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Abstract:

Craniofacial fibrous dysplasia (CFD) may be associated with major cosmetic or functional consequences. However, management recommendations for CFD are currently unavailable. Therefore, this systematic literature review aimed to review the existing approaches for CFD management and propose a management algorithm. The focus question was “What are the different options for CFD treatment and their complication rates?” The MEDLINE database was searched, and 33 articles evaluating a total of 1154 patients were reviewed. The bias assessment showed that 20 of the 33 studies had a high or intermediate risk of bias, mainly because of retrospective data collection and small patient numbers. Radical surgery showed a lower recurrence rate than debulking, but its use should be weighed against the morbidity caused by the reconstruction performed in this technique. Orbital decompression using a radical technique or debulking is effective in cases showing exophthalmos or dystopia. Surveillance is a viable option for asymptomatic and/or non-progressive lesions. In cases showing optic nerve compression, prophylactic decompression should be avoided, and decompression should be performed only when patients show diminished visual acuity or visual field defect. Although bisphosphonates have shown efficacy in pain management, their posology requires further discussion. A management algorithm is presented.

Keywords: fibrous dysplasia of bone; craniofacial fibrous dysplasia; decompression, surgical; cytoreduction surgical procedures; diphosphonates

1. Introduction

Fibrous dysplasia (FD) is a rare mosaic bone disorder affecting bone formation and bone resorption and leading to the development of expansile fibro-osseous lesions. This pathology can affect a single bone (monostotic FD) or several bones (polyostotic FD).[1] It may be isolated or may occur as a part of McCune-Albright syndrome (MAS), along with café-au-lait macules and hyperfunctioning endocrinopathies.[2] It results from a postzygotic gain-of-function mutation in the GNAS gene,[3] which encodes the α subunit of the G_s protein, leading to inappropriate intracellular signalling (upregulation in cyclic AMP-mediated signalling). Consequently, bone marrow stromal cells are unable to differentiate into normal marrow components, but instead proliferate to form fibro-osseous lesions.

Craniofacial involvement, particularly jaw involvement, is common and occurs in up to 90% of polyostotic cases.[4–6] Craniofacial fibrous dysplasia (CFD) may be identified by visible deformity, bone pain, functional impairment (limited mouth opening, malocclusion, diplopia, etc), or nerve damage. The optic nerve is particularly at risk when the orbit is affected, and optic nerve damage is associated with the risk of permanent loss of visual acuity and/or visual field defect.[5,7] Visible deformities also require attention since they can lead to social isolation and depression. However, CFD may also be discovered fortuitously on imaging.

At present, there is no consensus on the management of CFD,[8] and no medical treatment to limit the expansion of these lesions is currently available. Bisphosphonates are frequently used but are only effective for pain relief. Moreover, the drugs prescribed and their posology vary depending on the prescribing team.[8–10] Denosumab is also currently under investigation.[11,12] FD can be cured with

complete surgical resection.[13] However, complete surgical resection in patients with CFD may lead to severe functional or aesthetic sequelae, necessitating complex free-flap reconstruction. Moreover, complete resection may be impossible when the cranial base is involved. While debulking and contouring surgeries are alternatives to complete resection, they are associated with high relapse rates.[14,15] Optic nerve compression may occur in cases showing optic canal involvement, necessitating surgical decompression.[5,16–18] Jaw CFD may necessitate orthodontic treatment or even orthognathic surgery. In several cases showing mild involvement, care will be limited to surveillance. However, the delay between clinical and radiological examinations and the length of the surveillance is left to the clinician's judgement. Thus, the management of this condition is challenging, and needs to be tailored to the patient while remaining multimodal. A multidisciplinary approach including facial surgeons, rheumatologists, endocrinologists, orthodontists, dentist, and general practitioners working closely together is essential to ensure optimal treatment outcomes.[19]

Considering these multiple treatment options, this study aimed to systematically review the scientific literature on CFD management and summarise the results in order to propose a management algorithm.

2. Material and methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] This study followed the Declaration of Helsinki on medical protocol and ethics. Due to the bibliographic nature of this study, it was granted an exemption in writing by the University of Lille IRB.

2.1 Focused question

The research question of this study was, “What are the different options for CFD treatment and their complication rates?”

2.2 Search strategy

The search was performed on the MEDLINE database using the following search algorithm: (((fibrous dysplasia of bone) OR (craniofacial fibrous dysplasia) OR ((fibrous) AND (dysplasia))) AND ((jaw) OR (palate) OR (orbit) OR (alveolar process) OR (dental arch) OR (nasal bone) OR (mandible) OR (zygoma) OR (frontal) OR (maxilla) OR (craniofacial) OR (craniomaxillofacial) OR (maxillofacial))). All articles published between 1995 and 2022 were considered. This study included articles assessing the efficacy and/or the risks of a treatment approach for CFD and comparing different treatments or the rate of recurrence of CFD. Case reports, systematic reviews, duplicate studies, non-human studies, and studies in a language other than English were excluded. Studies were first screened based on an evaluation of the title and

abstract, after which the potential articles were carefully assessed according to the eligibility criteria of this review.

2.3 Data extraction

Data extracted from these studies included information regarding the year of publication, study design, primary and secondary objectives, number of patients included, mean age, sex, type of FD, site of disease, treatment, primary and secondary outcomes, recurrence, and dental management.

The type of FD was categorised as follows on the basis of skeletal involvement: monostotic (MFD), polyostotic (PFD), or MAS. The site of involvement was categorised into the mandible, maxilla, palate, alveolar bone, nasal bone, zygoma, and orbit. Symptoms were categorised as functional impairment, pain, deformity, decreased visual acuity, exophthalmos, and other nerve damage. The types of treatment were listed as complete resection, debulking, optic nerve decompression and orbital decompression, bisphosphonate treatment, and monitoring.

