Inferior alveolar nerve allogenic repair following mandibulectomy: a systematic review

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Abstract

Purpose: Processed nerve allografts (PNA) are an alternative to nerve autografts to reconstruct the inferior alveolar nerve (IAN) when it is damaged. The purpose of this study was to report the results of IAN reconstruction using PNA in the context of aggressive benign mandibular pathology.

Material and method: A systematic literature review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement through the MEDLINE (Pubmed) and Scopus (Elsevier) databases. Studies concerning reconstructive surgeries of IAN by PNA, performed at the same time as the surgical resection of the benign pathologies of the mandible were included. The following data were analyzed: gender and patient age, cause of mandibular resection, graft dimensions, sensory recovery at least 6 months after surgery according to the MRC scale, and adverse events related to the intervention.

Results: The initial search yielded 290 studies and 5 were included in the final review. A total of 33 patients underwent 36 IAN reconstructions; 14 patients were female (42.4%) and mean age was 30 years old. The mean length of graft used was 64.0 ± 9.1 mm. The most common pathology that led to nerve resection was ameloblastoma (52%). Among the reconstructions for which follow-up data were available, functional sensory recovery occurred in 92.9% of cases.

Conclusion: PNA are a reliable, safe, and effective alternative to nerve autografts for the rehabilitation of the IAN with 92.9% of functional recovery according to the reported literature, avoiding any comorbidity associated with the use of a donor site.

Key Words: inferior alveolar nerve; mandibular nerve; mandibular nerve injury; benign neoplasm; mandible; nerve allograft

INTRODUCTION

An injury of the inferior alveolar nerve (IAN) provokes a permanent anesthesia that impacts patients' quality of life, especially during their social interactions. Dysfunctions such as speech disorders, drooling, persistence of food at the corner of the lips, or involuntary injuries of the inner surfaces of the cheeks have been frequently reported in patients with IAN damages (1–6).

Currently, the two most common options used by surgeons consist in therapeutic abstention, with all the consequences described above, and nerve autograft. The advantage of the latter is that it consists in the use of a material with preserved architecture and nervous biology. However, as it requires a donor site, it presents with limited quantity and certain comorbidities (loss of sensation on the donor site, scar, possible formation of a neuroma) (7–9).

More recently, a technique using processed nerve allografts (PNA) was proposed as an alternative and introduced on the American market in 2007 (10). Avance® Nerve Graft (Axogen Inc., Alachua, FL) are currently the only PNA available for sale. Processed nerve allografts are derived from human cadaveric peripheral nerves. They have been cleansed from all the cells, from the major histocompatibility complex, from the myelin and the acellular debris. The specificity of this product is a treatment used to eliminate chondroitin sulfate, which is an enzyme that inhibits axonal regeneration (11–15)

Avance nerve allograft is contraindicated for use in any patient in whom soft tissue implants are contraindicated (unbalanced diabetes, on-going chemotherapy, immunosuppressed patient).

This device has been widely used in upper limb reconstructive surgery, and was reported as effective when used as autografts, without the need for a donor site (16–20). In 2011, Shanti *et al.* introduced their use for reconstruction of the IAN in one patient and reported a functional sensory recovery on a 7 months old nerve damage (21). However, to date there are few data in the international literature concerning the efficacy of PNA for IAN repair.

The aim of this systematic literature review is to report the sensory recovery following IAN reconstruction using PNA after mandibulectomy in the context of aggressive benign mandibular pathology.

MATERIAL AND METHODS

Study design

To address the research purpose, a systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (22). The following question of research was established: Does immediate reconstruction of the IAN with PNA allow a functional sensory recovery in patients who undergo mandibular resection because of a benign pathology?

Information sources and search strategy

This study investigated publications on the topic of PNA use for IAN reconstruction caused by benign mandibular pathologies. The electronic search was performed using the following databases: MEDLINE (Pubmed) and SCOPUS (Elsevier), without time limitation. The final search was performed on November 10th, 2019. The following search strategy was used in both databases: (“inferior alveolar nerve*” or “inferior dental nerve*” or “mandibular nerve*” or “trigeminal nerve*”) AND (“nerve allograft*” or “allograft*” or “processed nerve allograft*” or “mandibular nerve reconstruction*”). A manual search was also conducted

based on the reference lists of the included studies and previous reviews in case they included additional relevant citations that were missed out by the electronic search. After identifying the records in the databases, these were collected in an Excel table (Microsoft, Redmond, WA), and duplicates were removed.

