Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following 131I treatment: a systematic review

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CRD summary
The authors concluded that most paediatric and adolescent patients with well-differentiated thyroid carcinoma and pulmonary metastases did not achieve a complete response to iodine-131 therapy, but disease-specific morbidity and mortality remained low; careful dosing was required to minimise the adverse effects. Quality deficits in the review and the included studies make it uncertain whether the conclusions are supported.

Authors' objectives
To examine the disease-related morbidity, response to treatment, survival rate, and adverse effects of treatment with iodine-131 (131I), for children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases.

Searching
PubMed, the Cochrane Database of Systematic Reviews, and EMBASE were searched for studies published since 1990. The search was restricted to English-language articles and the search terms were indicated.

Study selection
Studies were eligible if they evaluated outcomes for paediatric and adolescent patients with well-differentiated thyroid carcinoma, with pulmonary metastases, who were treated with 131I. The patients had to be aged 21 years or less at the diagnosis of carcinoma, pulmonary metastases had to be diagnosed at presentation or upon follow-up, and outcomes had to include the clinical response to 131I and mortality. Studies including patients with known exposure to environmental radiation were excluded. Study designs were not specified.

In the included studies, histopathology was available for two thirds of the patients, 92% of whom had papillary carcinoma. In 12.5% of patients, pulmonary metastases were diagnosed at follow-up. The cumulative 131I doses ranged widely from 88 to 1,230 millicuries; the number of treatments was variable and often was not specified. Only one study presented data for patients based on their radiation dose.

Two independent researchers performed the searches and selected the studies, based on these inclusion criteria.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors provided a table of the data analysed from the included studies. The response to treatment was subdivided into complete, partial, or no response. Complete response was a negative whole body scan and a thyroglobulin level of less than 10 nanograms per mL in the hypothyroid state. Partial response was a persistent, improved disease based on a whole body scan or chest X-ray, or improvement but no suppression of thyroglobulin to <10ng/mL in the hypothyroid state, or both. No response was no change or worsening on a whole body scan, or increasing thyroglobulin levels, or both. The recurrence of disease, one year after diagnosis and the start of 131I therapy, was subdivided into local, regional, or distant recurrence.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
The results were summarised narratively in the text and reported in a table.

Results of the review

Database of Abstracts of Reviews of Effects (DARE)
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Nine studies were included in the review, with 112 patients (range five to 26). All studies had a retrospective uncontrolled design. Where specified, the follow-up periods ranged from 0.6 to 45 years. Of the 112 patients, 47.3% were complete responders to therapy, 38.4% were partial responders, and 14.3% were nonresponders.

Four studies (61 patients) reported recurrence. This occurred in 9.8% of patients; three patients had regional recurrence, two had distant recurrence, and one had regional and distant recurrence.

All of the studies reported mortality. Three of the 112 patients had died by the end of follow-up; a 97.3% survival rate.

One study reported lung function tests (spirometry) in 10 patients; six showed evidence of restrictive lung disease and nine were partial responders to $^{131}$I therapy.

Six studies (83 patients) reported adverse events. Two studies reported serious adverse events; one patient had radiation injury or pneumonitis leading to early bronchiectasis, and one patient had gastric cancer after eight years of follow-up.

Authors' conclusions
The results of the review suggested that most paediatric and adolescent patients with well-differentiated thyroid carcinoma and pulmonary metastases did not achieve a complete response to $^{131}$I therapy, but disease-specific morbidity and mortality appeared to remain low. Repeated $^{131}$I for these patients should therefore be used cautiously to avoid adverse effects in a disease with a natural course that was favourable overall.

CRD commentary
This review had some deficits in conduct and reporting. It addressed a clear question and the inclusion criteria were defined for participants, interventions, and outcomes, but not for study design. The literature search included three relevant databases, but only limited information on the search terms was given. Only English-language studies were included and relevant studies in other languages might have been omitted. No additional searches of reference lists or for unpublished data were reported and relevant studies not in the electronic databases might have been overlooked. The review methods were only partly defined, with no explicit details of the methods of data extraction and data analysis, and with no validity assessment of the studies.

The included studies were all uncontrolled and retrospective, leaving them open to bias, and the samples were small, which might have been due to the rarity of the disease. There were no details of the relationships between dosage and treatment response, and the variable follow-up times.

The authors’ conclusions were cautious and supported by the data presented, but it is unclear to what extent these data were complete and reliable.

Implications of the review for practice and research
Practice: The authors stated that caution should be used in the repeated administration of $^{131}$I for patients with well-differentiated thyroid carcinoma and pulmonary metastases, to minimise the risk of adverse effects.

Research: The authors stated that long-term prospective studies were needed to analyse the disease-specific morbidity and mortality, recurrence rate, dose-specific response, and dose-related adverse effects of $^{131}$I in the patient population, to determine the amount of $^{131}$I needed to provide the greatest benefit, in a disease with an outcome known to be favourable, without causing therapy-related harm. Molecular and genetic studies were needed to differentiate between complete, partial, and non responders to therapy.

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