2.4 Protocol bias assessment

Bias was assessed using the QUADAS-2 tool. The parameters used were the data-collection protocol, the number of patients, the duration of follow-up, and the availability of data on postoperative complications.

Data-collection protocol: studies were categorised as high-risk if they involved retrospective collection and low-risk if they employed prospective collection or better studies type.

Number of patients: studies with ≤8 patients were considered high-risk; those with 9-19 patients were categorised as intermediate-risk; and those with ≥20 patients were categorised as low-risk.

Duration of follow-up: studies with no data on follow-up were considered high-risk; those with follow-up periods less than one year or imprecise data as judged by the authors were considered intermediate-risk; and those with follow-up periods ≥ 1 year were considered low-risk.

Availability of data on postoperative complications: studies with missing data for postoperative complications or inaccurate data as judged by the authors were considered high-risk, and those that did not meet these criteria were considered low-risk.

3. Results

The search identified 1,052 articles. Of these, 33 were finally included *(Figure 1)*. The main extracted data are listed in Table 1. Overall, 1154 patients (414 male patients, 626 female patients, and 114 patients whose sex was unknown; mean age, 21.63 years) were included in the 33 selected articles. Based on the available data, 419, 239, and 310 patients had MFD, PFD, and MAS, respectively. The most common symptoms were deformity, pain, diplopia, exophthalmos, and functional impairment.

3.1 Radical resection versus debulking

The 33 articles included 13 studies focusing on radical treatment.[2,7,14,15,21–29] These articles reported 236 cases of radical surgery with reconstruction using free flaps, bone grafts, or titanium implants or without reconstruction, and the authors of these studies reported good surgical outcomes. Complications included infection (n = 4), aesthetic sequelae, palatal fistula (n = 2), and resorption of the grafted bone (n = 1). Disease recurrence was reported in 22 cases (recurrence rate, 9.32%).

Thirteen articles focused on debulking.[2,14,15,22–31] These articles described 203 cases of debulking with bone grafts or titanium implants or without reconstruction and reported good results. Complications included infection (n = 1), aesthetic sequelae, and bleeding (n = 1). Disease recurrence was observed in 77 cases (recurrence rate, 37.93%).

Three articles examined the influence of age.[28,29,31] Denadai *et al.*[28] found that patients in the debulking group were younger (12.57 vs. 19.22 years), had more recurrences (71% vs. 15%) and underwent more interventions (2.4 vs. 1 intervention). The final Whitaker score and complication rate (14% vs 11%) were similar. In their

study, Park *et al.*[31] showed a higher tumour growth rate before and after debulking in patients under 16 years of age. Finally, Maher *et al.*[29] found that resection of more than 90% of the lesion in children was associated with a reduced risk of recurrence.

3.2 Optic nerve decompression

Sixteen of the included articles focused on optic nerve decompression.[2,7,14–18,23,25,29,32–37] Of the 246 cases of optic nerve decompression included in these studies, 162 involved therapeutic decompressions (affected visual acuity or visual field).[2,7,14,15,17,18,23,25,29,32–36] During the follow-up period, 47 cases showed a reduction in visual acuity. Complications included diplopia, infection, ectropion, and immediate postoperative visual acuity loss. Eighty-four patients underwent prophylactic decompression despite showing no change in visual acuity or in visual field, and 16 of these patients finally showed a decrease in visual acuity during the follow-up period.[7,15–17,29,33,34,36] The complications described were similar to those of therapeutic decompression. However, according to Cruz *et al*., narrowing of the optic foramen resulted in reduced visual acuity in only one out of 19 patients.[37]

3.3 Orbital decompression

Six of the selected articles focused on orbital decompression.[3,13,16,32,33,38] These articles described a total of 71 cases of orbital decompression in patients with exophthalmos or dystopia. Fifty-six cases involved decompression by radical surgery with reconstruction by bone graft, free flap, or titanium implant or without reconstruction, and the authors reported good results.[13,16,32,33] During the follow-up period, one case showed a reduction in visual acuity. Complications included

diplopia, infection, supraorbital nerve anaesthesia (n = 2), and cerebrospinal fluid leaks (n = 2). The remaining 15 cases involved debulking decompression with good outcomes.[3,33,38] None of the cases showed postoperative loss of visual acuity. Complications included diplopia, infection, and ectropion.

3.4 Bisphosphonate treatment

Seven of the included articles dealt with bisphosphonates.[3,9,10,39–42] These articles described a total of 121 cases treated using these drugs, including pamidronate (n = 34) [9,39–41], alendronate (n = 22) [9,10,42], zoledronate (n = 20) [9,42], olpadronate (n = 38) [42], and risedronate (n = 4).[42] The reported complications included myalgia (n = 4), leukopenia (n = 2), and hypocalcaemia (n = 8). Five of the seven articles reported improvement or stabilisation of pain.[3,9,39,40,42] One randomised double-blind clinical trial found no improvement in pain.[10] Five articles reported a reduction in bone turnover.[9,10,39,40,42] No cases of osteonecrosis were described in these articles. Similarly, Tessaris et *al.*[41] found no evidence of jaw osteonecrosis after treatment with pamidronate in 13 patients.

3.5 Dental management

Only one article focused on dental management.[25] Fattah *et al.*[25] recommended a conservative approach. Orthodontic treatment allowed correction of malocclusions and was combined with orthognathic surgery, if necessary.[25]

3.6 *Monitoring*

Monitoring was evaluated in eight articles with a total of 306 cases, most of which involved stable lesions without symptoms.[3,17,23,26,29,33,35,39] Fourteen patients showed disease progression.

3.7 Bias assessment

The results of the bias assessment of the included studies are shown in *Figure 2*. Twenty of the 33 studies showed a high or intermediate risk of bias, mainly due to retrospective data collection and small patient numbers.

