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Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones (Review)

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[Intervention Review]

Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones

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ABSTRACT

Background

Grade I or low-grade chondrosarcoma (LGCS) is a primary bone tumour with low malignant potential. Historically, it was treated by wide resection, since accurate pre-operative exclusion of more aggressive cancers can be challenging and under-treatment of a more aggressive cancer could negatively influence oncological outcomes. Intralesional surgery for LGCS has been advocated more often in the literature over the past few years. The potential advantages of less aggressive treatment are better functional outcome and lower complication rates although these need to be weighed against the potential for compromising survival outcomes.

Objectives

To assess the benefits and harms of intralesional treatment by curettage compared to wide resection for central low-grade chondrosarcoma (LGCS) of the long bones.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4), MEDLINE and Embase up to April 2018. We extended the search to include trials registries, reference lists of relevant articles and review articles. We also searched 'related articles' of included studies suggested by PubMed.

Selection criteria

In the absence of prospective randomised controlled trials (RCTs), we included retrospective comparative studies and case series that evaluated outcome of treatment of central LGCS of the long bones. The primary outcome was recurrence-free survival after a minimal follow-up of 24 months. Secondary outcomes were upgrading of tumour; functional outcome, as assessed by the Musculoskeletal Tumor Society (MSTS) score; and occurrence of complications.

Data collection and analysis

We used standard methodological procedures recognised by Cochrane. We conducted a systematic literature search using several databases and contacted corresponding authors, appraised the evidence using the ROBINS-I risk of bias tool and GRADE, and performed a meta-analysis. If data extraction was not possible, we included studies in a narrative summary.

Main results

We included 18 studies, although we were only able to extract participant data from 14 studies that included a total of 511 participants; 419 participants were managed by intralesional treatment and 92 underwent a wide resection. We were not able to extract participant data from four studies, including 270 participants, and so we included them as a narrative summary only. The evidence was at high risk of performance, detection and reporting bias.

Meta-analysis of data from 238 participants across seven studies demonstrated little or no difference in recurrence-free survival after intralesional treatment versus wide resection for central LGCS in the long bones (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.92 to 1.04; very low-certainty evidence). MSTS scores were probably better after intralesional surgery (mean score 93%) versus resection (mean score 78%) with a mean difference of 12.69 (95% CI 2.82 to 22.55; P value < 0.001; 3 studies; 72 participants; low-certainty evidence). Major complications across six studies (203 participants) were lower in cases treated by intralesional treatment (5/125 cases) compared to those treated by wide resection (18/78 cases), with RR 0.23 (95% CI 0.10 to 0.55; low-certainty evidence). In four people (0.5% of total participants) a high-grade (grade 2 or dedifferentiated) tumour was found after a local recurrence. Two participants were treated with second surgery with no evidence of disease at their final follow-up and two participants (0.26% of total participants) died due to disease. Kaplan-Meier analysis of data from 115 individual participants across four studies demonstrated 96% recurrence-free survival after a maximum follow-up of 300 months after resection versus 94% recurrence-free survival after a maximum follow-up of 251 months after intralesional treatment (P value = 0.58; very low-certainty evidence). Local recurrence or metastases were not reported after 41 months in either treatment group.

Authors' conclusions

Only evidence of low- and very low-certainty was available for this review according to the GRADE system. Included studies were all retrospective in nature and at high risk of selection and attrition bias. Therefore, we could not determine whether wide resection is superior to intralesional treatment in terms of event-free survival and recurrence rates. However, functional outcome and complication rates are probably better after intralesional surgery compared to wide resection, although this is low-certainty evidence, considering the large effect size. Nevertheless, recurrence-free survival was excellent in both groups and a prospective RCT comparing intralesional treatment versus wide resection may be challenging for both practical and ethical reasons. Future research could instead focus on less invasive treatment strategies for these tumours by identifying predictors that help to stratify participants for surgical intervention or close observation.

PLAIN LANGUAGE SUMMARY

The effect of type of surgery for outcome in low-grade chondrosarcoma

Background and review question

Chondrosarcomas are one of the most common types of bone cancer, with varying degrees of severity. These tumours grow from cartilage forming cells, within the bone, or on the surface of the bone. Low-grade chondrosarcomas (LGCS) are tumours that grow slowly over time and do not generally metastasize and people do not usually die from this disease. In the late 20th century, the condition was treated by cutting out large portions of bone surrounding the tumour (wide resection). However, surgeons today more commonly treat these tumours by scraping the tumour out of the bone (intralesional treatment). In this way, the bone structure is preserved and more extensive surgery can be avoided. Therefore, people are potentially less disabled and complications can be reduced. This is only appropriate if the survival outcome of the cancer treatment is not compromised compared to wide resection. We reviewed the evidence for the harms and benefits of both types of surgery on outcomes in people with LGCS, including tumour recurrence after surgery (local recurrence), level of physical functioning and complications after surgery.

Search date

The evidence is current to April 2018.

Study characteristics

We identified 14 studies that were suitable for analysis with a total of 511 participants; 92 were treated by wide resection compared to 419 by intralesional treatment. Age of the participants varied from 13 to 82 years with a mean age of 48 years. Women outnumbered men in the studies by just over one and a half times, which reflects that LGCS are more common in women. People were followed-up for between 24 to 300 months after surgery. In addition, there were four studies including 270 participants, from which we could not extract the exact data, but were used to confirm the statistical analysis.

Key results

We found that there was little or no difference in rates of local recurrence between treatment types. In 94% to 96% of the cases, the tumour was successfully removed after a single operation. In the few cases where disease recurred, a second operation was needed. People with LGCS probably have better functionality after less aggressive intralesional treatment, and complication rates were probably lower compare to wide surgical resection. Less than 0.3% of all people with LGCS died due to their disease, irrespective of the surgical technique.

Certainty of evidence

Overall certainty of the studies was very low, as all studies only described the results of the treatment in hindsight and none of the studies randomly selected patients between treatment groups.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Intralesional treatment versus wide resection for central, low-grade (grade I) chondrosarcoma in the long bones

Intralesional treatment versus wide resection for central, low-grade (grade I) chondrosarcoma in the long bones

Patient or population: people with central, low-grade (grade I) chondrosarcoma in the long bones

Settings: hospital

Intervention: intralesional treatment

Comparison: wide resection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Wide resection	Intralesional treatment				
Recurrence-free survival (24-300 months' follow-up)	**54 per 1000** (19 to 111)	**68 per 1000** (34 to 116)	RR 0.98 (0.92 to 1.04)	238 (7 studies)	⊕⊝⊝⊝[1] **Very low**	
Functional outcome based on MSTS score (percent) Scale 0% to 100%, with 100% indicating no functional limitations	The mean MSTS was 78% and ranged across control groups from 72.1% to 94.3%	The mean MSTS was 93% and ranged across intervention groups from 89.3% to 98.6%	MD 12.7 (2.8 to 22.6)	72 (3 studies)	⊕⊕⊝⊝ **Low** [2]	
Overall rate of major complications (24-300 months' follow-up)	**230 per 1000** (150 to 337)	**40 per 1000** (13 to 82)	RR 0.23 (0.10 to 0.55)	203 (six studies)	⊕⊕⊝⊝ **Low** [2]	
Pathological upgrading of tumour	N/A	N/A	N/A	N/A	N/A	Only 2 cases in the overall data had a transition towards grade II chondrosarcoma, based on the narrative reporting of results

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **MSTS:** Musculoskeletal Tumor Society; **N/A:** not applicable; **RR**: risk ratio

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

[1]All included studies were observational studies, which have an initial low level of evidence. We downgraded the evidence level since there were serious risks of bias.
[2]All included studies were observational studies, which have an initial low level of evidence. We downgraded the evidence since there were serious risks of bias. However, we upgraded them considering the large effect.

BACKGROUND

Description of the condition

Chondrosarcoma is the most common primary malignant bone tumour after osteosarcoma (Bauer 1995; Eriksson 1980; Healey 1986; Rosenthal 1984), and is characterised by a heterogeneous group of bone malignancies with a cartilaginous origin (Fletcher 2013). Chondrosarcoma constitute 20% to 27% of all primary bone tumours (Murphey 2003). Reported overall incidence is 1:200,000 to 1:500,000, with men and women being more or less equally affected (ESMO 2012; Giuffrida 2009). Incidence is highest between the 3rd and 7th decade of life (ESMO 2012; Jundt 2008). Chondrosarcoma vary from low-grade, relatively benign to high-grade or dedifferentiated tumours with very poor survival. Conventional chondrosarcoma can originate outside the bone (periosteal or peripheral chondrosarcoma) or within the bone (central chondrosarcoma); the latter accounts for 75% of all of these tumours. Tumours can either be intra-compartmental (Enneking stage IA) or extra-compartmental (Enneking stage IB (Enneking 1986)). Oncological outcome is predominately determined by histological grading, ranging from I to III, with higher-grade tumours associated with worse prognosis. Central grade I (low-grade (LG)) chondrosarcoma (LGCS) tumours tend to grow slowly and rarely metastasize, resulting in an 83% to 89% 10-year survival rate (Bjornsson 1998; Evans 1977; Fiorenza 2002). Microscopically, they exhibit a matrix rich in hyaline cartilage (Gelderblom 2008). The most important clinical symptom is persistent (nocturnal) pain, although LGCS can be asymptomatic. Treatment of LGCS is primarily surgical, since these tumours are generally resistant to radiation or systemic therapy (Eriksson 1980; Lee 1999).

In clinical practice, the treating physician is presented with a diagnostic dilemma. In a substantial number of cases, it is difficult to differentiate central LGCS from its benign equivalent, enchondroma (Eefting 2009; Geirnaerdt 1997; Mirra 1985; Randall 2005). Intermediate- and high-grade chondrosarcoma display typical signs, such as perilesional oedema and cortical destruction. Enchondroma can be managed conservatively with observation or treated with intralesional curettage. Malignant transformation of a solitary enchondroma is rare. On the other hand, intermediate- and high-grade chondrosarcoma display a much more aggressive course, with 10-year survival rates ranging from 53% to 64% and 29% to 38%, respectively, and a higher incidence of local recurrence and distant metastases (Bjornsson 1998; Fiorenza 2002; Giuffrida 2009). They are treated with 'en bloc' resection (wide resection) with reconstruction (prosthesis) or amputation, which hampers joint and limb function. Historically, orthopaedic surgeons tended to treat LGCS in a similar fashion. More recently, there has been a tendency to perform intralesional surgery in LGCS by extended intralesional curettage, preferably with local adjuvant therapy, such as phenolisation, the use of polymethyl methacrylate (PMMA) and application of cryotherapy (Donati 2010; Leerapun 2007; Schreuder 1998; Van der Geest 2008; Veth 2005). Some studies suggest that intralesional surgery could lead to higher local recurrence rates, which in itself could lead to upgrading towards high-grade chondrosarcoma (Andreou 2011). LGCS tumours located in the pelvis and axial skeleton tend to be more aggressive and require other treatment strategies, often similar to higher-grade tumours (Gelderblom 2008). Therefore, we have described only treatment of tumours in the long bones in this review.

Description of the intervention

Intralesional surgery in LGCS is carried out by curettage. During this procedure, the tumour is accessed through a cortical window, extensive curettage is carried out and often supplemented with the use of a high-speed burr. After curettage, local adjuvant therapy can be applied, either by phenolisation or cryotherapy (see How the intervention might work). In a large number of cases, bone cement (PMMA) is used as an additional adjuvant and filler. The cavity is filled, where necessary, with bone graft or cement; larger cortical windows can then be refashioned to the bone followed by routine wound closure. In some cases, prophylactic hardware (metal pins and plates often used to help repair fractured bones) is used to prevent fracturing. Depending on the site of the tumour, patients are prohibited from weight bearing six to 12 weeks after surgery. Generally, curettage is indicated if the joint surface is unaffected, if the lesion is contained in bone or a sufficient bony architecture remains after surgery. The most serious complications after curettage are fracture of the treated site and infection.

