exp Subtotal Thyroidectomy/
14. exp Thyrotropin/
15. (thyroidectom$ or TSH or thyreotropin$).ab,ti,ot.
16. or/8-15
17. 4 and 7 and 16
18. exp meta analysis/
19. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
20. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
21. exp Literature/
22. exp Biomedical Technology Assessment/
23. hta.tw,ot.
24. (health technology adj6 assessment$).tw,ot.
25. or/18-24
26. (comment or editorial or historical-article).pt.
27. 25 not 26
28. exp Randomized Controlled Trial/
29. exp Controlled Clinical Trial/
30. exp Clinical Trial/
31. exp Comparative Study/
32. exp Drug comparison/
33. exp Major clinical trial/ 34. exp Randomization/
35. exp Crossover procedure/
36. exp Double blind procedure/
37. exp Single blind procedure/
38. exp Placebo/
39. exp Prospective Study/
40. ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
41. (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
42. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
43. (cross over or crossover).ab,ti.
44. or/28-43
46. 27 or 44
47. 17 and 46

Appendix 2. Adverse events

Characteristic	Pacini 2006	Pilli 2007	Vaiano 2007	Chianelli 2009
Intervention (I) Control (C)	I: rhTSH C: THW	I1: 1850 MBq I2: 3700 MBq	I: rhTSH C: THW	I: rhTSH C: THW
Deceased patients [n]	I: 0 C: 0 Total: 0	I1: 0 I2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Adverse events [n / %]	I: 0 C: 0 Total: 0	I1: 0 I2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Serious adverse events [n / %]	I: 0 C: 0 Total: 0	I1: 0 I2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Drop-outs due to adverse events [n / %]	I: 0 C: 0 Total: 0	I1: 0 I2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Hospitalisation [n / %]	I: 0 C: 0 Total: 0	I1: 0 I2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Out-patient treatment [n / %]	I: 0 C: 0 Total: 0	I1: u I2: u Total: u	I: u C: u Total: u	I: 0 C: 0 Total: 0
Symptoms [n / %]	I: 8/24(33%) C: 8/27 (30%) Total: 16/51 (31%)	I1: u I2: u Total: u	I: u C: u Total: u	I: 0 C: 0 Total: 0

Footnotes
rhTSH: recombinant human thyroid-stimulating hormone; THW: thyroid hormone withdrawal; u: unclear

Appendix 3. Billewicz scale for scoring of symptoms and signs of hypothyroidism

Billewicz scale	
Symptoms **Physical signs**	Diminished sweating, dry skin, cold intolerance, weight increase, constipation, hoarseness, paranaesthesia, deafness (8 items) Slow movements, coarse skin, cold skin, periorbital puffiness, pulse rate, ankle jerk (6 items)
Validated instrument	Yes

(*Continued*)

Possible answers	3-level response choices
Minimum score	-53
Maximum score	72
Direction of scale	Patients with hypothyroidism have higher index scores than those with euthyroid status. Scores below -30 indicate euthyroidism, above 30 hypothyroidism
Minimal important difference	Not evaluated

Appendix 4. Short form-36 (SF-36) health-related quality of life questionnaire

SF-36 questionnaire	
Physical health (physical functioning, physical role, bodily pain, general health) **Mental health** (vitality, social functioning, emotional role, mental health)	Physical functioning (10 items), physical role (4 items), bodily pain (2 items), general health (5 items) Vitality (4 items), social functioning (2 items), emotional role (3 items), mental health (5 items)
Mental component summary	35
Validated instrument	Yes
Possible answers	5-level response choices
Minimum score	0
Maximum score	100
Direction of scale	Scores above 50 are better than the general population average for all scales, while scores below 50 are worse
Minimal important difference	Not evaluated

CONTRIBUTIONS OF AUTHORS

CHAO MA: Drafting the protocol/review, data selection and analysis.

JIAWEI XIE: Drafting and co-drafting of the protocol/review.

WANXIA LIU: Searching, selection of studies.

GUOMING WANG: Assistance with data selection.

SHUYAO ZUO: Searching, selection of studies.

XUFU WANG: Searching, selection of studies.

FENGYU WU: Searching, selection of studies.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- West China Hospital Evidence-Based Medicine Center, China.

External sources

- West China Hospital Evidence-Based Medicine Center, China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Interrater agreement for study selection and evaluation of key risk of bias elements using the kappa statistic mentioned in the protocol was not performed in this review.

The planned subgroup analysis of 'dose of human recombinant TSH' was not carried out because a dose of 0.9 mg human recombinant thyrotropin is routinely used.

INDEX TERMS

Medical Subject Headings (MeSH)

Hypothyroidism [prevention & control]; Iodine Radioisotopes [*therapeutic use]; Neoplasm, Residual; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]; Thyroid Neoplasms [pathology; *radiotherapy]; Thyrotropin [*therapeutic use]

MeSH check words

Humans