4. Discussion

4.1 Radical resection versus debulking

Radical resection is a major surgical technique requiring complex reconstruction, sometimes using a free flap, particularly in extensive lesions. It is often seen as a source of sequelae.[22] However, it is not always feasible, particularly when high-risk structures such as the base of the skull are involved.

Therefore, some authors have suggested the possibility of debulking, which allows partial resection of the lesion and yields satisfactory local control of the disease.[3,24,30,38] Although this technique may be less likely to cause sequelae, it does appear to be more likely to lead to recurrence, showing much higher recurrence rates than radical surgery.[14,15] Gabbay *et al.*[14] compared 37 cases of radical resection versus 21 cases of debulking and found that radical resections were associated with more complications (13.5% vs. 4.8%) but less recurrence at 1 year (24.3% vs. 66.7%), with comparable rates of patient satisfaction. Boyce *et al.*[15] also demonstrated a greater risk of recurrence after debulking (82%) than after radical surgery (45%) in 36 patients with PFD followed-up for an average of 13.5 years. Finally, Ni *et al.*[27] compared the quality of life before and after radical surgery and debulking and showed that quality of life significantly improved after debulking, whereas the difference was not significant in those who underwent radical resection.

These findings should be weighed against the fact that the natural history of the disease favours progressive stabilisation of the tumour, particularly up to the end of adolescence, except in cases of MAS.[31] In addition, debulking exposes the patient to multiple treatments with similar long-term results.[14,28] In the light of these data, radical surgery may be preferable in symptomatic patients aged >16 years when the

lesion appears to be accessible to complete resection, shows significant progression, and does not present a significant risk of major sequelae. However, if resection is not possible or the patient refuses, debulking may be a viable technique for local control of the disease. Finally, monitoring should be limited to asymptomatic patients or those aged <16 years.

4.2 Optic nerve decompression

Some authors have recommended prophylactic decompression in cases of optic foramen involvement.[16,18,35] However, prophylactic decompression is associated with a non-negligible risk of visual impairment.[35] Furthermore, some patients undergoing a narrowing of the optic foramen do not develop any visual impairment *(Figure 3)*.[37] Paradoxically, patients who were monitored had a lower risk of visual deterioration than patients who underwent prophylactic surgery.[17]

Therapeutic decompression has also shown good results in improving vision.[34,36] Tan *et al.*[36] compared six cases of prophylactic decompression with 12 cases of therapeutic decompression. One-third of the cases of prophylactic decompression showed deterioration of vision at follow-up, whereas therapeutic decompression prevented deterioration of vision in a quarter of the patients. Culter *et al.*[34] compared six cases of prophylactic decompression with 13 cases of therapeutic decompression. While the prophylactic decompression group showed loss of visual acuity in one case and stable status in five cases, six patients showed improvement in the therapeutic decompression group. Thus, therapeutic decompression appeared to be even better than prophylactic orbital decompression.[17] Therefore, the risk-benefit balance is in favour of optic nerve decompression only in cases showing reduced visual acuity or

visual field defect. However, this step may be performed as part of a more extensive surgical procedure.

4.3 Orbital decompression

Orbital decompression is performed in cases showing symptoms such as exophthalmos or dystopia.[3] Similar to the approach for the other facial bones, radical decompression is performed to allow complete excision of the lesion or debulking.[3,33,38] The complications of this procedure are similar to those of radical decompression and debulking of other facial bones, with the added possibility of reduced visual acuity.[32] The authors showed good aesthetic and functional results with few complications for each technique.[3,38]

Data on the recurrence rate are limited. However, given the natural history of the disease and the recurrence rates of surgery for other facial bones, an interesting possibility is that radical orbital decompression surgery may show fewer recurrences than orbital debulking. Thus, as with the other facial bones, radical surgery is indicated for symptomatic lesions that can be completely removed, while debulking is preferred otherwise.

4.4 Bisphosphonate treatment

The use of bisphosphonates for FD has been described, but the protocols, drugs used, and posology differed among teams, making analysis difficult. However, these drugs appear to influence disease progression and pain, although one study reported no effect on pain.[9,10,39,40,42] Finally, the safety of bisphosphonate treatment was satisfactory, since no complication was reported to be associated with these

treatments, apart from elevated body temperature, hypocalcaemia, leukopenia, and myalgia.[9,40,41]

Although further trials to develop a precise protocol seem necessary, a recent systematic review and meta-analysis suggested that this treatment is relevant and safe for the management of the disease, particularly for pain, since it is minimally invasive and carries little risk of complication.[43] Moreover, other drugs such as desonumab are also being studied.[11,12]

4.5 Dental management

Very few studies on dental management were found in the literature, and only one study was included in this review. Pacino *et al.* [24] described prosthetic rehabilitation with or without implants following radical or debulking surgery, but Fattah *et al.* [25] presented a more conservative approach wherein orthodontic treatment was performed for the malocclusion while waiting for the lesion to stop growing, which could then allow radical removal surgery in one stage *(Figure 4)*. However, further studies on the appropriate mode of dental management are needed.

4.6 Monitoring

Few studies have evaluated surveillance. However, it appears to be a viable option in asymptomatic patients with stable lesions.[3,23] After 16 years of age, tumour growth tends to diminish in most cases, and lesions can remain stable for years.[31] In the context of orbital surgery in a meta-analysis of 241 patients, Amit *et al.*[17] showed that vision remained stable in 75.6% of cases that involved prophylactic decompression and 95.1% of monitored cases.

4.7 Proposal for a management algorithm

The authors have proposed a management algorithm on the basis of the findings of this study. The first step is characterisation of the disease and evaluation of its consequences (signs and symptoms). Clinical examination in conjunction with CT imaging of the facial mass can precisely characterise the lesion, the number of associated lesions, and their extension. Biopsy is not essential in cases with a typical lesion, but should be performed if there is the slightest doubt. Bone scintigraphy should be used to identify other skeletal lesions in the context of PFD or MAS.