How the intervention might work

Extended intralesional curettage removes malignant tumour cells, but by definition will likely leave some microscopic cells behind. As a result, local adjuvant therapy is often performed. Phenol has a proven cytotoxic effect on LGCS cells and is used with the intention to kill tumour cells that cannot be reached with the curette (Verdegaal 2012). The strongest evidence exists for cryotherapy, whereby liquid nitrogen is sprayed or poured into the bone cavity (Van der Geest 2008). It is thought that local freezing extends the surgical margin. In some centres, the bone cavity is filled with PMMA, and it is hypothesised that the heat released during the exothermic reaction as it sets has an additional cytotoxic effect on tumour cells. Given the relatively mild nature of LGCS, we hypothesise that these measures are sufficient to treat the disease. The major benefit of curettage compared to wide resection is improved functional outcome as a result of joint preservation and the avoidance of large bony resections or ablative surgery. Although people might be temporarily disabled due to decreased weight bearing after curettage, long-term functionality can often fully be restored.

Why it is important to do this review

LGCS has an overall incidence rate that is relatively low compared to other types of cancer. To our knowledge, there are no prospective, randomised controlled trials (RCTs), given the low number of people affected. In literature, only small, retrospective studies have been published comparing intralesional treatment with wide resection (Aarons 2009; Bauer 1995; Donati 2010; Etchebehere 2005; Leerapun 2007; Schreuder 1998; Van der Geest 2008). This type of study is often subject to a high degree of bias and the numbers are often too small for meaningful statistical analysis. A systematic review is necessary to search for and summarise the available evidence. Hickey 2011 performed a meta-analysis on this specific topic and it showed that intralesional therapy is not necessarily inferior to wide resection. Since then, several studies have been published, which justifies an updated overview. This review will be important, since intralesional treatment may have significant functional benefits compared to resection. Therefore, if the intralesional treatment is equally beneficial from a recurrence and survival point of view, it may be better to perform curettage instead of wide resection.

OBJECTIVES

To assess the benefits and harms of intralesional treatment by curettage compared to wide resection for central low-grade chondrosarcoma (LGCS) of the long bones.

METHODS

Criteria for considering studies for this review

Types of studies

Since no RCTs or other prospective studies were available, we included retrospective cohort studies comparing oncologic outcome of intralesional treatment of LGCS to wide resection in the long bones (i.e. humerus, radius, ulna, femur, tibia and fibula). In addition, we included case series with at least 20 participants. We also included studies examining other types of chondrosarcoma, from which we retrieved data related to central LGCS. If RCTs become available in literature, they still will be eligible for inclusion in future versions of the review.

Types of participants

We included all participants with central LGCS in the long bones. We did not apply age restrictions.

Types of interventions

We compared intralesional treatment (curettage) with or without adjuvant (phenol and ethanol, cryosurgery, bone cement or combinations) to wide resection, including amputation.

Types of outcome measures

We prespecified the following outcomes, which are also included in the 'Summary of findings' table.

Primary outcomes

Primary outcome was recurrence-free survival (defined as local recurrence and/or metastases), with a minimum follow-up duration of two years after index surgery.

Secondary outcomes

We considered the following secondary outcomes:

- incidence of pathological upgrading of tumour;
- functional outcome based on Musculoskeletal Tumor Society (MSTS) score, if available. The MSTS score is a well-accepted and commonly used score to determine function after surgery for bone tumours (Enneking 1993). It includes six categories (pain, function, emotional acceptance, use of supports, walking ability and gait), with numerical values from 0 to 5 points; in total 30 points can be reached, often also presented as percentage, with 100% equalling 30 points, and 30 points or 100% indicating no functional limitations;
- overall rate of major complications based on the following adverse events, if available: fracture, infection, re-operation (due to reasons other than progression of disease) or thromboembolic events. Grading of adverse events is outside the scope of this review.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4), in the Cochrane Library (Appendix 1);
- MEDLINE via Ovid (1946 to April 2018) (Appendix 2);
- Embase via Ovid (1980 to 2018, week 17) Appendix 3).

We did not apply language restrictions.

Searching other resources

We extended our search to the reference lists of relevant articles and review articles, as well as contacting study authors to provide missing information. We also scanned related articles suggested by PubMed. In addition, we searched for ongoing trials by scanning online trials registries, such as Current Controlled Trials (http://www.isrctn.com), and ClinicalTrials.gov, and searched for oral and poster abstracts presented in appropriate meetings (e.g. EMSOS, ISOLS).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database and removed duplicates. Three review authors (EFD, PCJ, KG) examined the remaining references independently. We excluded those studies that clearly did not meet the inclusion criteria. In addition, we obtained copies of the full text of potentially relevant references. Three review authors (EFD, PCJ, KG) independently assessed the eligibility of retrieved publications. We resolved disagreements by discussion between the three review authors and if necessary by involving the fourth review author (MS). We documented our reasons for exclusion.

Data extraction and management

For included studies, we extracted the following data.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design and methodology
- Study population:
  - total number enrolled;
  - patient characteristics;
  - age
- Intervention details:
  - definition/details
- Comparison:
  - definition/details
- Risk of bias in study (see below)
- Duration of follow-up

- Outcomes:
  * for each outcome, we extracted the outcome definition and unit of measurement (if relevant). For adjusted estimates, we have recorded variables adjusted for in analyses.
- Results:
  * we extracted the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants (if applicable).

We extracted the following information.

- For time-to-event data (survival and disease progression), we extracted the log of the hazard ratio (log (HR)) and its standard error from study reports. If these are not reported, we attempted to estimated the log (HR) and its standard error using the methods of Parmar 1998.
- For dichotomous outcomes we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate an odds ratio (OR).
- For continuous outcomes, we extracted the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

We noted the time points at which outcomes were collected and reported.

Three review authors (EFD, PCJ, KG) independently extracted the data onto a data abstraction form specially designed for the review. We resolved differences between review authors by discussion or by appeal to a fourth author (MS) if necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias using ROBINS-I, since all studies were non-randomised, retrospective studies (Sterne 2016). We achieved consensus on seven domains through which bias might be introduced into non-randomised studies for interventions (bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result). The first two domains, covering confounding and selection of participants into the study, addressed issues before the start of the interventions that were compared ("baseline"). The third domain addressed classification of the interventions themselves. The other four domains addressed issues arising after the start of interventions: biases due to deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result (Sterne 2016).

Important confounders of interest in this Cochrane Review include the following.

- Tumour stage (Enneking 1A or 1B)
- Surgical techniques and local adjuvants
- Pathological diagnosis
- Time period of treatment

Three review authors (EFD, PCJ, KG) applied the 'Risk of bias' tool independently and resolved differences by discussion or by appeal to a fourth review author (MS). We summarised results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted results of meta-analyses in light of the findings with respect to risk of bias. Each of the seven domains of bias contains signalling questions to facilitate judgements of risk of bias. The full signalling question and response framework for each outcome is provided in Sterne 2016. Following completion of the signalling questions, we determined a 'Risk of bias' judgement for each domain and obtained an overall 'Risk of bias' judgement for each outcome and result assessed. Overall risk of bias has four categories ranging from low risk of bias (the study is at low risk of bias across all domains) to critical risk of bias (the study is at critical risk of bias in at least one domain). If there was insufficient information to assess the risk of bias in one or more key domains, but there was no indication that there was any critical or serious risk of bias in any of the other domains, then we have designated the overall classification as 'no information'.

Measures of treatment effect

We used the following measures of the effect of treatment.

- We had hoped to use hazard ratios (HRs) for time-to-event data but the data only allowed us to compute the risk ratio (RR) and OR.
- For dichotomous outcomes, we used the RR.
- For continuous outcomes, we used the mean difference (MD) between treatment arms.

Unit of analysis issues

No cluster-RCT or cross-over RCTs were available for inclusion. We could not identify multiple groups within the studies presented.

Dealing with missing data

We did not impute missing outcome data for the primary outcome. If data were missing we contacted study authors to request data only on the outcomes for the participants they had assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between studies that could not be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there had been evidence of substantial heterogeneity, we would have investigated and reported the possible reasons for this.

Assessment of reporting biases

Reporting bias was assessed as part of the 'Risk of bias' tool (Sterne 2016).

Data synthesis

In case of clinically and statistically homogeneous studies, we pooled their results in meta-analyses using the Cochrane Collaboration's statistical software, Review Manager 2014. Although there were no signs of significant heterogeneity, due to subtle differences in diagnostics and treatments, we used a random-effects model. If individual time-to-event data were present, we extracted them to compute the Kaplan-Meyer curve of recurrence-free survival. For time-to-event data we were only able to compute RRs and ORs. For dichotomous outcomes, we

calculated the RR for each study and pooled them. For continuous outcomes, we pooled the MDs between the treatment arms at the end of follow-up.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analysis.

Sensitivity analysis

We did not perform sensitivity analyses excluding studies at high risk of bias, since all studies were at high risk of bias.

Main outcomes of 'Summary of findings' table for assessing the certainty of the evidence

We presented the overall certainty of the evidence for each main outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results (Langendam 2013). We created Summary of findings for the main comparison based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), and using GRADEpro GDT (GRADEpro GDT 2015). We used the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We downgraded the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The main outcomes were recurrence-free survival, MSTS scores and rates of major complications.

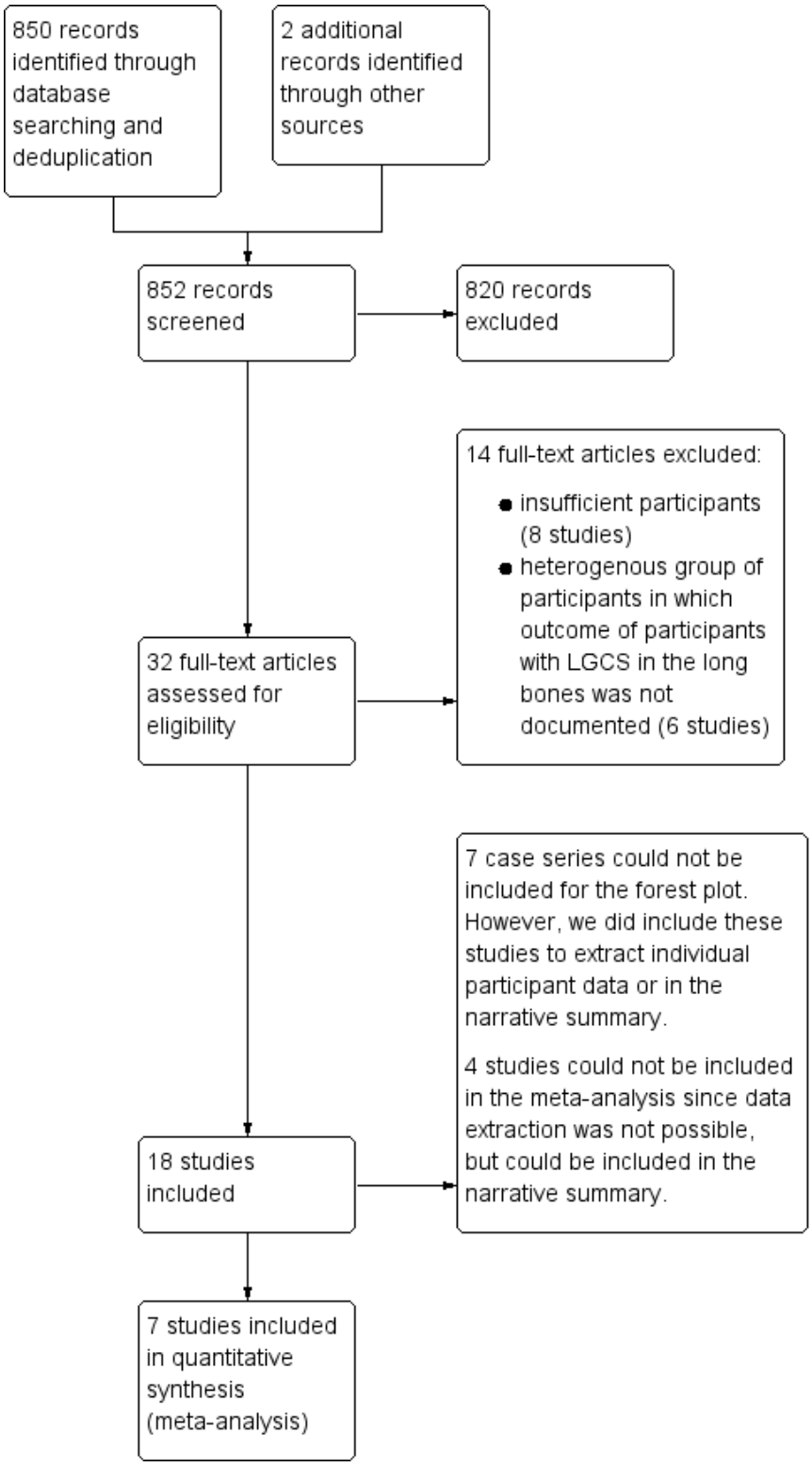
RESULTS

Description of studies

Results of the search

No studies were identified through CENTRAL. The MEDLINE and Embase searches identified 331 and 519 records respectively, and handsearching yielded two additional studies. After removal of duplicate studies and title and abstract screening, we included a total of 32 studies for potential eligibility, (see Figure 1 for flow-chart (Moher 2009)). We fully reviewed the full texts of all 32 selected papers for eligibility and we excluded 14 studies because their sample size was too small, or they had not documented data concerning recurrence-free survival for LGCS in the long bones (see Excluded studies). We included a total of 18 studies in this review. Of these, seven studies were suitable for meta-analysis; details of these studies can be found in the Characteristics of included studies section. In addition, we used participant data from seven case series in the narrative summary or to assess recurrence-free survival and included four studies for qualitative analysis only, since we could not extract participant data, and are described in the Characteristics of included studies section.

