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[Intervention Review]

Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases

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ABSTRACT

Background

Differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases has been observed in follow-up studies. The management of this condition remains controversial. Most studies support blind radioactive iodine treatment while others negate this approach.

Objectives

To assess the effects of radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.

Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE, *The Cochrane Library*, China National Infrastructure (CNKI) and paper collections of conferences held in Chinese.

Selection criteria

Randomised controlled clinical trials and prospective controlled clinical trials.

Data collection and analysis

Two authors independently extracted data and interviewed authors of all potentially relevant studies by electronic mail to verify randomisation procedures. One author entered data into a data extraction form and the second one verified the results of this procedure.

Main results

Because of the absence of any suitable randomised or prospective controlled trial in this area, results currently cannot be presented.

Authors' conclusions

The currently available evidence is insufficient to reliably assess the potential of radioiodine treatment for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.

PLAIN LANGUAGE SUMMARY

Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases

The main method for the treatment of differentiated thyroid carcinomas (a cancer of the thyroid gland) is total or near-total thyroidectomy (surgical removal of the thyroid) followed by radioactive iodine therapy (iodine-131) and treatment with thyroid hormones (mainly thyroxine). The metastatic disease of this thyroid carcinoma or spread of the tumour includes local recurrence and distant metastases. Metastatic disease is a factor that worsens prognosis of patients with differentiated thyroid carcinoma. After surgery or as the primary treatment, located metastases should, if possible, be removed by an experienced surgeon. For unremovable metastases which can gather radioiodine, iodine-131 therapy is an accepted procedure.

Differentiated thyroid carcinoma is typically able to produce thyroglobulin, the protein in the thyroid gland from which the thyroid hormones thyroxine and triiodotyrosine are synthesized, and gather radioiodine. Thyroglobulin is produced only by thyroid cells. If all normal and malignant thyroid tissue is successfully removed, any thyroglobulin subsequently detected in a patient with differentiated thyroid carcinoma is thought to be the product of recurrent malignancy. Thus, radioiodine diagnostic whole-body scanning and measurement of serum thyroglobulin levels are the two main methods for detecting metastatic disease of differentiated thyroid carcinoma. Undetectable thyroglobulin levels with negative radioiodine whole body scan suggest complete remission, whereas detectable or elevated thyroglobulin is associated with the presence of radioiodine uptake in local or distant metastases.

Up to now, to treat or not to treat these patients who have thyroglobulin positive and radioactive iodine negative metastases with radioiodine remains controversial. Some doctors advocate blind iodine-131 treatment for thyroglobulin positive and radioactive iodine negative metastases. Radioiodine therapy may be especially justified in patients with higher thyroglobulin levels (greater than 10 mg/L) and negative iodine-131 whole body scan and who are at high risk of any recurrence. However, high-dose radioactive iodine therapy is not without risk; especially an increased prevalence of cancers of the bladder, salivary gland, colon and female breast has been reported.

Unfortunately, no firm evidence from randomised or prospective controlled trials for or against radioiodine treatment for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases could be found. Further prospective controlled trials of high-quality and large scale are needed to guide clinical practice.

BACKGROUND

Description of the condition

Metastatic disease of differentiated thyroid carcinoma

Clinically detectable thyroid carcinomas constitute less than one percent of all human cancers. The annual incidence rate of thyroid cancers in various parts of the world ranges from 0.5 to 10 cases per 100,000 population (Schlumberger 1998). Most thyroid cancers are differentiated papillary or follicular carcinomas arising from follicular cells. The predominant method for treatment of differentiated thyroid carcinomas is total or near-total thyroidectomy followed by iodine-131 remnant ablation and thyroxine therapy (Holzer 2000; Hundahl 2000). Metastatic disease of differentiated thyroid carcinoma includes local recurrence and distant metastases. Metastatic disease is a factor that worsens prognosis of patients with differentiated thyroid carcinoma. Fortunately, differentiated thyroid carcinoma has an excellent prognosis, despite the presence of lymph-node metastases in 5% to 20% of patients and distant metastases in 10% to 15%. Ten-year survival is 80% to 95% (Mackenzie 2004). After surgery or as the primary treatment, the metastases of differentiated thyroid carcinoma should be debulked by an experienced surgeon, where practical. For unresectable metastases which can accumulate radioiodine, iodine-131 therapy has been a commonly accepted procedure.