In cases showing a stable lesion without pain, clinical and radiological surveillance is preferable. Surveillance should be performed with a CT scan every 5 years for adults and every 2 years for children under 16 years of age, due to their growth potential. Bisphosphonate treatment is indicated for patients showing pain, and surgical treatment may be discussed if bisphosphonate treatment is unsuccessful.

In cases showing optic foramen involvement, decompression of the optic nerve is indicated only if the patient shows a decrease in visual acuity or visual field defect, with no indications for prophylactic optic foramen decompression. In cases showing exophthalmos, dystopia, and/or reduced visual acuity in the case of orbital involvement, radical or debulking orbital decompression may be proposed depending on the extension of the lesion. If there are no signs of impairment, regular radiological and neuro-ophthalmological monitoring is required, including fundus examination, visual acuity and visual field measurements.

When the patient presents with facial asymmetry, functional impairment, damage to other nerves or progression of the lesion, surgical treatment is indicated. In such cases,

CT imaging will be used to assess whether the lesion can be removed. If the lesion can be removed with a low risk of major sequelae, radical excision surgery with reconstruction using a free flap is indicated. Debulking is indicated in cases where low-risk, sequelae-free removal of the lesion is not possible (PFD or MAS). However, debulking should be discussed before 16 years of age, given the greater risk of recurrence. Thus, the management algorithm can be summarised as follows. *(Figure 5)*

5. Conclusion

CFD is a rare condition with no clear recommendations for its management. Our literature review showed that radical surgery of the orbit and other facial bones remains the gold standard whenever feasible. Decompression of the optic nerve is only useful in cases involving reduced visual acuity; prophylactic optic nerve decompression should not be performed. Monitoring is essential in cases showing asymptomatic, stable disease. Finally, bisphosphonates are useful for pain management.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

4 References

[1] DiCaprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am 2005;87:1848–64. https://doi.org/10.2106/JBJS.D.02942.

[2] Valentini V, Cassoni A, Marianetti TM, Terenzi V, Fadda MT, Iannetti G. Craniomaxillofacial Fibrous Dysplasia: Conservative Treatment or Radical Surgery? A Retrospective Study on 68 Patients: Plastic and Reconstructive Surgery 2009;123:653–60. https://doi.org/10.1097/PRS.0b013e318196bbbe.

[3] Bertin H, Huon J-F, Guillot P, Longis J, Corre P, Bordereau S, et al. Fibrous dysplasia of the orbital region: Series of 12 cases and review of the literature. Journal Français d'Ophtalmologie 2020;43:467–76. https://doi.org/10.1016/j.jfo.2019.10.012.

[4] Yang L, Wu H, Lu J, Teng L. Prevalence of Different Forms and Involved Bones of Craniofacial Fibrous Dysplasia. J Craniofac Surg 2017;28:21–5. https://doi.org/10.1097/SCS.0000000000002830.

[5] Carbonare MD, Manisali M. Surgical management of syndromic versus non-syndromic craniofacial fibrous dysplasia: a systematic review and meta-analysis. British Journal of Oral and Maxillofacial Surgery 2022;60:1166–75. https://doi.org/10.1016/j.bjoms.2022.06.002.

[6] Pan KS, Taylor J, Szymczuk V, Boyce AM. Lesion Expansion in Gnathic Fibrous Dysplasia: Natural History, Indicators of Progression, and Response to Bisphosphonates. J Bone Miner Res 2023. https://doi.org/10.1002/jbmr.4886.

[7] Goisis M, Biglioli F, Guareschi M, Frigerio A, Mortini P. Fibrous dysplasia of the orbital region: current clinical perspectives in ophthalmology and cranio-maxillofacial surgery. Ophthalmic Plast Reconstr Surg 2006;22:383–7. https://doi.org/10.1097/01.iop.0000229761.37416.3e.

[8] Pitak-Arnnop P, Dhanuthai K, Hemprich A, Pausch NC. Craniofacial fibrous dysplasia: current status of the literature. Rev Stomatol Chir Maxillofac 2010;111:244–6. https://doi.org/10.1016/j.stomax.2010.05.001.

[9] Wang Y, Wang O, Jiang Y, Li M, Xia W, Meng X, et al. Efficacity and safety of bisphosphonate therapy in McCune-Albright syndrome-related polyostotic fibrous dysplasia: a single-center experience. Endocr Pract 2019;25:23–30. https://doi.org/10.4158/EP-2018-0328.

[10] Boyce AM, Kelly MH, Brillante BA, Kushner H, Wientroub S, Riminucci M, et al. A randomized, double blind, placebo-controlled trial of alendronate treatment for fibrous dysplasia of bone. J Clin Endocrinol Metab 2014;99:4133–40. https://doi.org/10.1210/jc.2014-1371.

[11] Pan KS, Boyce AM. Denosumab Treatment for Giant Cell Tumors, Aneurysmal Bone Cysts, and Fibrous Dysplasia-Risks and Benefits. Curr Osteoporos Rep 2021;19:141–50. https://doi.org/10.1007/s11914-021-00657-z.

[12] Meier ME, Clerkx SN, Winter EM, Pereira AM, van de Ven AC, van de Sande MAJ, et al. Safety of therapy with and withdrawal from denosumab in fibrous dysplasia and McCune-Albright syndrome: an observational study. J Bone Miner Res 2021;36:1729–38. https://doi.org/10.1002/jbmr.4380.

[13] Fadle KN, Hassanein AG, Kasim AK. Orbitocranial Fibrous Dysplasia: Outcome of Radical Resection and Immediate Reconstruction With Titanium Mesh and Pericranial Flap. J Craniofac Surg 2016;27:e719–23. https://doi.org/10.1097/SCS.0000000000003033.