Figure 1. Study flow diagram



Included studies

Design of the studies

There were no RCTs or quasi-RCTs available. Aarons 2009, Bauer 1995, Chen 2017, Campanacci 2013, Donati 2010, Etchebehere 2005 and Gunay 2013 were retrospective studies comparing intralesional treatment versus wide resection. The remaining 11 studies were retrospective case series or cohort series available for qualitative analysis on recurrence-free survival (Di Giorgio 2011; Dierselhuis 2016; Funovics 2010; Hanna 2009; Kim 2015; Kim 2018;

Leerapun 2007; Mermerkaya 2014; Mohler 2010; Van der Geest 2008; Verdegaal 2012). The case series included only participants that were treated by intralesional surgery and were not controlled by wide resection.

Sample sizes

In total, the comparative studies included 238 participants (sample sizes from 8 to 85), 146 managed by intralesional management and 92 by wide resection. The case series included in the narrative summary studied 249 participants (sample sizes from 21 to 108), managed by intralesional treatment. The four studies that were only included in the qualitative analysis included 270 participants (sample sizes from 55 to 85).

Participants

Age, gender and follow-up

The mean age of the participants was 45.8 years (range 13 to 80), in participants included in the meta-analysis, and 51.5 (range 18 to 82), in the cases series. A slight female preponderance was present in the cohort included in the meta-analysis, with a male to female ratio of 1:1.3. Mean follow-up was 85.2 months (range 24 to 300), in the studies included in the meta-analysis and 56.8 months (range 26 to 134), in the case series.

Disease severity

Aarons 2009, Chen 2017, Dierselhuis 2016, Hanna 2009, Kim 2015, Kim 2018 and Mermerkaya 2014 included only Enneking stage IA tumours. Bauer 1995, Campanacci 2013, Etchebehere 2005 and Gunay 2013 included both Enneking stage IA and IB. It is unclear whether Di Giorgio 2011, Donati 2010 and Mohler 2010 included only stage IA or both tumour stages.

Excluded studies

We excluded the following eight studies: Ahlmann 2007, Okada 2009, Ozaki 1996, Puri 2009, Schreuder 1998 and Souna 2010 did not include a sufficient number of participants; and Errani 2017 and Lee 1999 studied a heterogeneous group of LGCS (either primary, secondary, in the axial skeleton or in extremities). These studies did not document the outcome of participants with primary LGCS in the long bones, and we could not, therefore, include them in the meta-analysis or narrative summary, since the majority of study participants did not meet our inclusion criteria. Full exclusion details can be found in Characteristics of excluded studies.

Andreou 2011, Angelini 2012, de Camargo 2010, Ma 2009, Meftah 2013 and Streitbuerger 2009 contained valuable data on the outcome of treatment of LGCS, however we could not extract the exact data from the studies due to their heterogeneous nature. In all cases we attempted to contact the study authors for individual participant data, which could not be obtained. We have summarised these studies under Characteristics of studies awaiting classification.

Risk of bias in included studies

Overall, there was a high risk of bias in the included comparative studies (see Figure 2 and Figure 3). This bias was mainly caused by confounding bias, in selection of participants (selection bias) and in classification of interventions. In these studies, identification of confounding variables was absent and thus we did not perform analysis of confounding. Selection bias was apparent in these retrospective studies, as there was no control of the inclusion of participants. In addition, insight into the choice of intervention for a specific participant is very probably related to participant characteristics, such as aggressiveness, or staging of the tumours, or both. About half of the studies suffered from missing data (attrition bias). Measurement of outcomes and selection of reported results (reporting bias) are less likely to be problematic. There were also suspected other biases because groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

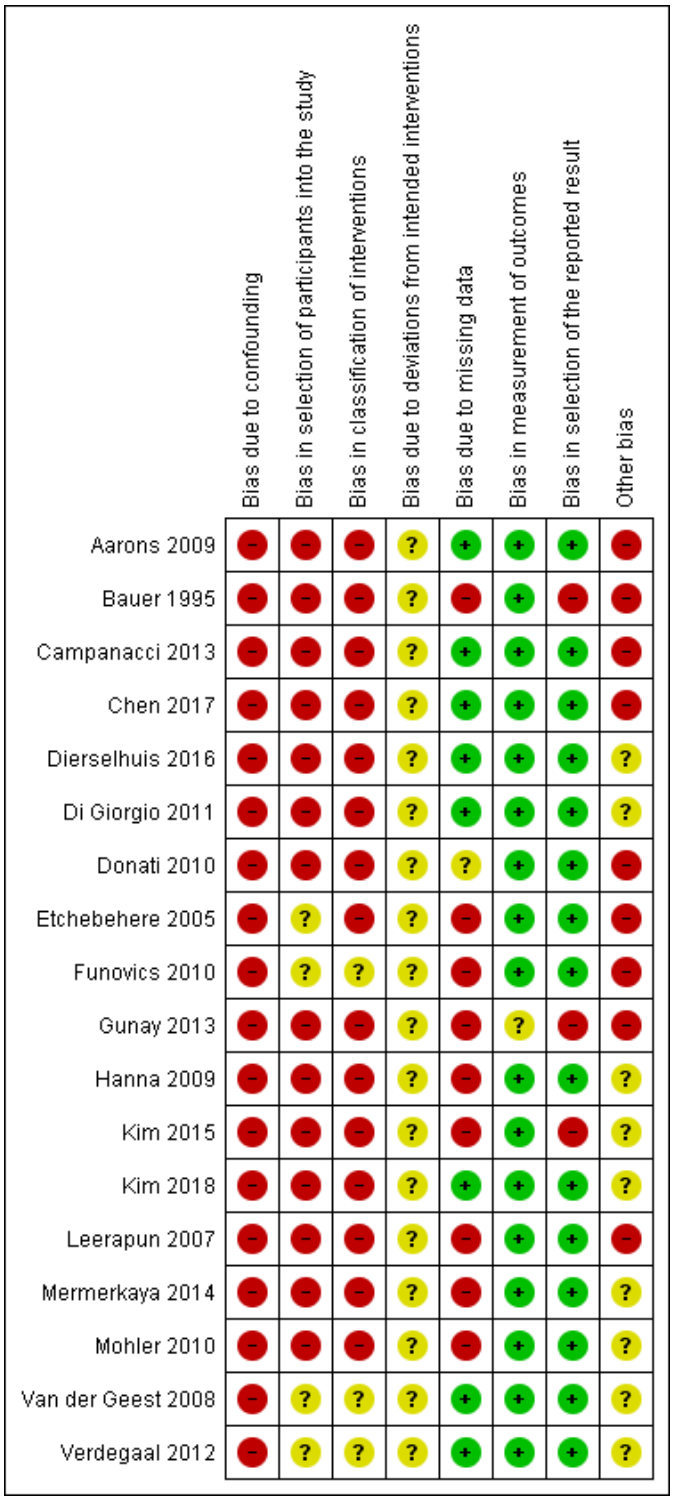
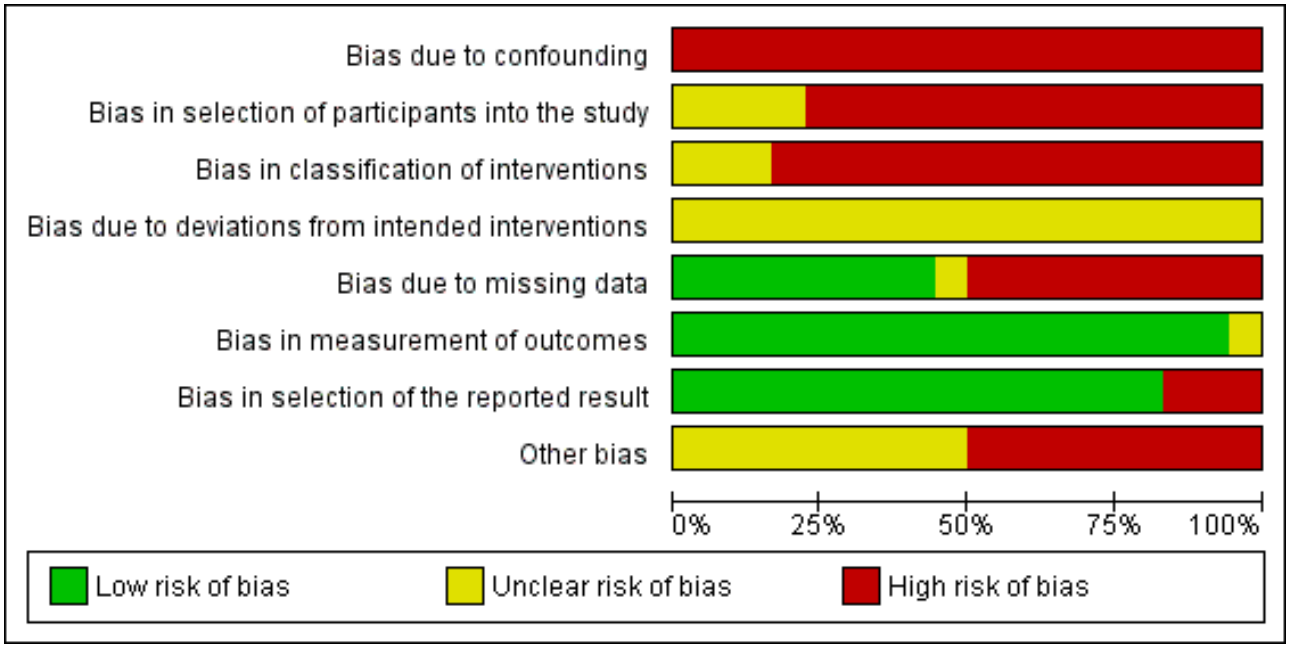


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Bias due to confounding

Risk of bias due to confounding was high in all studies

Bias in selection of participants into the study

Risk of bias in selection of participants into the study was high in all studies, except for Etchebehere 2005, which we regarded as unclear risk.

Bias in classification of interventions

Risk of bias in classification of interventions was high in all studies, except for Funovics 2010, Van der Geest 2008, Verdegaal 2012, which were regarded as unclear.

Bias due to deviations from intended intervention

Risk of bias due to deviations from intended intervention was unclear in all studies

Bias due to missing data

In Aarons 2009, Campanacci 2013 and Chen 2017 there was a low risk of bias due to missing data. There was a high risk of bias in Bauer 1995, Etchebehere 2005, and Gunay 2013, and an unclear risk in Donati 2010.

Bias in measurement of outcomes

Risk of bias in measurement of outcomes was low in all studies, except for Gunay 2013, which we regarded as unclear risk.

Bias in selection of the reported result

Risk of bias in selection of the reported result was low in Aarons 2009, Campanacci 2013, Chen 2017, Donati 2010 and Etchebehere 2005. High risk of bias was expected in Bauer 1995 and Gunay 2013.

Other bias

In all studies there was a risk of bias as groups were not controlled for experience of the surgeon, and pre-operative functioning level of the participants. Nevertheless, all studies took place in tertiary referral hospitals, where we would expect to find an experienced operating team.

From risk of bias to certainty of evidence

As all outcomes were based on solely observational studies, the entry point of the outcomes on a certainty-of-evidence level was low. Further adjustment of the level of certainty of the evidence is indicated under Effects of interventions section.

