131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review

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CRD summary
The authors concluded that, given the paucity of evidence available, it is currently impossible to determine the lowest effective activity for radioiodine ablation of the thyroid remnant for undifferentiated thyroid cancer. Despite poor reporting of the review methods and the failure to systematically assess study quality, the review was in most respects well-conducted and these cautious conclusions are likely to be reliable.

Authors' objectives
To determine the effectiveness of approximately 30 millicuries (mCi) of radioiodine compared with approximately 100 mCi in ablation of the thyroid remnant among patients with differentiated thyroid cancer.

Searching
MEDLINE and EMBASE were searched from 1966 to March 2006; the search terms were reported. The references of articles retrieved were handsearched. There were no restrictions by language or publication status.

Study selection
Studies of patients with differentiated thyroid cancer receiving ablation with single administered activities of approximately 30 mCi (low) and/or approximately 100 mCi (high) radioiodine ablation were eligible for inclusion. Studies of any design were eligible, provided that at least 5 patients had received a specific administered activity and that the rate of successful ablation was reported for at least one of the doses of interest. Studies were excluded if participants had previously received radioiodine treatment or external radiotherapy; all participants had either distant or lymph node metastases; both low and high activities were administered and it was not possible to extract separate data; patients received activities of over 200 mCi; or if radioiodine was administered in fractionated doses.

Most of the included studies focused on a single activity, but some included comparisons of high activities (in most cases 50 to 150 mCi) versus low activities (in most cases 30 mCi), or compared several different activities (e.g. 30 versus 50, 50 versus 100, 30 versus 100 mCi). Some of the studies in the review included patients with lymph node or distant metastases, but they usually comprised only a small proportion of the total sample. The participants varied in terms of the extent of pre-ablation thyroid surgery they had received and in the method used to stimulate production of thyroid stimulation hormone (TSH) before ablation. In most studies the participants discontinued thyroid hormone replacement before ablation, while in others, all or some of the participants were administered recombinant human TSH instead or as well. About a third of studies recommended a pre-surgery low-iodine diet. Many studies performed a pre-ablation scan using radioiodine at a variety of administered activities.

The included studies varied in their definition of successful ablation, with some determining success by visual inspection and interpretation of the follow-up scan, while others used quantitative measures of radioiodine uptake or whole-body scan. The timing of the follow-up diagnostic scan varied from about 3 to 12 months after ablation.

The review included randomised controlled trials (RCTs), cohort studies and case series.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Aspects of study validity were discussed in the text (e.g. study design, sample size), but the authors did not state that they systematically assessed validity.

Data extraction
The proportion of successful ablations in each study group was extracted, and the odds of success were calculated for...
each study group in observational studies; risk ratios (RRs) were calculated for controlled studies. The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

**Methods of synthesis**
The odds of ablation success in all observational studies were converted into logarithms and combined separately for low and high activities, using the inverse variance method, to calculate a pooled odds ratio. DerSimonian and Laird random-effects models were used to calculate pooled RRs with 95% confidence intervals (CIs) for controlled observational studies and (as a separate analysis) for RCTs. The results were grouped by study design and stratified by the extent of thyroid surgery received by participants before remnant ablation (total or near-total thyroidectomy versus less extensive surgery or not reported). Sensitivity analyses were conducted for some comparisons, excluding studies in which some patients with distant metastatic disease and those in which the high activity group received less than 75 mCi. Subgroup analyses were conducted to examine the effect on success rates of the following variables: the extent of the reported surgery before ablation, postsurgical remnant size, preablation scans and the use of recombinant human TSH. Statistical tests were conducted to check for heterogeneity in the meta-analyses. Publication bias was assessed using funnel plots and investigated using the 'trim and fill' estimation.

**Results of the review**
Fifty-nine studies (n=6,986) were included: 6 RCTs (n=977), 12 prospective cohorts (n=985) and 41 retrospective record reviews (n=5,024).

The RCTs in the review were small and underpowered and most studies of low activity were small. Many studies in the review were uncontrolled and prone to selection bias and confounding.

**Ablation success.**
Findings among the 6 RCTs were inconsistent: some comparisons supported a superior effect associated with high activity while others supported equal effectiveness of low and high activities. Three different dose comparisons were reported. None of the pooled RRs were statistically significant and the 95% CIs were wide.

Among the observational studies in which all participants had had total or near-total thyroidectomy (n=47), success rates varied but were consistently lower in the low-activity group. Out of 26 estimates in the high-activity groups, success rates were ≥80% in 14 and ≥90% in 5 (range: 50 to 100%). In the low-activity groups (9 estimates), the success rates in the largest 2 studies were about 70% (range: 10 to 80). Overall pooled success rates were 79% in the high-activity groups and 51% in the low-activity groups. In observational studies in which not all participants had total or near-total thyroidectomy, out of 18 estimates in the high-activity groups, success rates were ≥80% in 8 and ≥90% in 5 (range: 28 to 96%). Out of 15 estimates in the low-activity groups, success rates were ≥80% in 5 (range: 28 to 96%). Overall pooled success rates were 79% in the high-activity group and 69% in the low-activity group.

Among controlled observational studies (n=16), the pooled RR for successful ablation significantly favoured the high-activity group (RR 0.90, 95% CI: 0.83, 0.97, p=0.01). The statistical heterogeneity in this estimate approached significance (p=0.051). The exclusion of studies in which the high-dose group received less than 75 mCi resulted in a larger effect estimate (RR 0.85, 95% CI: 0.76, 0.97, p=0.012). A funnel plot showed evidence of publication bias among these 16 studies. A 'trim and fill' estimate to compensate for publication bias produced non significant results.

The results of subgroup analyses were also reported.

**Authors’ conclusions**
Given the paucity of good-quality evidence currently available, it is not possible to determine the lowest effective activity for radioiodine ablation of the thyroid remnant following primary surgery for undifferentiated thyroid cancer.

**CRD commentary**
The review objectives and inclusion criteria were clear and the search was thorough. However, it was not clear whether
steps were taken to minimise the risk of error and bias in the review process by having more than one reviewer make
decisions about study selection and data extraction, and no systematic assessment of study validity was reported. These
factors make it difficult to evaluate the reliability of the data presented. Suitable statistical methods were used,
prominence was given to the studies with lower design-related risk of bias, and heterogeneity between the studies was
investigated and well-addressed in the text. Despite poor reporting of the review methods and the failure to
systematically assess study quality, the review was in most respects well-conducted and the authors’ cautious
conclusions seem likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that it is unclear whether an administered activity as low as 30 mCi can be used instead of
100 mCi for radioiodine ablation of the thyroid remnant following primary surgery for undifferentiated thyroid cancer.
Caution is required if using activities of 30 mCi.

Research: The authors stated that well-powered RCTs are needed in this area, with ablation success and recurrence rates
as outcomes. They note that two such studies are planned in the UK and in France.

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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.