Detection of metastatic disease of differentiated thyroid carcinoma

Patients with differentiated thyroid carcinoma are at a high risk of local recurrence and distant metastases. Therefore, it is essential to carry out a long-term follow-up throughout the patient's life. Differentiated thyroid carcinoma is typically well differentiated to be able to synthesize thyroglobulin, the protein in the thyroid gland from which the thyroid hormones thyroxine and triiodotyrosine are synthesized, and accumulate radioiodine. Thus, radioiodine diagnostic whole-body scanning and measurement of serum thyroglobulin levels are the two main methods for detecting metastatic disease of differentiated thyroid carcinoma. Generally, thyroglobulin and iodine-131 whole body scan, two 'markers' of differentiated thyroid carcinoma when utilized at the same time, are usually correlated with each other in follow-up studies (Ozata 1994; Pacini 1999). Undetectable thyroglobulin levels with negative radioiodine whole body scan suggest complete remission, whereas detectable or elevated thyroglobulin is associated with the presence of radioiodine uptake in local or distant metastases.

About 10% to 15% thyroglobulin positive and radioactive iodine negative metastases have been reported in large series (Brendel 1990; De Keizer 2001; Koh 2003; Mazzaferri 2001; Mertens 1999; Muller-Gartner 1988; Pacini 2001; Pineda 1995; Schlumberger 1997). Differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases may result from the hypothesis that thyroglobulin synthesis and radioiodine uptake reflect different functions of thyroid tissues. The serum thyroglobulin levels may not predict radioiodine uptake, nor does radioiodine uptake predict thyroglobulin levels (Ozata 1994). For example, Hurthle cell carcinomas may be able to synthesize thyroglobulin but have poor radioiodine uptake capability (Stojadinovic 2001). Radioactive iodine negative metastases may be due to the loss of differentiation, or dispersed microscopic metastases which are too small to be visualized (Chao 2005-1;

Fatourechi 2000; Sherman 1994) or improper patient preparation before radioiodine whole body scan. For a detailed overview of differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases, readers are referred to Chao et al (Chao 2005-1; Chao 2005-2).

Description of the intervention

Radioiodine is a β -, γ -emitting radionuclide with a physical half-life of 8.1 days, a principal γ -ray of 364 keV, and a principal β -particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. At present, iodine-131 is the most commonly used radioactive iodine for the management of metastatic disease of differentiated thyroid cancer (Schlumberger 1998). Therapy is applied through oral administration of iodine-131 as sodium iodide.

Up to now, to treat or not to treat these patients who have thyroglobulin positive and radioactive iodine negative metastases with radioiodine remains controversial (Fatourech 2002; McDougall 1997; Pacini 2001; Samaan 1985). Thyroglobulin is produced only by thyroid follicular cells. If all normal and malignant thyroid tissue is successfully ablated, any thyroglobulin subsequently detected in a patient with differentiated thyroid carcinoma can only be the product of recurrent malignancy. This concept led to the initial studies that indicated the usefulness of isolated and serial serum thyroglobulin determinations as a marker for differentiated thyroid carcinoma and as an indicator of the effect of surgical and iodine-131 therapy (Clark 2002; Spencer 1996). Therefore, some researchers (De Keizer 2001; Koh 2003; Pacini 1987; Pineda 1995; Schlumberger 1988; Tian 2003; Van Tol 2003) advocate blind iodine-131 treatment for thyroglobulin positive and radioactive iodine negative metastases based on the improvement in various parameters of disease activity, such as significant reduction of serum thyroglobulin and the detection of neoplastic foci not seen with diagnostic doses of iodine-131. However, a low or even undetectable thyroglobulin offers no guarantee for the absence of recurrent or metastatic disease (Brendel 1990; Maxon 1983).

When thyroglobulin level is considered as an index of tumour burden, a decreased thyroglobulin level in 63% of patients with thyroglobulin positive and radioactive iodine negative metastases and the 62% positive post-therapy whole-body scanning results suggest a therapeutic effect of iodine-131. Therefore, radioiodine therapy may be justified in patients with thyroglobulin levels of greater than 10 mg/L and negative iodine-131 diagnostic whole body scan and who are at high risk of any recurrence (Chao 2005-2).