[14] Gabbay JS, Yuan JT, Andrews BT, Kawamoto HK, Bradley JP. Fibrous dysplasia of the zygomaticomaxillary region: outcomes of surgical intervention. Plast Reconstr Surg 2013;131:1329–38. https://doi.org/10.1097/PRS.0b013e31828bd70c.
[15] Boyce AM, Burke A, Cutler Peck C, DuFresne CR, Lee JS, Collins MT. Surgical Management of Polyostotic Craniofacial Fibrous Dysplasia: Long-Term Outcomes and Predictors for Postoperative Regrowth. Plast Reconstr Surg 2016;137:1833–9. https://doi.org/10.1097/PRS.0000000000002151.
[16] Papay FA, Morales L, Flaharty P, Smith SJ, Anderson R, WAlker JM, et al. Optic nerve decompression in cranial base fibrous dysplasia. J Craniofac Surg 1995;6:5–10; discussion 11-14. https://doi.org/10.1097/00001665-199501000-00004.
[17] Amit M, Collins MT, FitzGibbon EJ, Butman JA, Fliss DM, Gil Z. Surgery versus watchful waiting in patients with craniofacial fibrous dysplasia--a meta-analysis. PLoS One 2011;6:e25179. https://doi.org/10.1371/journal.pone.0025179.
[18] Satterwhite TS, Morrison G, Ragheb J, Bhatia S, Perlyn C, Wolfe SA. Fibrous dysplasia: management of the optic canal. Plast Reconstr Surg 2015;135:1016e–24e. https://doi.org/10.1097/PRS.0000000000001295.
[19] Burke A, Collins M, Boyce A. Fibrous dysplasia of bone: craniofacial and dental implications. Oral Diseases 2017;23:697–708. https://doi.org/10.1111/odi.12563.
[20] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097.
[21] Dasukil S, Boyina KK, Nayak B, Chakraborty K, C S L, Panda R. Surgical Correction of Craniofacial Fibrous Dysplasia Involving Orbits: A Unique Application of Patient-Specific Implants. J Craniofac Surg 2022;33:226–9. https://doi.org/10.1097/SCS.0000000000007944.
[22] Ozek C, Gundogan H, Bilkay U, Tokat C, Gurler T, Songur E. Craniomaxillofacial fibrous dysplasia. J Craniofac Surg 2002;13:382–9. https://doi.org/10.1097/00001665-200205000-00004.
[23] Wei Y-T, Jiang S, Cen Y. Fibrous dysplasia of skull. J Craniofac Surg 2010;21:538–42. https://doi.org/10.1097/SCS.0b013e3181d0243f.
[24] Pacino GA, Cocuzza S, Tonoli G, Boscolo Rizzo P, Tirelli G, Tofanelli M, et al. Jawbone fibrous dysplasia: retrospective evaluation in a cases series surgically treated and short review of the literature. Acta Biomed 2020;92:e2021018. https://doi.org/10.23750/abm.v92i1.9904.
[25] Fattah A, Khechoyan D, Phillips JH, Forrest CR. Paediatric craniofacial fibrous dysplasia: the Hospital for Sick Children experience and treatment philosophy. J Plast Reconstr Aesthet Surg 2013;66:1346–55. https://doi.org/10.1016/j.bjps.2013.05.031.
[26] Valentini V, Cassoni A, Terenzi V, Della Monaca M, Fadda MT, Rajabtork Zadeh O, et al. Our experience in the surgical management of craniofacial fibrous dysplasia: what has changed in the last 10 years? Acta Otorhinolaryngol Ital 2017;37:436–43. https://doi.org/10.14639/0392-100X-1081.
[27] Ni Y, Yang Z, Xu H, Lu P, Wang W, Liu F. Assessment of preoperative and postoperative quality of life of 24 patients with fibrous dysplasia of the mandible. Br J Oral Maxillofac Surg 2019;57:913–7. https://doi.org/10.1016/j.bjoms.2019.08.001.

