

Neo-adjuvant denosumab and disease recurrence in giant cell tumour of bone: Has the magic bullet lost its magic?

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Background

Denosumab is currently being used as a neo-adjuvant systemic therapy in an effort to reduce local disease recurrence and facilitate intra-lesional curettage of giant cell tumour of bone (GCTB) despite limited and conflicting evidence to support such use. While a number of early case series¹⁻³ suggested neo-adjuvant denosumab was associated with a reduced disease recurrence, subsequently published studies had result conflicting with this⁴⁻⁸.

Objective

To assess the effect of neo-adjuvant denosumab on disease recurrence in skeletally mature individuals with giant cell tumours of bone treated with curettage.

Methods

A comprehensive search strategy incorporating the Methodological Expectations for Cochrane Intervention Reviews (MECIR) was implemented which included database and citation searches, hand searching of selected journals and screening of key study references lists. Randomised controlled trials (RCT) or non-randomised studies (NRS) with control groups that evaluated the effect of neo-adjuvant denosumab on disease recurrence in skeletally mature individuals with GCTB treated with curettage were included for analysis (Figure 1).

For the dichotomous outcome of recurrence, the risk ratio with 95% confidence interval was calculated for each study in which it was not already reported. This was done using the Mantel-Haenszel method in the Cochrane collaboration computer program Review Manager (RevMan).