Adverse effects of the intervention

Risks for differentiated thyroid carcinoma-related morbidity or mortality have not been well described, particularly for patients without evidence of tumour mass by other imaging modalities (Alexandre 1998). Furthermore, high-dose radioactive iodine therapy is not without risk. An increased prevalence of cancers of the bladder, salivary gland, colon (de Vathaire 1997), and female breast has been reported.

How the intervention might work

Some authors (Cailleux 2000; De Keizer 2001; Koh 2003; Mazzaferri 2001; Pacini 1987; Pineda 1995; Schlumberger 1997; Tian 2003; Tenenbaum 1996; Van Tol 2003) are in favour of an empiric

iodine-131 therapy on the basis of improvements in various parameters of disease activity.

First, thyroglobulin levels measured after iodine-131 thyroid remnant ablation are a well-known marker of tumour course. An elevated thyroglobulin level correlates well with persistent disease (Pacini 2001). Because the production of thyroglobulin and the incorporation of radioactive iodine represent distinct differentiated functions of follicular cells, differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases is suspected by the presence of detectable serum thyroglobulin in the absence of iodine-131 uptake. Serum thyroglobulin measurement is more sensitive than a diagnostic radioiodine whole body scan for the detection of recurrences and metastases (DeGroot 1990; Mazzaferri 2003; Sherman 1998; van den Bergh 1993), even in patients with negative radioiodine whole body scans (Brendel 1990; Koh 2003; Pineda 1995). A significant reduction in the thyroglobulin level can be obtained after iodine-131 therapy. In patients with positive thyroglobulin and negative radioiodine whole body scan, an elevation in the thyroglobulin level may be the first evidence (Black 1991; Pineda 1993; Sherman 1994) or the only method by which metastatic or recurrent disease is detected (Schlumberger 1988). Pacini et al (Pacini 2001) compared the changes in serum thyroglobulin levels between treated and untreated patients with differentiated thyroid carcinoma; they noted a reduction in thyroglobulin levels and a disappearance of lung uptake with repeated therapy, and they recommended treating all patients with positive thyroglobulin and negative diagnostic radioiodine whole body scan once with 3700 MBq of radioactive iodine and continuing therapy until post-therapy whole body scan results become negative. Pineda et al (Pineda 1995) noted that in a significant proportion of patients (50%), the therapeutic effectiveness of radioactive iodine treatment is indicated by a conversion to negative radioiodine whole body scan, a statistically significant decrease in the mean thyroglobulin level, and a reduction in the serum thyroglobulin level to 5 ng/mL or less. These studies suggest that empiric radioactive iodine therapy may be useful for diffuse lung uptake, especially in young and middle-aged patients with negative chest radiographs and diagnostic negative radioiodine whole body scans.

Second, a therapeutic dose of radioactive iodine increases the sensitivity of the radioiodine whole body scan and allows the detection of neoplastic foci not seen with a diagnostic dose of radioactive iodine (Cailleux 2000; Pacini 1987; Pacini 2001; Pineda 1993; Schlumberger 1997).

Third, the poor prognosis of patients with metastatic differentiated thyroid carcinoma will be improved if it is detected and treated with radioactive iodine early rather than late (Schlumberger 1999). More importantly, radioactive iodine therapy is effective mostly in patients with small foci of recurrent disease. Negative radioiodine whole body scan was successfully treated with high doses of radioactive iodine after the administration of recombinant human thyroid stimulating hormone (Rudavsky 1997). Controlled clinical studies are warranted to evaluate the safety and efficacy of recombinant human thyroid stimulating hormone in the radioactive iodine therapy of metastatic differentiated thyroid carcinoma.

Why it is important to do this review

For the time being, there is no consensus as to radioactive iodine therapy for thyroglobulin positive and radioactive iodine negative metastases in differentiated thyroid carcinoma. The use of radioiodine treatment has been associated with marked benefits. However, the quality and the effects of these trials have not been systematically reviewed and assessed. Therefore, this review aims to summarise the existing evidence of the comparative effects and safety of radioiodine treatment for thyroglobulin positive and radioactive iodine negative metastases.