Effects of interventions

See: **Summary of findings for the main comparison** Intralesional treatment versus wide resection for central, low-grade (grade I) chondrosarcoma in the long bones

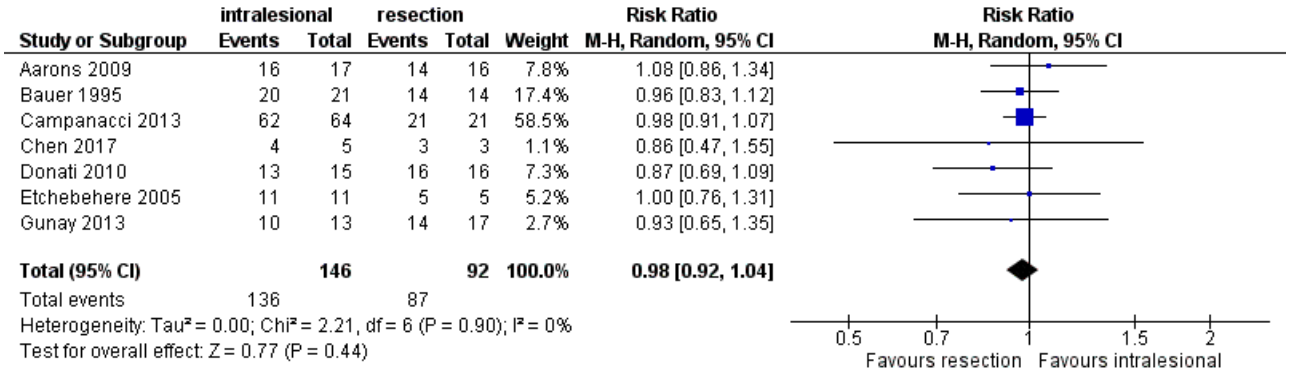
Quantitative synthesis: controlled studies included in meta-analysis

Data from the comparative studies are represented in the Summary of findings for the main comparison.

Recurrence-free survival

There is very low-certainty evidence (observational studies with a serious risk of bias) from seven studies (n = 238) that the difference in recurrence-free survival after intralesional treatment versus wide resection for central LGCS in the long bones is not statistically significant (RR 0.98; 95% CI 0.92 to 1.04; Analysis 1.1; Figure 4). There was one participant with upgrading of tumour to grade II, treated with second surgery with no evidence of disease at known follow-up (Campanacci 2013). As is shown in Figure 4, $I^2 = 0\%$, which implies that there was no evidence of substantial heterogeneity.

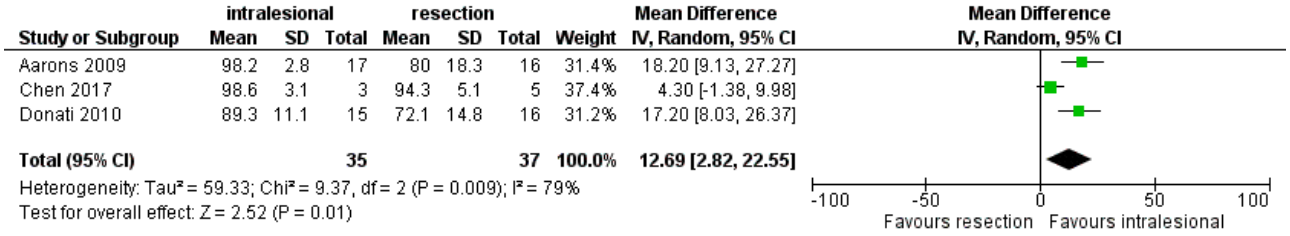
Figure 4. Forest plot of comparison 1. Comparative studies, outcome 1.1 recurrence-free survival. Event = recurrence-free survival



Functional outcome

There is low-certainty evidence (observational studies with a serious risk of bias) from three studies (n = 72) that intralesional surgery is more effective in acquiring higher MSTS scores than wide resection (93% versus 78%, respectively; mean difference 12.7; 95% CI 2.8 to 22.6; P < 0.001; Analysis 1.2; Figure 5). We upgraded the certainty of evidence from very low to low due to the large effect.

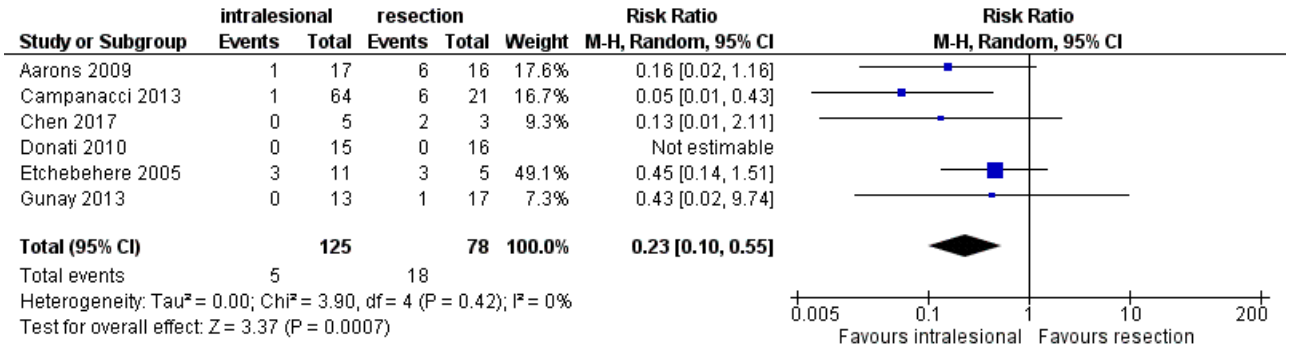
Figure 5. Forest plot of comparison 1. Comparative studies, outcome 1.2 function by MSTS score



Major complications

There is low-certainty evidence (observational studies with a serious risk of bias) from six studies (n = 203) that intralesional surgery is more effective in preventing major complications (5/125) as compared to wide resection (18/78 cases), with RR 0.23 (95% CI 0.10 to 0.55; Analysis 1.3; Figure 6). We upgraded the certainty of evidence from very low to low due to the large effect.

Figure 6. Forest plot of comparison 1. Comparative studies, outcome 1.3 complications. Event = major complication (e.g. fracture, infection)



Narrative summary of case series and studies not included in meta-analysis

Several studies were case series describing one type of treatment, or we were unable to extract data from them, so we have included these studies in the narrative summary only because we could not include them in the meta-analysis.

Recurrence-free survival (case series, exact participant data available)

Recurrence-free survival in the case series in which curettage with adjuvant was applied, was 96% in Di Giorgio 2011 (23 participants), 95% in Dierselhuis 2016 (108 participants), 95% in Hanna 2009 (39 participants), 100% in Kim 2015 (36 participants), 100% in Kim 2018 (24 participants), 100% in Mermerkaya 2014 (21 participants) and 91% in Mohler 2010 (22 participants), all in line with the meta-analysis. In Di Giorgio 2011, there was one participant with upgrading of tumour to grade II, treated with second surgery with no evidence of disease at known follow-up. We were unable to synthesise data from these case series into the meta-analysis due to lack of control group.

Recurrence-free survival (comparative studies or case series, exact participant data not available)

Funovics 2010 treated 70 participants with LGCS in the trunk and extremities. Local recurrence occurred in eight participants (11.4%), all in the intralesional (17.9%), or marginal (14.3%), and none in the wide resection group. Recurrence-free survival was significantly better for participants with extremity lesions compared to truncal lesions with 94.0% and 91.5% at 24 and 48 months, in line with the meta-analysis. Leerapun 2007 analysed 70 participants with LGCS in the long bones that were treated either by marginal or wide resection, or by intralesional treatment. Overall five-year recurrence-free survival was 89%, which was not in line with the meta-analysis. There was no difference in survival between intralesional excision (79%) and wide resection (91%) respectively, in line with the meta-analysis. Overall mortality was 2.9%, with one participant after development of a dedifferentiated out of local recurrence and one after local recurrence with upgrading to grade II tumour after resection, which is not in line with the meta-analysis. Verdegaal 2012 analysed 85 participants with LGCS in the long bones, treated by intralesional surgery with local adjuvant. After mean follow-up of 6.8 years there was a 94% recurrence-free survival, in line with the meta-analysis. No metastases, upgrading of tumour or death due to disease was observed, also in line with the meta-analysis. Van der Geest 2008 treated 130 tumours in 123 participants with curettage and cryotherapy. They included active enchondromas (n = 18), aggressive enchondromas (n = 57) and LGCS (n = 55). During follow-up two participants (2%) suffered from a local recurrence, both were participants with an enchondroma. None of the participants with LGCS had a local recurrence, or other oncologic events, in line with the meta-analysis.

Functional outcome (case series, exact participant data available)

The following studies documented MSTS scores: Di Giorgio 2011 (mean 90%); Hanna 2009 (mean 94%); Kim 2018 (mean 92%); Mermerkaya 2014 (mean 95%); and Mohler 2010 (mean 91%). These results were all in line with the meta-analysis.

Major complications (case series, exact participant data available)

In Di Giorgio 2011, major complications occurred in 13% of participants; in Dierselhuis 2016, 15%; and in Kim 2015, 17%; these results were not in line with the meta-analysis. In Kim 2018, no complications occurred, in Mermerkaya 2014 and Mohler 2010, 5% of participants suffered from complications, in line with the meta-analysis.

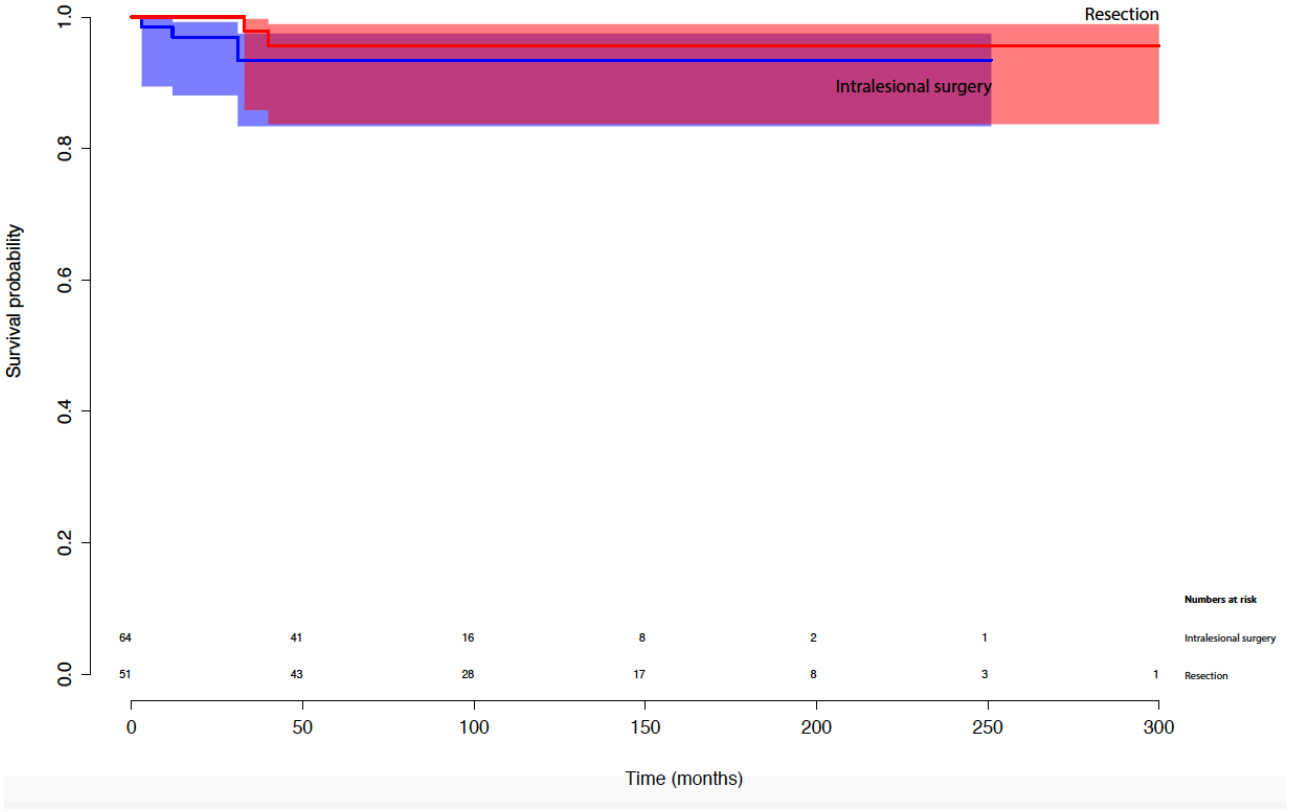
Major complications (comparative studies or case series, exact participant data not available)

Complications occurred in 13% of participants in Funovics 2010, with 5% in the intralesional group versus 29% in the wide resection group (P value = 0.002), in line with the meta-analysis. In Verdegaal 2012, one participant (1.2%) suffered from a wound infection and two participants (2.4%) from a femoral fracture, in line with the meta-analysis. Verdegaal 2012 re-operated on 11 participants for suspected recurrences, which were confirmed in five cases. Eighteen post-operative fractures occurred (14%) in the series from Van der Geest 2008, which was not in line with meta-analysis.