[28] Denadai R, Raposo-Amaral CA, Marques FF, Ghizoni E, Buzzo CL, Raposo-Amaral CE. Strategies for the Optimal Individualized Surgical Management of Craniofacial Fibrous Dysplasia. Ann Plast Surg 2016;77:195–200. https://doi.org/10.1097/SAP.0000000000000640.
[29] Maher CO, Friedman JA, Meyer FB, Lynch JJ, Unni K, Raffel C. Surgical treatment of fibrous dysplasia of the skull in children. Pediatr Neurosurg 2002;37:87–92. https://doi.org/10.1159/000065110.
[30] Zeng H, Lu J, Teng L, Jin X, Xu J, Zhang C, et al. Surgical treatment of craniomaxillofacial fibrous dysplasia: functionally or aesthetically? J Craniofac Surg 2013;24:758–62. https://doi.org/10.1097/SCS.0b013e3182869674.
[31] Park J-W, Jung JH, Park S-J, Lim SY. Evaluation of natural growth rate and recommended age for shaving procedure by volumetric analysis of craniofacial fibrous dysplasia. Head Neck 2020;42:2863–71. https://doi.org/10.1002/hed.26337.
[32] Ricalde P, Horswell BB. Craniofacial fibrous dysplasia of the fronto-orbital region: a case series and literature review. J Oral Maxillofac Surg 2001;59:157–67; discussion 167-168. https://doi.org/10.1053/joms.2001.20487.
[33] Rahman AMA, Madge SN, Billing K, Anderson PJ, Leibovitch I, Selva D, et al. Craniofacial fibrous dysplasia: clinical characteristics and long-term outcomes. Eye (Lond) 2009;23:2175–81. https://doi.org/10.1038/eye.2009.6.
[34] Cutler CM, Lee JS, Butman JA, FitzGibbon EJ, Kelly MH, Brillante BA, et al. Long-term outcome of optic nerve encasement and optic nerve decompression in patients with fibrous dysplasia: risk factors for blindness and safety of observation. Neurosurgery 2006;59:1011–7; discussion 1017-1018. https://doi.org/10.1227/01.NEU.0000254440.02736.E3.
[35] Satoh K, Mitsukawa N, Abe T. Is prophylactic decompression of the optic canal necessary in surgical correction of fronto-orbital fibrous dysplasia?: a review of 11 consecutive cases. J Craniomaxillofac Surg 2014;42:1614–6. https://doi.org/10.1016/j.jcms.2014.04.031.
[36] Tan Y-C, Yu C-C, Chang C-N, Ma L, Chen Y-R. Optic nerve compression in craniofacial fibrous dysplasia: the role and indications for decompression. Plast Reconstr Surg 2007;120:1957–62. https://doi.org/10.1097/01.prs.0000287338.28018.c7.
[37] Cruz AAV, Constanzi M, de Castro FAA, dos Santos AC. Apical involvement with fibrous dysplasia: implications for vision. Ophthalmic Plast Reconstr Surg 2007;23:450–4. https://doi.org/10.1097/IOP.0b013e318158e9a8.
[38] Choi JW, Lee SW, Koh KS. Correction of proptosis and zygomaticomaxillary asymmetry using orbital wall decompression and zygoma reduction in craniofacial fibrous dysplasia. J Craniofac Surg 2009;20:326–30. https://doi.org/10.1097/SCS.0b013e31819922d3.
[39] Couturier A, Aumaître O, Gilain L, Jean B, Mom T, André M. Craniofacial fibrous dysplasia: A 10-case series. Eur Ann Otorhinolaryngol Head Neck Dis 2017;134:229–35. https://doi.org/10.1016/j.anorl.2017.02.004.
[40] Kos M, Luczak K, Godzinski J, Klempous J. Treatment of monostotic fibrous dysplasia with pamidronate. J Craniomaxillofac Surg 2004;32:10–5. https://doi.org/10.1016/j.jcms.2003.07.009.
[41] Tessaris D, Matarazzo P, Lala R, Defabianis P. Odontoiatric perspectives and osteonecrosis of the jaw as a possible adverse effect of bisphosphonates therapy in fibrous dysplasia and McCune-Albright syndrome. J Pediatr Endocrinol Metab 2016;29:333–6. https://doi.org/10.1515/jpem-2015-0300.

[42] Majoor BC, Appelman-Dijkstra NM, Fiocco M, van de Sande MA, Dijkstra PS, Hamdy NA. Outcome of Long-Term Bisphosphonate Therapy in McCune-Albright Syndrome and Polyostotic Fibrous Dysplasia. J Bone Miner Res 2017;32:264–76. https://doi.org/10.1002/jbmr.2999.
[43] Bertin H, Moussa MS, Komarova S. Efficacy of antiresorptive agents in fibrous dysplasia and McCune Albright syndrome, a systematic review and meta-analysis. Rev Endocr Metab Disord 2023. https://doi.org/10.1007/s11154-023-09832-2.

Table and Figures:

Table 1: Main data from the included studies

NAME	TYPE OF STUDY	NUMBER OF PATIENTS	M/F	MEAN AGE	TREATMENT (n)	RECURRENCE (n)/ FOLLOW UP	COMPLICATION OR PROGRESSION (n)
Papay et al.,1995	R	5	4/1	16.8	ROD (5) / POND (5)	ROD (No data) / POND (No data) / 2.4 years	0
Ricalde and Horswell,2001	R	6	3/3	17	ROD (6) / TOND (3)	0 / 1 year	ROD and TOND (1: vision loss)
Maher et al.,2002	R	28	17/11	11.4	Ra (7) / De (17) / Mo (4) / POND (3) / TOND (2)	De and Mo (10) / 13.7 years	Unspecified (3: infections) / TOND (1: vision loss)
Ozek et al.,2002	R	13	6/7	17	Ra (4) / De (9)	Ra (1) /De (7) / 4,5 years	Ra (2: infection / 1: sequelae)
Kos et al.,2004	P	6	2/4	14.5	Pamidronate (6)	Pamidronate (0) / 19 Months	Pamidronate (0)
Cutler et al.,2006	R	91	39/52	24.3	POND (6) / TOND (12) / Other (no data)	POND and TOND 9.86 years / No data for others	POND (1: vision loss) TOND (2: vision loss) Other (no data)
Goisis et al.,2006	R	10	No data	18.8	Ra (10) / POND (3) / TOND (1)	Ra (0) / 53.2 Months	Ra (1: bone graft resorption)

Cruz et al.,2007	P	21	4/17	25.48	Optic canal narrowing (19) / involved roof (23) / 4 wall involved (9)	No data /6 years	Optic canal narrowing (1: vision loss)
Tan et al.,2007	R	18	7/11	21	POND (6) / TOND (12)	No data / 1 year	POND (2: visual loss) / TOND (6: visual loss)
Choi et al.,2009	R	5	2/3	21	ODe (5)	0 / 23 Months	ODe (0)
Rahman et al.,2009	R	42	22/20	16.7	ROD (23) / ODe (4) / POND (1) / TOND (2) / Mo (15)	Mo (2) / 12,6 years	Unspecified (3: infection, 3: diplopia, 3: cranial nerve palsies, 2: pain, 1: epistaxis, 1: hypertrophic scar, 1: anaemia, 1: ectropion)
Valentini et al.,2009	R	95	No data	24.6	Ra (61) / De (7) / TOND (4)	De (1) / 7.6 years	Ra (1: infection / 2: palatal fistula)
Wei et al.,2010	R	81	31/50	23.94	Ra (n=41) / De (23) / TOND (6) / Mo (11)	Unspecified (7) / > 1 years but imprecise	TOND (1: vision loss) / Unspecified (2: fever)
Amit et al.,2011	MA	241	50/191	20	POND (41) / TOND (86) / Mo (241)	No data / 54 Months	POND (8: vision loss) / TOND (33: vision loss) / Mo (11: vision loss)
Fattah et al.,2013	R	37	17/20	9.9	Ra (13) / De (14) / TOND (2)	Ra (1)/ De (8) / 5.8 years	No data
Gabbay et al.,2013	R	97	58/39	16	Ra (37) / De (21)/ TOND (16)	Ra (9) / De (14) / 5,8 years	Ra (5: hematoma, infection, and Dental injury) / De (1: bleeding)