OBJECTIVES

To assess the effects of radioactive iodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to consider randomised controlled clinical trials and prospective controlled clinical trials with a duration of follow-up of at least one year.

Types of participants

The diagnosis of differentiated thyroid carcinoma had to be established according to the definite pathophysiological evaluation of the surgical specimen. Trials which included patients of any age or sex who suffered from differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases after total or near-total thyroidectomy followed by iodine-131 remnant ablation and L-thyroxine suppression therapy were eligible. Patients with positive anti-thyroglobulin antibodies were excluded.

Diagnostic criteria

The thyroglobulin value "off L-thyroxine therapy" equal to or greater than 10 ng/mL or "on L-thyroxine therapy" equal to or greater than 1 to 5 ng/mL (according to the sensitivity of the test) is defined as positive in the absence of circulating anti-thyroglobulin antibodies. The thyroglobulin value off "on-L-thyroxine therapy", equal to or less than 1 to 5 ng/mL (according to the sensitivity of the test) is regarded as undetectable in the absence of circulating anti-thyroglobulin autoantibodies.

Radioactive iodine negative metastases in all cases had to be established by the conventional whole body scan performed 48 to 72 hrs after administration of a tracer dose of 5 to 10 mCi radioactive iodine.

Types of interventions

Trials evaluating radioactive iodine treatment versus control interventions or no treatment.

Types of outcome measures

Primary outcomes

- survival rate at the end of follow-up;
- tumour size at the end of follow-up;

- adverse effects (for example, irradiation-induced genetic defects, infertility, carcinogenesis and leukemogenesis) (De Keizer 2001; Hyer 2002; Schlumberger 1998) - the number of patients developing at least one severe adverse event listed above will be evaluated).

Secondary outcomes

- serum thyroglobulin concentration at the end of follow-up or positive rate of post-therapy radioactive iodine whole body scan;
- mortality related to differentiated thyroid carcinoma or iodine-131 within the duration of whole follow-up period and all-cause mortality;
- healthy-related quality of life, ideally measured by using a validated instrument;
- costs;
- symptoms of hypothyroidism (for example, reproductive failure/infertility, myxoedema, tiredness, lethargy, slowing of mental function, cold intolerance, cardiac complications).

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 1, 2008);
- MEDLINE (until May 2008);
- EMBASE (until May 2008).

The described search strategy (for a detailed search strategy see [Appendix 1](#)) was used for MEDLINE. For use with EMBASE and the other databases this strategy was slightly adapted. We also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials).

There were no language restrictions when searching for trials.

We searched the following web sites' references: International Council for the Control of differentiated thyroid carcinoma, Thyroid Disease Manager, and World Health Organization. In addition, we planned to contact trialists and other experts in the field for overlooked, unpublished or ongoing trials.

Searching other resources

We also hand searched the following journals for identification of trials:

- Chinese Journal of Isotope (1989 to May 2008);
- Radiological Practice (1989 to May 2008);
- Chinese Journal of Endocrinology and Metabolism (1984 to May 2008);
- Chinese clinical trials and research database.

We also planned to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health-technology assessment reports noticed.

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. Interrater agreement for study selection will be measured using the kappa statistic (Cohen 1960). Differences will be marked and if these studies are later on included, the influence of the primary choice will be subjected to a sensitivity analysis. Where differences in opinion exist, they will be resolved by a third party. If resolving disagreement is not possible, the article will be added to those 'awaiting assessment' and authors will be contacted for clarification.

An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection was attached (Moher 1999).

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we planned to maximize yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) obtained priority.

Data extraction and management

For studies that fulfilled inclusion criteria, two authors (MC and XJW) were planned to independently abstract relevant population and intervention characteristics using standard data extraction templates with any disagreements to be resolved by discussion, or if required by a third party. Any relevant missing information on the trial would have been sought from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

We planned to assess the methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, and loss to follow up; and classify them as 'adequate', 'inadequate', or 'unclear' according to the guidelines of *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). Sensitivity analyses were planned to be undertaken on the basis of whether those quality factors were adequate, inadequate, or unclear. Differences were to be resolved by discussion among the review authors.