Individual participant data

Kaplan-Meier analysis of the data from 115 individual participants (wide resection n = 51, intralesional surgery n = 64), across four studies (Aarons 2009, Bauer 1995, Donati 2010, Etchebehere 2005), demonstrates 96% recurrence-free survival after a maximum follow-up of 300 months after resection versus 94% recurrence-free survival after a maximum follow-up of 251 months after intralesional treatment (P value = 0.58; Figure 7). Local recurrence or metastases were not reported after 41 months in either treatment group.

Figure 7. Kaplan Meyer survival curve of recurrence-free survival of participants with LGCS in the long bones. P = 0.58



DISCUSSION

The objective of this systematic review was to compare the outcome of intralesional surgery versus wide resection for central LGCS of the long bones. The primary endpoint was recurrence-free survival with a minimal follow-up of two years after index surgery. Secondary endpoints were incidence of tumour upgrading, functional outcome (as measured by the MSTS score) and the overall rate of complications.

Summary of main results

The review found little or no difference in recurrence-free survival after intralesional surgery as compared to wide resection in LGCS of the long bones (Analysis 1.1). Intralesional surgery probably led to better functional outcome (Analysis 1.2), and demonstrated lower major complication rates (Analysis 1.3). Taking into account all limitations from the included studies, we graded the evidence for these outcomes as very low and low certainty. With respect to the qualitative analysis, all but one study (Leerapun 2007), were in line with the meta-analysis concerning recurrence-free survival. In four case series (Di Giorgio 2011; Dierselhuis 2016; Kim 2015; Van der Geest 2008), there were a relatively high number of post-operative fractures, either due to non-aggressive plating or use of cryosurgery.

Overall completeness and applicability of evidence

There is very low-certainty evidence on the treatment of LGCS in the long bones based on the retrospective comparative studies and case series. However, the participants included in the studies and the applied techniques represent the known patient population and are therefore relevant to current practice. All the studies documented the event of a local recurrence or other signs of disease. All local recurrences occurred within 41 months after index surgery; 63% of the participants had a minimal follow-up of five years. Aarons 2009, Chen 2017, Di Giorgio 2011, Donati 2010, Hanna 2009, Mermerkaya 2014 and Mohler 2010 measured functional outcome in 175/487 (36%) of the participants. The studies did not describe the time-point at which they assessed functional outcome, however we hypothesised that the studies had documented it at the final stage of follow-up. The occurrence of major complications was documented in most participants (413/487; 85%), except in Bauer 1995 and Hanna 2009. However, several studies did not document loss to follow-up (Donati 2010; Etchebehere 2005; Gunay 2013; Hanna 2009; Kim 2015; Mermerkaya 2014; Mohler 2010). This might have biased outcomes, since participants that died due to disease or were referred to other centres may not have been included.

Quality of the evidence

Certainty (quality) of the evidence was very low according to GRADE (Summary of findings for the main comparison), and 'Risk of bias' assessment, since only retrospective comparative studies and case series were available for inclusion in this review. Observational studies initially have a low level of evidence certainty, and consequently, we downgraded the included studies considering the high risk of biases. For the secondary outcomes (functional outcome and complications), there was a large effect, which allowed us to upgrade the level of evidence by one level. To date, there are no prospective studies available in literature nor any RCTs. However, we were able to extract individual data from 115 participants, which enabled as to compute a Kaplan Meyer curve of recurrence-free survival. In this way, progression of disease for LGCS could be reconstructed in detail. It is not to be expected that the level of evidence will increase in studies to come, unless prospective cohort studies evaluating a treatment strategy are designed.

Potential biases in the review process

The oncological outcomes presented in many of the comparative studies should be interpreted with caution, as these studies are highly susceptible to selection bias, since people treated by intralesional curettage tended to have less aggressive LGCS (Aarons 2009; Bauer 1995; Donati 2010; Gunay 2013). Moreover, case series only reported the outcome of intralesional surgery, while people with more aggressive tumours radiologically were managed with wide resection, and thus excluded. Furthermore, case series concerning intralesional treatment might be subject to publication bias favouring the series in which participants do well. An important distinction should also be highlighted with respect to Enneking stage IA and IB disease. Cortical breakthrough may be a sign of increased local aggressiveness; the implication in terms of treatment modality is unclear and raises the question as to whether these lesions should be treated along the same lines or not. Only Bauer 1995 and Gunay 2013 reported treatment of Enneking stage IB explicitly. Bauer 1995 treated four cases with stage IB, three by intralesional treatment and one by wide resection. None of these tumours developed a local recurrence. Gunay 2013 treated all 11 cases with stage IB LGCS by wide resection. Of these, two (18%) developed a local recurrence. This rate is higher than that reported by other studies in this review, but is nevertheless comparable to their overall rate of local recurrence (6/30 participants (20%)).

Agreements and disagreements with other studies or reviews

We are uncertain whether intralesional surgery improves recurrence-free survival, functional outcome and complication rates compared to wide resection, as we assessed the certainty of the evidence as being very low. Nevertheless, this analysis seems in line with the previously published meta-analysis of Hickey 2011. It should be noted that one study that we included in the narrative summary observed death due to disease (Leerapun 2007), one case after intralesional treatment and one case after wide resection. This is in conflict with the results from all the other included studies. We are not able to solve the controversy whether local recurrence precedes upgrading of tumour, or that local recurrence is the consequence of a underdiagnosed higher-grade tumour. Although speculative, it is not unthinkable that the absence of (high-certainty) magnetic resonance imaging in the 1970's and 1980's could have led to a higher rate of underdiagnosed tumours. This is supported by the fact that death due to disease is no longer seen in studies that are published after 2010, although this could also be subject to publication bias.

AUTHORS' CONCLUSIONS

Implications for practice

There was very limited and very low-certainty evidence on how to treat central low-grade chondrosarcoma (LGCS) of the long bones. We only found retrospective comparative studies or case series, which are greatly biased by patient selection. Based on these data, there is evidence of very low certainty that recurrence-free survival is equal between intralesional treatment and wide resection. There is evidence of very low certainty that intralesional surgery increases functional outcome as reported by Musculoskeletal Tumor Society (MSTS) scores. The included studies described many forms of adjuvants, such as phenolisation, the use of nitrogen, anhydrous alcohol and the application of polymethyl methacrylate (PMMA). Details regarding the use of these adjuvants were lacking in most studies and so we could not assess them.

Among the papers included in the meta-analysis and Kaplan Meyer calculation, there were no local recurrences after 41 months. Only three cases have been reported in modern literature where local recurrence occurred beyond five years for this tumour subtype. Verdegaal 2012 and Meftah 2013 reported cases of local recurrence at 64 months, 91 months and 67 months respectively.

Implications for research

Considering the low incidence of this disease and the oncologic sequelae, such as local recurrence, future research is best performed in a multinational setting. The current level of evidence supporting intralesional treatment of LGCS is of very low certainty. Nevertheless, in our opinion a prospective randomised controlled trial comparing intralesional treatment versus wide resection may be unwarranted for both practical and ethical reasons. As this review has demonstrated, local recurrence after intralesional treatment occurs in approximately 5% of people only, with no demonstrable negative effect on patient survival. Future research should, perhaps, instead focus on less invasive treatment strategies for these tumours by identifying predictors that help to stratify people for surgical intervention or close observation. During the development of this review, the World Health Organization (Fletcher 2013), renamed LGCS as an atypical cartilaginous tumour (ACT). By definition, they are now tumours of borderline or low malignant potential. Although outside the scope of this review, considering the very low number of reported local recurrences and the fact the metastasis is so rare, there may even be a case for observation of smaller, less active lesions, especially those without cortical scalloping.

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CHARACTERISTICS OF STUDIES

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

Aarons 2009

Methods	**Study design**: retrospective cohort study **Country**: USA **Setting**: single-centre; hospital; 1989-2005
Participants	**Total participants**: n = 33 (resection n = 16; intralesional n = 17) **Loss to follow-up:** 3 participants died to unrelated cause **Age mean (range):** resection 48 (21-80); intralesional 51 (14-76) **Sex M:F:** 12:21 **Inclusion criteria:** grade I CS of the long bones of the appendicular skeleton, treated operatively **Exclusion criteria:** local recurrent disease or metastasis at presentation; extracompartmental (stage IB) disease **Follow-up months (range):** 24-203
Interventions	**Resection:** resection with variable reconstructions: intercalary allograft, osteoarticular allograft, endoprosthesis, allograft-endoprosthesis composites **Intralesional:** 3 cycles of extended curetting; variable adjuvants (phenol, liquid nitrogen, PMMA, hydrogen peroxide, none) Selected prophylactic internal fixation
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** MSTS scores; complications
Notes	Individual participant data. Extra data (1 participant) were obtained from the study authors
Risk of bias	

Bias	Authors' judgement	Support for judgement

Aarons 2009 *(Continued)*

Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a retrospective study comparing 2 surgical techniques, the more aggressive technique might have been used for the more aggressive featured tumours. However, since only Enneking Grade IA tumours are included, it can be expected that baseline tumour characteristics are probably alike.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	There were no missing data concerning the pre-described outcomes.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Bauer 1995

Methods	**Study design**: retrospective cohort study **Country**: Sweden **Setting**: single-centre; hospital; 1967-1991
Participants	**Total participants**: original article n = 40. After exclusion n = 35 (resection n = 13; intralesional n = 22) **Loss to follow-up:** 2 participants moved abroad; 4 participants died due to unrelated causes **Age range:** 14-70 **Sex M:F:** 18:17 **Inclusion criteria:** histologically proven grade I CS, tumours in the extremities **Exclusion criteria:** tumours in the hand **Follow-up months (range):** 24-300
Interventions	**Resection:** resection with or without reconstructions: intercalary allograft, osteoarticular allograft, endoprosthesis **Intralesional:** intralesional curettage, filled either with bone chips or PMMA
Outcomes	Local recurrence and metastases
Notes	Individual participant data. Five participants were excluded from this analysis since they did not meet the inclusion criteria for this review: 3 participants were treated conservatively, 1 had a tumour in the foot and 1 in the patella

Bauer 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a retrospective study comparing 2 surgical techniques, with both Enneking grade IA and IB tumours. Intralesional treatment of grade IB tumours could lead to a higher local recurrence rate, although this is not reported. Participants are included over multiple decades (1960s to present), which does raise some concern over the ability to achieve a correct histopathology diagnosis (i.e. distinguishing these lesions from enchondroma and higher-grade CS) given imaging technology limitations.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Although the given individual participant data are complete, local recurrence might be underreported considering the available imaging techniques.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	High risk	Outcome parameters were not well pre-described.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Campanacci 2013

Methods	**Study design**: retrospective cohort study **Country**: Italy **Setting**: single-centre; hospital; 1994-2010
Participants	**Total participants**: n = 85 (resection n = 21; intralesional n = 64) **Loss to follow-up:** none **Age mean (range):** 50 (20-76) **Sex M:F:** 24:61 **Inclusion criteria:** participants treated for central grade 1 CS of long bones **Exclusion criteria:** insufficient follow-up (< 24 months) **Follow-up months (range):** 24-206
Interventions	**Resection:** resection with variable reconstructions: intercalary allograft, osteoarticular allograft, endoprosthesis, allograft-endoprosthesis composites