Zeng et al.,2013	R	10	2/8	23.44	De (10)	De (1) / 3 years	De (0)
Boyce et al.,2014	RCT	40	18/22	27.4	Alendronate (18) / Placebo (17)	Progression on paediatric subject / 24 Months	Alendronate (3: fractures, 1: oesophageal stricture, 1: nausea) / Placebo (3: fractures)
Satoh et al.,2014	R	11	7/4	25.63	POND (5) / TOND (1) / Mo (5)	POND (No data) / TOND (No data) / Mo (0) / 11.45 years	Unspecified (2: vision loss)
Satterwhite et al.,2015	R	9	No data	21	POND (7) / TOND (3)	No data / 5 years	TOND (3: vision loss)
Boyce et al.,2016	R	36	14/22	23.7	Ra (20) / De (38) / POND (7) / TOND (12)	Ra (9) / De (31) / TOND (6) / 13,5 years	POND (5: visual loss)
Denadai et al.,2016	R	20	11/9	9.31	Ra (13) / De (7)	Ra (2) / De (5) / 4.08 years	Ra (1: hematoma) / De (1: bleeding)
Fadle et al.,2016	P	22	10/12	29.5	ROD (22)	0 / 37.5 months	Ra (2: cerebrospinal fluid leak, 2: supraorbital anaesthesia, 1: infection)
Tessaris et al.,2016	P	13	6/7	20	Pamidronate (13)	No data / 30 Months	0
Couturier et al.,2017	R	10	5/5	43	Pamidronate (5) / Mo (2)	0 / 4 mouths to 9 years	0
Majoor et al.,2017	R	41	17/24	34.31	Olpadronate (38) Zolendronate (9) Risedronate (4) Alendronate (3)	No data / 12.3 years	Unspecified (10: mild gastrointestinal complaints, headaches or nausea)

Valentini et al.,2017	R	41	18/23	29	Ra (8) / De (7) / Mo (26)	Ra (0) / De (No data) / Mo (No data) / 51 Months	No data
Ni et al.,2019	R	24	6/18	40	Ra (13) / De (11)	No data	No data
Wang et al.,2019	R	22	6/16	5.4	Alendronate (1) Pamidronate (10) Zolendronate (11)	No data / 1 year	Unspecified (8: hypocalcemia, 2: leukopenia, 4: myalgia)
Bertin et al.,2020	R	11	9/2	25.6	ODe (6) / Bisphosphonate (3) / Mo (2)	0 (20,8 mouths)	ODe (3: diplopia)
Pacino et al.,2020	R	10	4/6	28.9	Ra (4) / De (6)	De (1) / 1 to 5 years	0
Park et al.,2020	R	33	17/16	15	De (33)	De (9) / 78 Months	No data
Dasukil et al.,2022	R	5	2/3	19.6	Ra (5)	0 (1 year)	0

R = retrospective / P = prospective / MA = meta-analysis / RCT = randomized controlled trial

Ra = radical surgery / De = Debulking surgery / Mo = Monitoring

POND = prophylactic optic nerve decompression / TOND = therapeutic optic nerve decompression

ROD = radical orbital decompression / ODe = Orbital debulking

Figure 1: PRISMA flowchart

Figure 2: Bias assessment

Data-collection protocol (D1):

- *High risk: retrospective collection*
- *Low-risk: prospective collection or better*

Number of patients (D2):

- *High-risk: ≤8 patients*
- *Intermediate-risk: 9-19 patients*
- *Low-risk: ≥20 patients*

Duration of follow-up (D3):

- *High-risk: no data on follow-up*
- *Intermediate-risk: follow-up periods less than one years or imprecise data*
- *Low-risk: follow-up period > 1 year*