The following characteristics were assessed:

Adequacy of the randomization process

- A - adequate sequence generation is reported using one of following approaches: random number tables, computer-generated random numbers, coin tossing, or shuffling.
- B - does not specify one of the adequate methods outlined in (A) but mentions the term 'random' only.
- C - other methods of allocation that appear to be biased.

Adequacy of the allocation concealment process

- A - adequate measures to conceal allocations such as central randomization, serially numbered, opaque, sealed envelopes, or another description that contains convincing elements of concealment.

B - unclearly-concealed trials in which the author do not report an allocation concealment approach at all.

C - inadequately-concealed allocation that reports an approach that does not fall into one of the categories in (A).

D - does not conceal allocation.

Potential for selection bias after allocation

A - trials where an intention-to-treat analysis is possible and few losses to follow up are noted.

B - trials which report exclusions, but exclusions were less than 10%.

C - no reporting on exclusions or exclusions of at least 10%, or wide differences in exclusions between groups.

Based on these criteria, studies will be broadly subdivided into the following three categories:

A - all quality criteria met (adequate): low risk of bias.

B - one or more of the quality criteria only partly met (unclear): moderate risk of bias.

C - one or more criteria not met (inadequate or not used): high risk of bias.

Dealing with missing data

Relevant missing data were planned to be obtained from authors, if feasible. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat (ITT) and per-protocol (PP) population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of last-observation-carried-forward (LOCF), ITT and PP will be critically appraised and compared to specification of primary outcome parameters and power calculation.

Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results will not be combined by means of meta-analysis. Heterogeneity will be identified by visual inspection of the forest plots, by using a standard I^2 -test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity will be specifically examined with I^2 (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases

Funnel plots were planned to be used in an exploratory data analysis to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies and publication

bias (Sterne 2001). Therefore, results would have been interpreted with caution (Lau 2006).

Data synthesis

If data are sufficiently similar, meta-analysis will be carried out using the Review Manager software. Statistical analysis will be performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). Results will be expressed as risk ratios (RR) for dichotomous outcomes. Continuous outcomes will include mean differences (MD) or the standardized mean differences (SMD), both with 95% confidence intervals (CI). A fixed effect model will be used unless there is significant heterogeneity, in which case a random effects statistical model will be employed.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned on regions of metastasis, treatment times, and sex of participants.

Sensitivity analysis

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

- "repeating the analyses excluding any unpublished studies,
- "repeating the analyses taking account of methodological study quality, as specified above,
- "repeating the analyses 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.

The robustness of the results will also tested by repeating the analyses using different measures of effect size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

RESULTS

Description of studies

Results of the search

The electronic searches and hand searches revealed 376 studies. Of these references, we excluded 373 citations. After reading the titles and abstracts, three potential controlled clinical trials were retrieved for further assessment. By reading the full article, we discovered that these were retrospective cohort studies (Koh 2003; Pacini 2001; Tian 2003).

For an overview (Figure 1), please see the adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection (Moher 1999).

Figure 1.

Risk of bias in included studies

Not possible.

Effects of interventions

In the absence of any suitable controlled trials in this area, we were unable to perform any analysis.

DISCUSSION

No evidence from randomised or prospective controlled trials for or against radioactive iodine treatment for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases based on the retrieved studies was available.

Current study data from uncontrolled trials regarding radioiodine versus no radioiodine treatment suggest that radioiodine treatment has a therapeutic effect when thyroglobulin level is considered an index of tumour burden. Further prospective controlled trials of high-quality and large scale are urgently needed in order to define the effectiveness and acceptability of radioiodine treatment.

Data from the three excluded retrospective cohort trials (Koh 2003; Pacini 2001; Tian 2003,) revealed that the administration of therapeutic doses of iodine-131 has therapeutic effects, at least for palliation in the short-term, and could localize previously undiagnosed recurrence in some patients with differentiated thyroid cancer who show an elevated thyroglobulin level but negative diagnostic iodine-131 whole-body scan. Another author (Chao 2005-2) reviewed ten case series and three trials relevant to patients with positive thyroglobulin and negative

diagnostic radioiodine whole body scintigraphy. A decrease in thyroglobulin levels was achieved in 63% of 314 patients with thyroglobulin positive and negative diagnostic radioiodine whole body scintigraphy metastases, which suggested that radioiodine therapy has a therapeutic effect when the thyroglobulin level is considered an index of tumour burden. Therefore, radioiodine treatment may be justified in high risk patients with thyroglobulin levels of above 10 ng/L and negative body scan.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no firm evidence for or against radioactive iodine treatment for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.