Campanacci 2013 *(Continued)*

	Intralesional: curettage with phenol/ethanol as local adjuvant in 69% of cases. Filling of the cavity was done with allogenic bone chips in 60 cases, PMMA in 3 cases and bone graft substitute in 1 case.
Outcomes	**Primary outcome:** local recurrence, metastases and/or upgrading of tumour **Secondary outcome:** complications
Notes	Aggregated data. We tried to contact the study author to obtain individual participant data, but we were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a retrospective study where tumours with more aggressive radiological features were treated by wide resection. Case selection may therefore influence the estimate of the treatment effect in favour of intralesional surgery since only the less aggressive cases were treated by curettage.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	There were no missing data concerning the pre-described outcomes.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Chen 2017

Methods	**Study design**: retrospective cohort study **Country**: Taiwan **Setting**: single-centre; hospital; 1998-2013
Participants	**Total participants**: original article n = 11. After exclusion n = 8 (resection n = 3; intralesional n = 5) **Loss to follow-up:** not clearly mentioned; 1 participant died due to unrelated cause **Age range:** 20-71 **Sex M:F:** unknown **Inclusion criteria:** stage IA CS

Chen 2017 *(Continued)*

	Exclusion criteria: locally recurrent or metastatic disease at present; participants diagnosed with so-called borderline, grade I-II CS from preoperative biopsy; secondary CS; extraosseous lesions; stage IB CS **Follow-up months (range):** 24-300
Interventions	**Resection:** wide excision, reconstruction with arthroplasty or extracorporeal irradiated bone **Intralesional:** curettage, adjuvant phenolisation or cryotherapy. Allograft
Outcomes	Local recurrence, progression of disease, complications, MSTS scores
Notes	Individual participant data. 3 participants with acetabular lesions were excluded for analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	Tumours were all stage IA tumours, and tumour size was not significantly different between groups. However, the latter could be a result of the small sample size. Mean tumour size was 6.9 ± 5.1 cm and 12.5 ± 3.1 cm in the intralesional group and resection group respectively, which suggests that the larger tumours were treated more aggressively. Moreover, participants in the resection group were significantly older (34.0 ± 13.3 years versus 61.0 ± 7.7 years P < 0.001), which might overestimate the risk of complications and underestimate functional outcome.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented
Bias due to missing data	Low risk	There were no missing data concerning the pre-described outcomes
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Di Giorgio 2011

Methods	**Study design**: case series **Country**: Italy **Setting**: single-centre; hospital; 1997-2008
Participants	**Total participants**: n = 23

Di Giorgio 2011 *(Continued)*

	Loss to follow-up: not mentioned **Age mean (range):** 45 (29-71) **Sex M:F:** 11:12 **Inclusion criteria:** intramedullary grade I CS of a long bone, with diagnosis based on clinical, radiological and histological findings **Exclusion criteria:** not mentioned **Follow-up months (range):** 30-132
Interventions	**Intralesional:** curettage, adjuvant phenol/ethanol and filling with either PMMA or bone chips
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** MSTS scores; complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a retrospective case series that only included cases treated intralesionally. Dimensions and stage of tumour are unknown, so there is a potential that mainly small, stage IA tumours were included and that larger, more aggressive tumours were treated by wide resection and excluded from the study.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	There were no missing data concerning the pre-described outcomes.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Dierselhuis 2016

Methods	**Study design**: case series **Country**: the Netherlands **Setting**: single-centre; hospital; 2006-2012

Dierselhuis 2016 *(Continued)*

Participants	**Total participants**: n = 112 **Loss to follow-up:** 4 **Age mean (range):** 54 (25-82) **Sex M:F:** 1:1.8 **Inclusion criteria:** intramedullary LGCS of a long bone, with diagnosis based on clinical, radiological and histological findings **Exclusion criteria:** previous treatment in other hospital **Follow-up months (range):** 24.3-97.5
Interventions	**Intralesional:** curettage, adjuvant phenol/ethanol and filling with either PMMA, bone chips or synthetic bone (Vitoss® or PRO-DENSE®)
Outcomes	**Primary outcome:** local recurrence or presence of residual tumour after surgery **Secondary outcome:** death from disease, metastasis, tumour upgrading or dedifferentiation, and type and rate of complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a case series that only describes one technique, which could be subject to selection bias. However, all types of CS1 in the long bones, with varying dimension up to 100 cm3 were included. However, stage IB tumours were not included and probably treated more aggressively.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	There were no missing data concerning the pre-described outcomes.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Donati 2010

Methods	**Study design**: retrospective cohort study

Donati 2010 *(Continued)*

	Country: Italy **Setting**: single-centre; hospital; 1977-1998
Participants	**Total participants**: n = 31 (resection n = 16; intralesional n = 15) **Loss to follow-up:** not mentioned **Age mean (range):** 35 (13-67) **Sex M:F:** 13:18 **Inclusion criteria:** grade I CS in the long bones **Exclusion criteria:** presence of Ollier's disease, inadequate radiographic documentation, < 60 months' follow-up, tumour in short bones or consultation only **Follow-up months (range):** 66-296
Interventions	**Resection**: resection with variable reconstructions: intercalary allograft, osteoarticular allograft, or endoprosthesis **Intralesional:** curettage, some with local adjuvant: phenol/ethanol or liquid nitrogen. Filling with PMMA, allograft or autograft. 3 participants had hardware stabilisation
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** MSTS scores; complications
Notes	Individual participant data

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This is a retrospective study comparing intralesional surgery versus wide resection, in which participants showing bone enlargement, moderate to deep scalloping and interruption of the cortex with invasion of the soft tissues were treated by wide resection. Hence, tumours showing more aggressive features were treated more aggressively as well. This could favour curettage over wide resection in terms of local recurrence.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Unclear risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.

Donati 2010 *(Continued)*

Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Etchebehere 2005

Methods	**Study design**: retrospective cohort study **Country**: Brazil **Setting**: single-centre; hospital; date unknown
Participants	**Total participants**: original article n = 23. After exclusion n = 16 (resection n = 5; intralesional n = 11) **Loss to follow-up:** unknown causes **Age mean (range):** unknown **Sex M:F:** unknown **Inclusion criteria:** grade I CS, confirmed by histology. Enneking stage 1A and 1B were included. **Exclusion criteria:** < 24 months' follow-up **Follow-up months (range):** 24-192
Interventions	**Resection:** wide resection with or without endoprosthesis **Intralesional:** curettage with or without adjuvant cauterisation and/or PMMA
Outcomes	Complications, evidence of disease
Notes	Individual participant data. We excluded 7 participants from this analysis since they did not meet the inclusion criteria for this review: 2 tumours were localised in a phalanx, 1 in a metatarsal, 1 in the scapula, 1 in the ischium and 2 were peripheral CSs

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	Unclear risk	Choice of treatment is not well described, therefore we cannot judge on what basis participants were treated by either treatment type.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Reason for loss to follow-up was not described.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.

Etchebehere 2005 *(Continued)*

Bias in selection of the reported result	Low risk	Although the given results have not been prespecified in all cases, the most important parameters (oncological results and complications) were well documented.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Funovics 2010

Methods	**Study design**: retrospective cohort study **Country**: Austria **Setting**: single-centre; hospital; 1968-2006
Participants	**Total participants**: n = 70 (wide resection n = 24, marginal n = 7, intralesional n = 39; trunk n = 17, extremity n = 53) **Loss to follow-up:** not mentioned **Age mean (range):** 40 (10-72) **Sex M:F:** 39:31 **Inclusion criteria:** diagnosis of LGCS in any bone based on clinical exploration, radiography and histological evaluation **Exclusion criteria:** not mentioned **Follow-up months (range):** 6-317
Interventions	**Intralesional:** curettage, high speed burring and PMMA, with or without plating **Resection:** resection with or without reconstruction (prosthesis and/or allograft)
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** complications
Notes	Tumours involving the hand and foot were included in the series, and cannot be excluded from the whole cohort as it is presented in the article. We tried to contact the study authors for additional data, which could not be obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	Unclear risk	In this study, for tumours in extremities, margins were intralesional, marginal or wide. It is not clear on which grounds participants were treated by one of the techniques.
Bias in classification of interventions	Unclear risk	See above

Funovics 2010 *(Continued)*

Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up, other than unrelated death, was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Gunay 2013

Methods	**Study design**: retrospective cohort study **Country**: Turkey **Setting**: single-centre; hospital; 1995-2011
Participants	**Total participant**s: n = 30 **Loss to follow-up:** not mentioned **Age mean (range):** 41 (16-69) **Sex M:F:** 12:18 **Inclusion criteria:** grade I CS, confirmed by histology. Enneking stage 1A and 1B were included. **Exclusion criteria:** < 24 months' follow-up **Follow-up months (range):** resection 75 (24-186); intralesional 73 (26-124)
Interventions	**Resection:** wide resection with reconstructions, including PMMA, allograft/autograft, endoprosthesis, intramedullary nailing, or Ilizarov external fixator **Intralesional:** curettage and local adjuvant, PMMA or bone autograft/allograft. 2 participants had hardware stabilisation
Outcomes	**Primary outcome:** local recurrence, metastases and/or upgrading of tumour **Secondary outcome:** complications
Notes	Aggregated data. We tried to contact the study author to obtain individual participant data but were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.

Gunay 2013 *(Continued)*

Bias in selection of participants into the study	High risk	Tumours that extended into the soft tissue (Enneking IB) or tumours that were larger > 8 cm were all treated by wide resection. Hence, tumours showing more aggressive features were treated more aggressively as well. This could favour curettage over wide resection in terms of local recurrence.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Unclear risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	High risk	Outcome parameters were not well pre-described.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Hanna 2009

Methods	**Study design**: case series **Country**: UK **Setting**: single-centre; hospital; 1999-2005
Participants	**Total participants**: n = 39 **Loss to follow-up:** not mentioned **Age mean (range):** 55 (32-82) **Sex M:F:** 10:29 **Inclusion criteria:** grade 0.5 and I CS, confirmed by histology **Exclusion criteria:** < 36 months' follow-up; lesions breaching the bone cortex and/or associated with a soft tissue mass **Follow-up months (range):** 61 (36-104)
Interventions	**Intralesional:** curettage and filling with PMMA
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** MSTS scores, metastases and/or upgrading of tumour and complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Hanna 2009 *(Continued)*

Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	This study included grade 0.5 tumours, which could be regarded as a more benign tumour. Therefore, the number of local recurrences given in the study might not reflect the true potential of LGCS to recur.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Kim 2015

Methods	**Study design**: case series **Country**: South Korea **Setting**: single-centre; hospital; 1997-2012
Participants	**Total participants**: n = 36 **losses to follow-up:** not mentioned **Age mean (range):** 46 (18-67) **Sex M:F:** 13:23 **Inclusion criteria:** grade I CS, confirmed by histology **Exclusion criteria:** < 24 months' follow-up; participants who underwent wide excision because of a pathological fracture or extraosseous extension; no use of anhydrous alcohol adjuvant; history of previous surgical treatment; insufficient information from the medical record **Follow-up months (range):** 62 (24-169)
Interventions	**Intralesional:** curettage and additional burring, treatment with anhydrous alcohol, followed by filling of the defect with bone graft or PMMA
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** metastases and/or upgrading of tumour, complications
Notes	

Kim 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	Tumours that showed signs of higher aggressiveness (pathological fracture and extra-osseous extension) were excluded. This could favour intralesional surgery as only the less aggressive tumours were analysed.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	High risk	Outcome parameters were not well pre-described.
Other bias	Unclear risk	Not applicable

Kim 2018

Methods	**Study design**: case series **Country**: South Korea **Setting**: single-centre; hospital; 2004-2013
Participants	**Total participants**: n = 24 **losses to follow-up:** not mentioned **Age mean (range):** 45 (18-62) **Sex M:F:** 9:15 **Inclusion criteria:** grade I CS, confirmed by histology. Principal indication for surgery was an endosteal erosion and tumour > 6 cm in longitudinal length **Exclusion criteria:** < 48 months' follow-up; ACT not in a long bone; escalated histological grade after definitive surgery; separated lesion that was not included within the range of curettage. 1 case was treated conservatively. In the event of extraosseous soft-tissue extension, the tumour was resected. **Follow-up months (interquartile range): 66** (50-84)
Interventions	**Intralesional:** curettage and additional burring, treatment with hydrogen peroxide and saline rinsing, followed by filling of the defect with bone graft or PMMA. In 16 participants, prophylactic hardware was used.
Outcomes	**Primary outcome:** local recurrence

Kim 2018 *(Continued)*

	Secondary outcome: metastases and/or upgrading of tumour, complications, MSTS scores
Notes	The data presented in this paper are from a different institute than Kim 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	Only stage 1A tumours were treated by curettage, which could favour local recurrence rates.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	There was no loss to follow-up.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Leerapun 2007

Methods	**Study design**: retrospective cohort study **Country**: USA **Setting**: single-centre; hospital; 1980-2001
Participants	**Total participants**: 70 (intralesional n = 13, wide resection n = 57) **Loss to follow-up:** not mentioned **Age mean (SD):** 37 ± 19.3 (intralesional) 43 ± 18.4 (wide resection) **Sex M:F:** 1:1.6 **Inclusion criteria:** intramedullary lesion of the appendicular extremity with definite histologic diagnosis of LGCS **Exclusion criteria:** variants of CS, including secondary peripheral CS, dedifferentiated CS, soft tissue CS, clear cell CS, synovial CS, and mesenchymal CS. Moreover, participants with tumours in the axial skeleton, pelvis, spine, foot, and hand were excluded. Grade 0.5 and borderline CS also excluded **Follow-up months (range):** 91 (4-274)
Interventions	**Intralesional:** curettage with phenolisation and bone graft or PMMA

Leerapun 2007 *(Continued)*

	Wide resection: not further specified
Outcomes	**Primary outcome:** disease-free survival **Secondary outcome:** local recurrences, metastases, death due to disease
Notes	The follow-up interval (see methods section, minimum 2 years) was insufficient, and individual participant data were not available for extraction. We tried to contact the study author to obtain individual participant data but were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	In the group of participants treated by resection, there were more with cortical disruption and soft tissue extension. Hence, tumours showing more aggressive features were treated more aggressively as well. This could favour curettage over wide resection in terms of local recurrence.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	High risk	Groups were not controlled for experience of the surgeon and pre-operative functioning level of the participants.