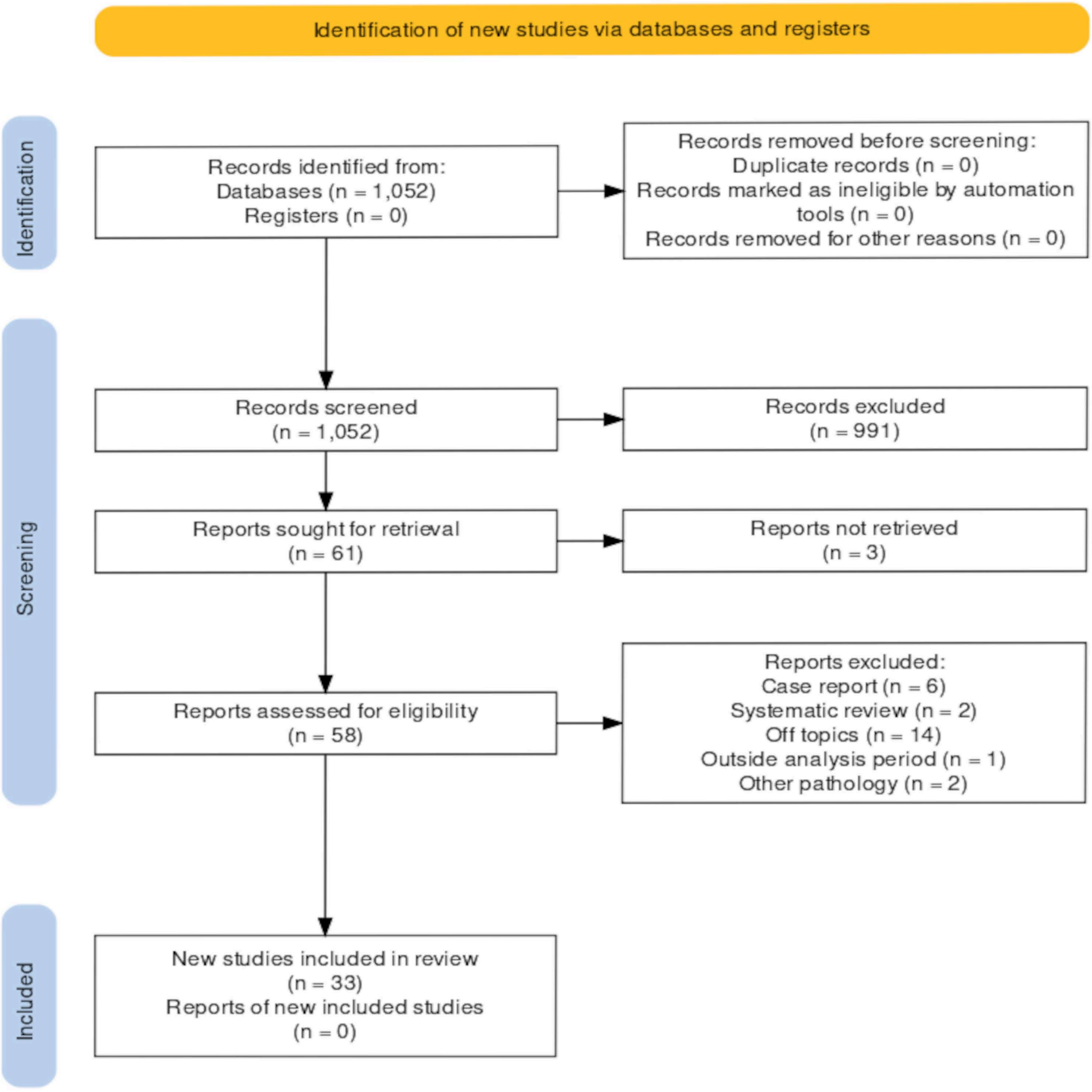
Postoperative complications (D4):

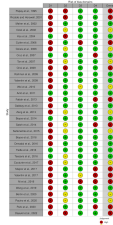
- *High-risk: missing or inaccurate data*
- *Low-risk: presence of data*

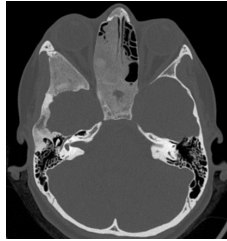
Figure 3: Findings in a case showing narrowing of the optic foramen without visual impairment

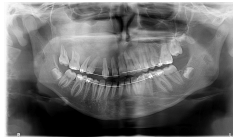
Figure 4: Findings in a case showing a right maxillary lesion managed by orthodontic treatment

Figure 5: Proposal for a management algorithm


Identification of new studies via databases and registers
Identification
Screening
Included
Records identified from:
Databases (n = 1,052)
Registers (n = 0)
Records removed before screening:
Duplicate records (n = 0)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Records screened
(n = 1,052)
Records excluded
(n = 991)
Reports sought for retrieval
(n = 61)
Reports not retrieved
(n = 3)
Reports assessed for eligibility
(n = 58)
Reports excluded:
Case report (n = 6)
Systematic review (n = 2)
Off topics (n = 14)
Outside analysis period (n = 1)
Other pathology (n = 2)
New studies included in review
(n = 33)
Reports of new included studies
(n = 0)


Risk of bias domains
Study
Nagaya M., 1999
Nuzzo and Nuzzaci, 2004
Oliveira et al., 2005
Gilad et al., 2006
Kaminty, 2006
Cicinelli et al., 2008
Ozkan et al., 2008
Cicek et al., 2009
Tarcan et al., 2009
Gilad et al., 2009
Gomez et al., 2009
Tsakiris et al., 2009
Ahn et al., 2010
Ashrafi et al., 2010
Turan et al., 2011
Jaleel et al., 2012
Hung et al., 2012
Ozkan et al., 2012
Salmon, 2013
Apostolakis et al., 2015
Bayoud, 2015
Dmoski et al., 2015
Tsakiris et al., 2016
Tsakiris et al., 2016
Gundabattini, 2017
Nappi et al., 2017
Tsakiris et al., 2017
Turan et al., 2017
Wdowiak, 2018
Bedrick, 2020
Pundir et al., 2020
Pundir et al., 2021
Rasmussen, 2021
Low risk
Some concerns
High






Facial CT Scan (-) contiguously
Fibrous Dysplasia?
Yes
No
Monostotic
Polyostotic
Pain
Yes
No
Exophthalmos
Child decompression
Yes
Orbital involvement
Exophthalmos Clinically
No
Yes
Optic nerve decompression
Optic nerve involvement
Impaired visual acuity (Visual Evoked Potentials)
No
Yes
Monitoring Visual acuity, visual field, Color, Retina, Fundoscopy
Optic nerve decompression
Yes
No
Deformation, functional disorder, Cosmetic disorder, Aggressive lesion
Yes
No
Monitoring CT scan (6 months) MRI (1 year) 6 months (2-5 years adult)
Age
< 18 years
> 18 years
Consistently removable lesion
Yes
No
Radical excision and reconstruction
Debulking
Monostotic