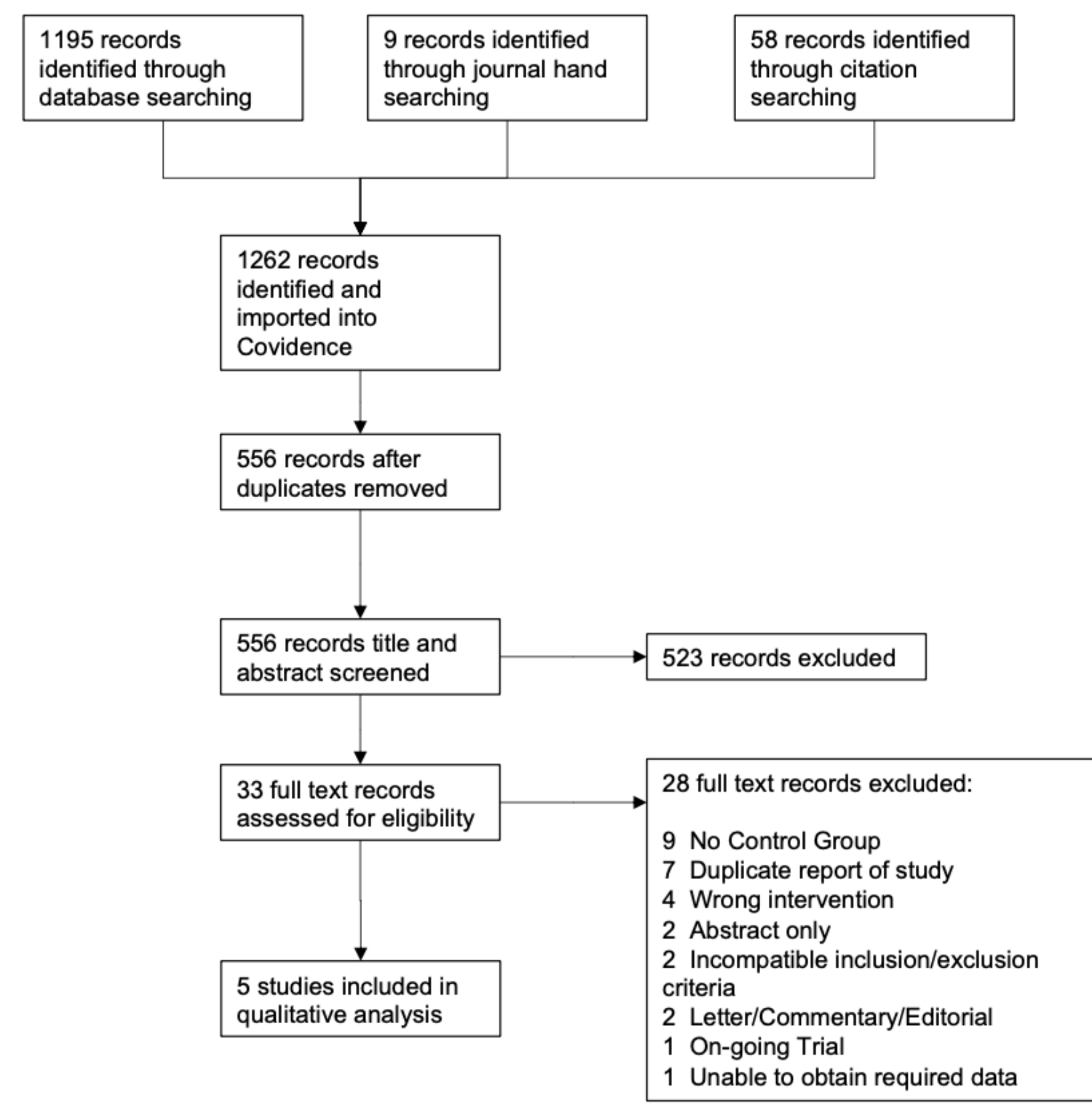


Figure 1. Flow diagram of study selection process

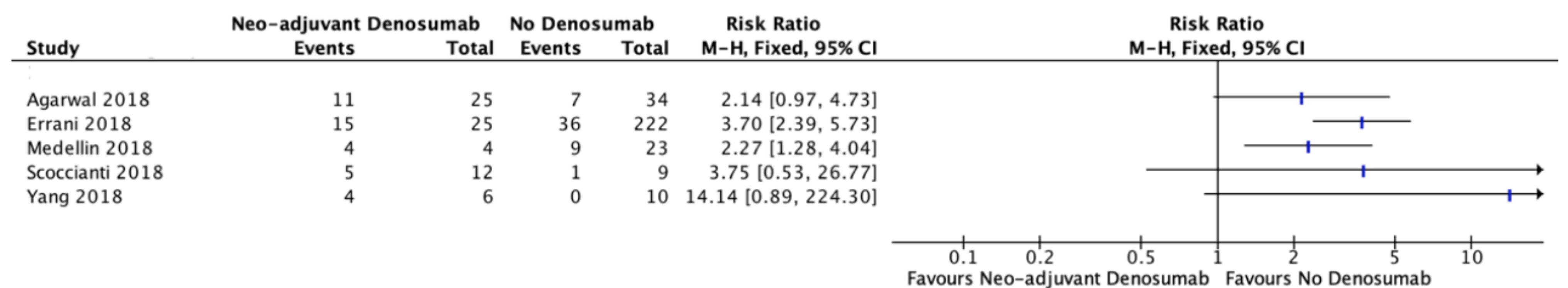


Figure 2. Relative risk ratio for local recurrence

M-H; Mantel-Haenszel, CI; Confidence Interval

Results

No RCTs were identified. Five NRS (n=370) met the review inclusion/exclusion criteria for the primary outcome measure of local disease recurrence and all five suggested that the use of neo-adjuvant denosumab was associated with an increased risk of local disease recurrence (Figure 2). A meta-analysis was deemed inappropriate given the degree of methodological heterogeneity between studies and overall poor quality of evidence.

Discussion

Conflicting evidence in the published literature between promising results of early case series and results of later historically controlled studies. This may be due, at least in part, to the longer follow up period in the historically controlled studies.

- Muller et al² 2016 (10.5% recurrence)
- Scoccianti et al⁴ 2018 (41% recurrence)
- Essentially the same patient cohort but with an additional 2 years of follow up.

Limitations

Poor quality of evidence with large variability in confounders such as Campanacci grade, tumour location and use of local adjuncts between groups and studies. Despite a number of studies employing statistical methods to mitigate effect of confounders this does not address underlying bias present in non-randomized studies such as those included in this systematic review.

Conclusion

The presence of significant risk of bias and methodological heterogeneity means that strong conclusions cannot be drawn from the available evidence. Given the consistency in direction and magnitude of effect seen across the included studies however there is a suggestion that the use of neo-adjuvant denosumab may be associated with an increased risk of local disease recurrence in GCTB.

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