Mermerkaya 2014

Methods	**Study design**: case series **Country**: Turkey **Setting**: single-centre; hospital; 2007-2012
Participants	**Total participants**: n = 21 **Loss to follow-up:** not mentioned **Age mean (range):** 49 (18-71) **Sex M:F:** 7:14 **Inclusion criteria:** Grade I CS, confirmed by histology

Mermerkaya 2014 *(Continued)*

	Exclusion criteria: < 24 months' follow-up; lesions breaching the bone cortex and/or associated with a soft tissue mass **Follow-up months (range):** 58.4 (24-85)
Interventions	**Intralesional:** curettage followed by application of high-speed burring, thermal cauterisation and PMMA
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** complications, MSTS scores
Notes	It was not possible to extract the data needed from the presented data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	Tumours that showed signs of higher aggressiveness (breaching the bone cortex and/or associated with a soft tissue mass) were excluded. This could favour intralesional surgery as only the less aggressive tumours were analysed.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Mohler 2010

Methods	**Study design**: case series **Country**: USA **Setting**: single-centre; hospital; 1997-2008
Participants	**Total participants**: original article n = 46. After exclusion n = 22 **Loss to follow-up:** not mentioned **Age mean (range):** 51.1 (37-73) **Sex M:F:** 7:15

Mohler 2010 *(Continued)*

	Inclusion criteria: enchondroma, grade 0.5 and I CS, assessed by clinical, radiological and histological results **Exclusion criteria:** < 18 months' follow-up **Follow-up months (range):** 59.8 (28-134)
Interventions	**Intralesional:** curettage and 3 cycles of liquid nitrogen application with burr drilling followed by cementation of the defect and internal fixation to prevent pathologic fracture
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** complications, MSTS scores
Notes	We excluded 24 participants from this case series since they did not meet the inclusion criteria for this review: enchondroma (n = 16) and/or follow-up too short (n = 6) and/or axial skeleton tumour (n = 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	High risk	Although we were able to exclude data of participants with enchondroma, grade 0.5 tumours were also included. Therefore, the number of local recurrences given in the study might not reflect the true potential of CS1 to recur.
Bias in classification of interventions	High risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	High risk	Number of participants lost to follow-up was not documented.
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

Van der Geest 2008

Methods	**Study design**: case series **Country**: the Netherlands **Setting**: single-centre; hospital; 1994-2003
Participants	**Total participants**: 123 (130 tumours); active enchondroma n = 18, aggressive enchondroma n = 57, LGCS n = 55 **Loss to follow-up:** 1

Van der Geest 2008 *(Continued)*

	Age mean (range): 49 (13-83) **Sex M:F:** not mentioned **Inclusion criteria:** surgical treatment was performed in case of invalidating pain, scalloping of the cortex of the involved bone or suspected low-grade malignancy after biopsy. Lesions with a clinical and radiologic latent appearance were followed periodically and only treated in case of transformation to aggressive behaviour. **Exclusion criteria:** none mentioned **Follow-up months (range):** 60 (24-144) for LGCS
Interventions	**Intralesional:** curettage, cryosurgery, filling of the cavity with homologous or autologous bone chips or PMMA (3 cases). Preventive plating if necessary
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** secondary operations, complications, functional outcome by means of the MSTS
Notes	Localisation of tumour not specified, data extraction not possible. Although MSTS scores were obtained, only differences in scores between subgroups were calculated. The scores themselves were not documented. We contacted the study authors, but were not able to obtain individual MSTS scores.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	Unclear risk	The methods section suggests that only stage 1A tumours were treated, but this is not fully documented. Moreover, exclusion criteria were not mentioned. So, it is not clear whether this study group reflects the spectrum of LGCS.
Bias in classification of interventions	Unclear risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	Loss to follow-up well documented, not likely to influence outcome rates
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Most outcomes were not fully defined in the methods section, however all relevant outcome parameters according to the literature were reported.
Other bias	Unclear risk	Not applicable

Verdegaal 2012

Methods	**Study design**: case series **Country**: the Netherlands

Verdegaal 2012 *(Continued)*

	Setting: single-centre; hospital; 1994-2005
Participants	**Total participants**: 85 **Loss to follow-up:** 5 **Age mean (range):** 47 (15-72) **Sex M:F:** not mentioned **Inclusion criteria:** likely presence of LGCS located in 1 of the long bones on the Gd-MRI scan **Exclusion criteria:** none mentioned **Follow-up months (range):** 82 (2-169)
Interventions	**Intralesional:** curettage, phenolisation and allograft bone chips
Outcomes	**Primary outcome:** local recurrence **Secondary outcome:** secondary operations, complications
Notes	Minimal follow-up was insufficient (4 months) and participants with limited follow-up could not be excluded from analysis because data were presented in aggregated form. We attempted to contact the study authors for additional data, which could not be obtained. Only 5 participants had follow-up < 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	Study authors did not use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.
Bias in selection of participants into the study	Unclear risk	The methods section suggests that only stage 1A tumours were treated, but this is not fully documented. Moreover, exclusion criteria were not mentioned. So, it is not clear whether this study group reflects the spectrum of LGCS.
Bias in classification of interventions	Unclear risk	See above
Bias due to deviations from intended interventions	Unclear risk	Post-operative rehabilitation was not documented.
Bias due to missing data	Low risk	Loss to follow-up well documented, not likely to influence outcome rates
Bias in measurement of outcomes	Low risk	Blinding of participants, assessors or personnel was not applied, however we judged that the occurrence of events was unrelated to blinding.
Bias in selection of the reported result	Low risk	Inclusion criteria were well described, the pre-specified outcomes were all reported.
Other bias	Unclear risk	Not applicable

ACT: atypical cartilaginous tumour; **CS:** chondrosarcoma; **Gd-MRI:** gadolinium-magnetic resonance imaging; **LGCS:** low-grade chondrosarcoma; **MSTS:** Musculoskeletal Tumor Society; **PMMA:** polymethyl methacrylate

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

Study	Reason for exclusion
Ahlmann 2007	Case series, sample size too small (< 20); n = 10
Errani 2017	35 participants with LGCS were treated by curettage. 33 were in the long bones, 2 were in the calcaneus. After excluding participants with a follow-up < 24 months, with enchondroma and/or with a tumour not in the long bones (e.g. calcaneus), only 12 participants treated by curettage remained, which was too small as a case series.
Lee 1999	86 participants with LGCS (central and exostotic) were treated by (marginal) resection or intralesional treatment, survival for LGCS localised in the extremities was not fully documented, and could therefore not be included in the meta-analysis or narrative summary. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained
Okada 2009	Insufficient number of cases (2) to include as a case series
Ozaki 1996	Data extraction shows that were only 3 participants with long bone LGCS included. All other tumours were of higher grade, or localised in the axial skeleton or pelvis.
Puri 2009	Insufficient number of cases (11 LGCS) to include as a case series
Schreuder 1998	Study analyses a total of 23 cases, however only 9 with a final diagnosis of LGCS. Of those 9 cases, only 3 cases have a minimum follow-up of 24 months.
Souna 2010	Insufficient number of cases (15) meeting the inclusion criteria to include as a case series

LGCS: low-grade chondrosarcoma; **MSTS:** Musculoskeletal Tumor Society

Characteristics of studies awaiting assessment *[ordered by study ID]*

Andreou 2011

Methods	**Study design**: case series **Country**: Germany **Setting**: single-centre; hospital; 1982-2004
Participants	**Total participants**: n = 115 (LGCS n = 56) **Loss to follow-up:** none **Age mean (range):** 47 (14-79) **Sex M:F:** 1.56:1 **Inclusion criteria:** primary central chondrosarcoma (all grades) **Exclusion criteria:** participants treated with palliative intent or with follow-up of < 5 years after diagnosis **Follow-up years (range):** mean follow-up period for survivors was 12 (5-24) years
Interventions	Only margins mentioned (intralesional, marginal, wide and radical)
Outcomes	Overall survival (%) at 5 and 10 years

Andreou 2011 *(Continued)*

Notes	56 participants were treated for LGCS in the axial skeleton and extremities, with recurrence-free survival of 73% and 68% at 5 and 10 years respectively. Survival for LGCS localised in the extremities was not fully documented since data of extremity LGCS and axial skeleton LGCS was mixed, and could therefore not be included in the meta-analysis or narrative summary. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained.

Angelini 2012

Methods	**Study design**: case series **Country**: Italy **Setting**: single-centre; hospital; 1990-2008
Participants	**Total participants**: n = 296 (LGCS; n = 87) **Loss to follow-up:** none **Age mean (range):** 50 (13-88) **Sex M:F:** not mentioned **Inclusion criteria:** primary conventional central CS (all grades) **Exclusion criteria:** incomplete documentation on clinical characteristics, treatment and outcome **Follow-up years (range):** 7 (1.6-19.8)
Interventions	For LGCS: intralesional (38%), resection (59%) and amputation (3%)
Outcomes	Overall survival (%) at 5, 10, and 15 years
Notes	87 participants with LGCS were treated and showed recurrence-free survival for local recurrence of 90% and 88% at 5 and 10 years respectively and 99% and 5 and 10 years for metastases. They did not find a statistical difference between participants treated by intralesional treatment versus wide resection, or between extremities or trunk site tumours. However, survival for LGCS localised in the extremities was not fully documented, and could therefore not be included in the meta-analysis or narrative summary. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained.

de Camargo 2010

Methods	**Study design**: case series **Country**: Brazil **Setting**: single-centre; hospital; 1986-2006
Participants	**Total participants**: n = 46 (LGCS n = 23) **Loss to follow-up:** none **Age mean (range):** 43.6 (18-79) for LGCS **Sex M:F:** 1:1.9

de Camargo 2010 *(Continued)*

	Inclusion criteria: primary conventional central chondrosarcoma (grade 1 and 2) **Exclusion criteria:** secondary, mesenchymal, dedifferentiated periosteal and grade 3 CSs. Follow-up of < 30 months for living participants **Follow-up months (range):** 99 (32-312)
Interventions	For LGCS: intralesional (n = 19) and wide resection (n = 3)
Outcomes	Overall survival rates, local recurrence rates
Notes	This study included 23 participants with LGCS, with 22 in the appendicular skeleton. Of those, 19 participants were treated by intralesional treatment, and 3 by wide resection. In total, 6 local recurrences occurred. However, it is not specified which tumours involved the long bones (tumours in hand, feet and shoulder girdle were included as well) and it is not specified in which participants the local recurrences occurred. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained.