Implications for research

Rigorously designed prospective, controlled clinical trials are required to evaluate radioactive iodine treatment for differentiated thyroid carcinoma patients with thyroglobulin positive and radioactive iodine negative metastases. The authors should at least report the outcomes on survival rate and tumour size. Adverse events should be critically assessed by standardized monitoring or an effective self-report system and attention should be paid to long-term adverse effects of radioiodine in larger populations.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Koh 2003	retrospective cohort study
Pacini 2001	retrospective cohort study
Tian 2003	retrospective cohort study

APPENDICES

Appendix 1. Search strategy

Search terms

Notes: Unless otherwise stated, search terms were free text terms; exp = exploded MeSH: Medical Subject Heading (Medline medical index term); the dollar sign (\$) stands for any character(s); the question mark (?) = substitute for one or no characters; ab = abstract; ti = title; ot = original title; pt = publication type; sh = MeSH: Medical subject heading (MEDLINE medical index term); adj = adjacency.

- 1.exp Thyroid Neoplasms/
- 2.((thyroid carcinom\$ or thyroid neoplasm\$) adj different\$).tw.
- 3.(different\$ adj (thyroid carcinom\$ or thyroid neoplasm\$)).tw.

(Continued)

4.or/1-3

5.radioactiv\$ iodine\$.tw.

6.iodine?131.tw.

7.iodine\$ 131.tw.

8.radioiodine\$.tw.

9.thyroglobulin\$.tw.

10.or/ 5-9

11.4 and 10

12.limit 11 to human

13.randomized controlled trial.pt.

14.controlled clinical trial.pt.

15.randomized controlled trials.sh.

16.random allocation.sh.

17.double-blind method.sh.

18.single-blind method.sh.

19.or/ 13-18

20.limit 19 to animal

21.limit 19 to human

22.20 not 21

23.19 not 22

24.clinical trial.pt.

25.exp clinical trials/

26.(clinic\$ adj25 trial\$).tw.

27.((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw.

28.placebo.sh.

29.placebo\$.tw.

30.random\$.tw.

45.limit 44 to animal31.research design.sh.

32.(latin adj square).tw.

33.or/ 24-32

34.limit 33 to animal

35.limit 33 to human

36.34 not 35

37.33 not 36

38.comparative study.pt.

39.exp evaluation studies/

40.follow-up studies.sh.

41.prospective studies.sh.

42.(control\$ or prospectiv\$ or volunteer\$).tw.

43.cross-over studies.sh.

44.or/ 38-43

45.limit 44 to animal

46.limit 44 to human

47.45 not 46

48.44 not 47

49.23 or 37 or 48

50.12 and 49

51.exp "Review Literature"/

52.exp Technology Assessment, Biomedical/

53.exp Meta-Analysis/

54.meta-analysis.pt.

(Continued)

55.((review\$ or search\$) adj10 (literature or medical database\$ or medline or pubmed or embase or cochrane or cinhal or psychinfo or psychlit or healthstar or biosis or current content\$ or systemat\$)).tw,kf,ot.

56.hta.tw,kf,ot.

57.(health technology adj6 assessment\$).tw,kf,ot.

58.(meta analy\$ or metaanaly\$ or meta?analy\$).tw,kf,ot.

59.or/33-40

60. 12 and 59

61. 50 or 60

WHAT'S NEW

Date	Event	Description
11 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

ANREN KUANG: drafting and co-drafting of the protocol and review.

GUANJIAN LIU: assistance with statistics and review draft.

TIEKUN MA: searching, selection of studies.

CHAO MA: data extraction, data analysis and data presentation.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Biomarkers, Tumor [*blood]; Iodine Radioisotopes [*therapeutic use]; Thyroglobulin [*blood]; Thyroid Neoplasms [blood] [*radiotherapy]

MeSH check words

Humans