Ma 2009

Methods	**Study design**: case series **Country**: China **Setting**: single-centre; hospital; 1996-2007
Participants	**Total participants**: n = 66 (LGCS; n = 22) **Loss to follow-up:** not mentioned **Age mean (range):** 45 (10-79) for LGCS **Sex M:F:** 4.1:1 **Inclusion criteria:** primary conventional central CS (grades I and II) **Exclusion criteria:** clear cell, mesenchymal or extraskeletal myxoid CS; CSs diagnosed as borderline grade I/II; and cases with recurrence of CS or a surgical history in another hospital **Follow-up months (range):** 24.8 (4-131)
Interventions	For LGCS: intralesional (n = 18), wide resection (n = 3) and radical (n = 1)
Outcomes	Local recurrence-free survival rate
Notes	The follow-up interval was insufficient in some participants, and individual participant data were not available for extraction because the outcomes were presented as aggregated data. Furthermore, hand tumours were also included in the series. Moreover, there are remarkable differences in local recurrence rates as presented in the table (72%) versus the body text (60%), which raises some concerns over the consistency of the work. We attempted to contact the authors for individual participant data with tumours in the long bones, which could not be obtained.

Meftah 2013

Methods	**Study design**: case series **Country**: USA

Meftah 2013 *(Continued)*

	Setting: single-centre; hospital; 1983-2006
Participants	**Total participants**: n = 42 (43 lesions) **Loss to follow-up:** 3 **Age mean (range):** 44.9 (21.8-66.4) **Sex M:F:** 1:2.2 **Inclusion criteria:** LGCS treated with intralesional curettage and cryosurgery **Exclusion criteria:** < 5 years of follow-up **Follow-up years (range):** 10.2 (5-22.5)
Interventions	Curettage with adjuvant cryosurgery, of which 2 different types were applied: a modified Marcove direct-pour technique (n = 32) and a technique with closed-circuit cryoprobes (n = 11)
Outcomes	Local or distant tumour recurrence, complications and functional outcome (MSTS scores)
Notes	43 tumours in 42 participants with LGCS in trunk and extremities were treated by intralesional surgery with adjuvant cryosurgery. After minimal 5 years' follow-up, there were 4 local recurrences (4 participants, 9.3%), all of which involved lesions that had had soft-tissue involvement at the time of presentation. No secondary recurrences or metastases developed during follow-up. Survival for LGCS localised in the extremities was not fully documented, and could therefore not be included in the meta-analysis or narrative summary. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained.

Streitbuerger 2009

Methods	**Study design**: case series **Country**: Germany **Setting**: single-centre; hospital; 1972-2004
Participants	**Total participants**: n = 80 (primary lesions n = 69) **Loss to follow-up:** not mentioned **Age mean (range):** 45.4 (16-80) **Sex M:F:** 1:1.05 **Inclusion criteria:** LGCS of the bone in axial skeleton and extremities **Exclusion criteria:** not mentioned **Follow-up months (range):** 78.5 (2-365)
Interventions	Only margins mentioned: intralesional (with or without PMMA), marginal, wide and radical
Outcomes	Local recurrence; switch of tumour grading; metastases; second local recurrence; death of disease
Notes	80 participants were treated for LGCS (both primary and secondary tumours in pelvis or extremities) by surgical margins ranging from intralesional to wide resection. During follow-up, 17.5% of participants developed a local recurrence, of whom 3 participants (21%) showed upgrading of tumour. Metastatic disease developed in 4 participants (4.9%), of whom 3 died of disease. This study included a heterogeneous group of participants with LGCS, and data of LGCS localised in the ex-

Streitbuerger 2009 *(Continued)*

tremities was not fully documented, and could therefore not be included in the meta-analysis or narrative summary. We attempted to contact the study authors for individual participant data with tumours in the long bones, which could not be obtained.

CS: chondrosarcoma; **LGCS:** low grade chondrosarcoma; **MSTS:** Musculoskeletal Tumor Society; **PMMA:** polymethyl methacrylate

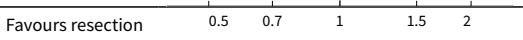
DATA AND ANALYSES

Comparison 1. outcome comparative studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence-free survival	7	238	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
2 Function by MSTS score	3	72	Mean Difference (IV, Random, 95% CI)	12.69 [2.82, 22.55]
3 Complications	6	203	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.10, 0.55]

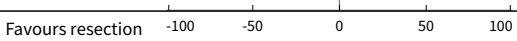
Analysis 1.1. Comparison 1 outcome comparative studies, Outcome 1 Recurrence-free survival.

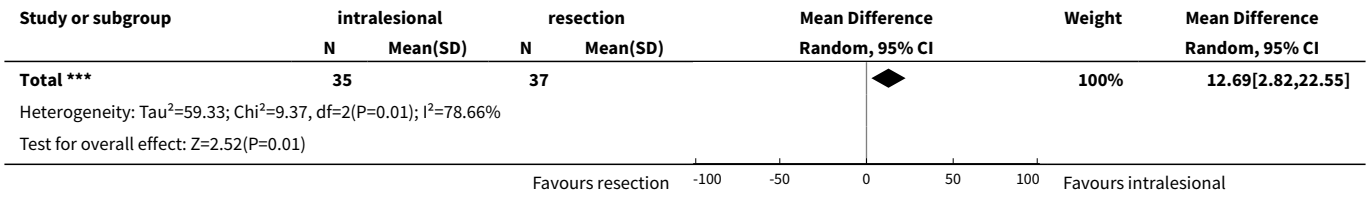
Study or subgroup	intralesional n/N	resection n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aarons 2009	16/17	14/16		7.76%	1.08[0.86,1.34]
Bauer 1995	20/21	14/14		17.39%	0.96[0.83,1.12]
Campanacci 2013	62/64	21/21		58.5%	0.98[0.91,1.07]
Chen 2017	4/5	3/3		1.07%	0.86[0.47,1.55]
Donati 2010	13/15	16/16		7.32%	0.87[0.69,1.09]
Etchebehere 2005	11/11	5/5		5.21%	1[0.76,1.31]
Gunay 2013	10/13	14/17		2.74%	0.93[0.65,1.35]
Total (95% CI)	**146**	**92**		**100%**	**0.98[0.92,1.04]**
Total events: 136 (intralesional), 87 (resection)					
Heterogeneity: Tau^2=0; Chi^2=2.21, df=6(P=0.9); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					



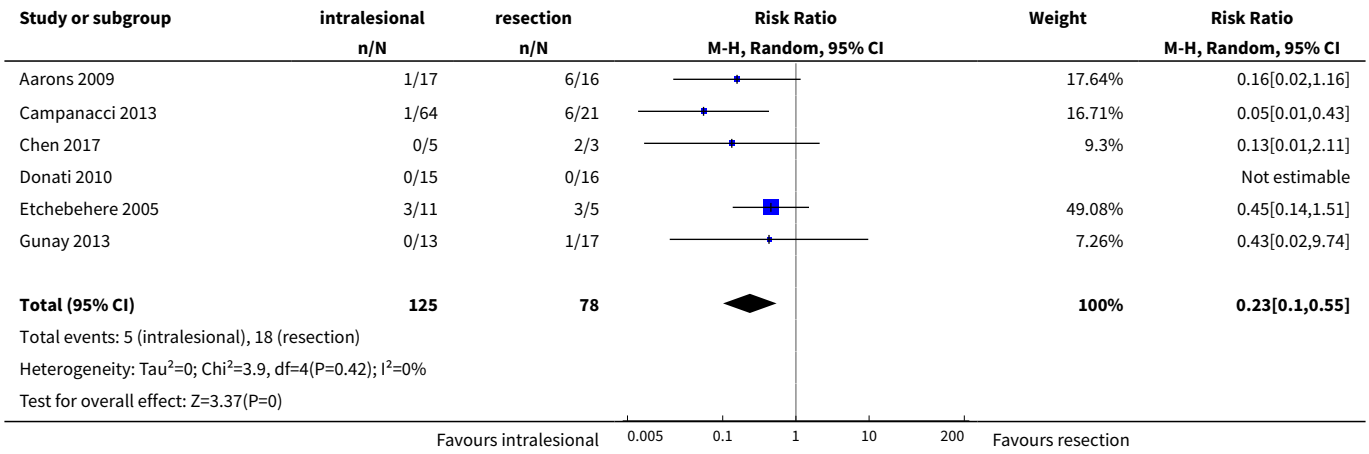
Analysis 1.2. Comparison 1 outcome comparative studies, Outcome 2 Function by MSTS score.

Study or subgroup	intralesional N	Mean(SD)	resection N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Aarons 2009	17	98.2 (2.8)	16	80 (18.3)		31.39%	18.2[9.13,27.27]
Chen 2017	3	98.6 (3.1)	5	94.3 (5.1)		37.41%	4.3[-1.38,9.98]
Donati 2010	15	89.3 (11.1)	16	72.1 (14.8)		31.2%	17.2[8.03,26.37]





Analysis 1.3. Comparison 1 outcome comparative studies, Outcome 3 Complications.



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Chondrosarcoma] explode all trees
#2 chondrosarcoma*
#3 MeSH descriptor: [Chondroma] explode all trees
#4 enchondroma* or chondroma*
#5 #1 or #2 or #3 or #4
#6 intra-lesion* or intralesion*
#7 MeSH descriptor: [Curettage] explode all trees
#8 curettage
#9 phenol* or ethanol or bone cement
#10 MeSH descriptor: [Cryotherapy] explode all trees
#11 cryotherapy
#12 #6 or #7 or #8 or #9 or #10 or #11
#13 Any MeSH descriptor with qualifier(s): [Surgery - SU]
#14 MeSH descriptor: [Amputation] this term only
#15 resect* or surgery or amputat*
#16 #13 or #14 or #15
#17 #5 and #12 and #16

Appendix 2. MEDLINE search strategy

1 exp Chondrosarcoma/
2 chondrosarcoma*.mp.
3 exp Chondroma/
4 (enchondroma* or chondroma*).mp.
5 1 or 2 or 3 or 4

6 (intra-lesion* or intralesion*).mp.
7 exp Curettage/
8 curettage.mp.
9 (phenol* or ethanol or bone cement).mp.
10 Cryotherapy/
11 cryotherapy.mp.
12 6 or 7 or 8 or 9 or 10 or 11
13 surgery.fs.
14 Amputation/
15 (resect* or surgery or amputat*).mp.
16 13 or 14 or 15
17 5 and 12 and 16

key:
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

Appendix 3. Embase search strategy

1 chondrosarcoma/
2 chondrosarcoma*.mp.
3 chondroma/
4 (enchondroma* or chondroma*).mp.
5 1 or 2 or 3 or 4
6 (intra-lesion* or intralesion*).mp.
7 curettage/
8 curettage.mp.
9 (phenol* or ethanol or bone cement).mp.
10 exp cryotherapy/
11 cryotherapy.mp.
12 6 or 7 or 8 or 9 or 10 or 11
13 su.fs.
14 exp amputation/
15 (resect* or surgery or amputat*).mp.
16 13 or 14 or 15
17 5 and 12 and 16

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword
fs=floating subheading

WHAT'S NEW

Date	Event	Description
15 April 2019	Amended	Typographical error corrected.

CONTRIBUTIONS OF AUTHORS

- EFD: designing search protocol, reviewing articles, collecting and analysing data, preparing manuscript
- KG: reviewing articles, collecting and analysing data, preparing manuscript. KG collected data from Dierselhuis 2016 independently from the database presented by the study authors.
- PCJ: designing search protocol, reviewing articles, collecting and analysing data, preparing manuscript
- MS: supervising manuscript, arbiter

DECLARATIONS OF INTEREST

- ED: none known.
- KG: none known.

- MS: none known..
- PJ: none known.

ED, MS and PJ are authors of the included study Dierselhuis 2016.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not, as stated in the protocol, perform sensitivity analyses excluding studies at high risk of bias. For time-to-event data we were unable to use hazard ratios as we were only able to compute risk ratios and odds ratios. We judged risk of bias according to ROBINS-I criteria, since all series were retrospective studies. In addition to the meta-analyses, we also performed a narrative summary, either when case series only presented data from one treatment type, or when full outcome data were not available but were still of value for this review. KG was added to the author team during the review process.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Neoplasms [mortality] [pathology] [*surgery]; Chondrosarcoma [mortality] [pathology] [*surgery]; Curettage [adverse effects] [*methods]; Disease-Free Survival; Kaplan-Meier Estimate; Neoplasm Grading; Neoplasm Recurrence, Local; Retrospective Studies

MeSH check words

Adolescent; Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged; Young Adult