Data collection methods

For the initial screening, 2 reviewers (MLD and NS) independently analyzed the titles and abstracts of all records using the following criteria: studies on the use of PNA for IAN reconstructive surgery performed at the same time as resection in the case of benign mandibular pathologies were included; systematic or narrative reviews of the literature were excluded.

The reasons for exclusion were noted individually and, in case of disagreement between the two reviewers, a third person (MD) was consulted. Disagreements between reviewers were resolved by discussion. For the articles to be included in the systematic review, the following inclusion criteria had to be met after reading the entire article: available data concerning patients (type of pathology, length of graft used, data on functional sensory recovery); patient follow-up at least 6 months after the surgery.

Data extraction

The following data were manually extracted from the included studies: publication year and authors; gender and patient age; cause of mandibular resection; graft dimensions; sensory recovery after at least 6 months according to the Medical Research Council (MRC) scale; and adverse events concerning the intervention. The patients included in those studies did not have pre-operative neurosensory deficit.

The MRC classification was used herein to quantify sensory recovery (23). However, two different scales were reported in the included studies concerning sensory recovery, and a correspondence between the two was established according to the clinical criteria of each classification (supplementary table). S3, S3+, or S4 grade are stated as functional sensory recovery according to Bagheri *et al.* (2012) (7). A sensitivity recovery described as normal by the authors but without the use of the MRC classification was also considered as functional sensory recovery. The extracted data were subjected to descriptive analysis. When patients' data were not available, the corresponding authors of the studies were contacted by email.

Qualitative/Risk of bias analysis/assessment

A qualitive assessment of selected studies was performed using the Modified Delphi process for case series (24), the Newcastle/Ottawa scale for case-control studies (25,26).

RESULTS

Characteristics of the included studies

The electronic search retrieved 317 records. After exclusion of 27 duplicates, 290 studies remained. After the screening of titles and abstracts, 17 studies were selected for full text reading and evaluation. Finally, 12 studies were excluded because they did not fulfill inclusion criteria (7–9,21,27–34), and 5 studies were included in this systematic review for data extraction and qualitative analysis (Figure 1). Two studies were case series (14,15), 2 were case reports (35,36), and 1 study was a case-control study (37). For the latter, the author was directly reached as patients' data were not available in the article, and data for 12 patients were finally obtained (18 patients included in this study) (37).

Studies' quality assessment

The Newcastle/Ottawa scale was used to assess the study from Zuniga *et al.* (2017). According to the rating system, this article is of poor quality (25,26) (appendix 1). For the case series, the Modified Delphi Process was used. The article by Zuniga *et al.* (2015) validates 10 criteria out of 20, and that of Salomon *et al.* (2016) 13 out of 20 (appendix 2).

Data from all included studies (Table 1)

A total of 33 patients underwent 36 nerve reconstructions (3 bilateral reconstructions). Fourteen patients were female (42.4%) and mean age was 30 years old. The mean length of graft used was 64.0 mm ± 9.1mm (Figure 2). The most common pathology that led to nerve resection was ameloblastoma (52%). For 6 patients (18.2%), the pathology was not specified (Figure 3). Among all patients, a functional sensory recovery was confirmed in 72.2% of the reconstructions (26 out of 36 reconstructions). No data on sensory recovery was available for 22.2% of the reconstructions (n = 8) (Figure 4). Two nervous repairs presented no functional sensory recovery (5.6%). Among the reconstructions for which the results were available, the functional sensory recovery rate was 92.9% (26/28 reconstructions). The minimum follow-up time was 6 months and up to 1 year.

DISCUSSION

The aim of this study was to assess functional sensory recovery in patients benefiting from a nerve reconstruction of the IAN by PNA in the context of benign mandibular pathology. In the present systematic review, a functional sensory recovery was found in 92.9% of cases.

To our knowledge, this work is the first on the subject in the field of maxillofacial surgery. Indeed, this recent technique was only described in a limited number of cases series or case reports. Most of the data available on PNA for IAN repair in the literature concern iatrogenic

injuries (fracture, orthognathic surgery, endodontic lesion of third molar removal), for which the damage is localized and the repair is done months after the initial injury (14,21,27). When a mandibulectomy is performed for benign pathologies, nerve reconstruction is performed at the same time and usually requires a longer length of PNA as the substance loss is bigger. Thus, considering these different characteristics, the present study focused on nerve reconstruction following benign mandibular resection in order to increase the homogeneity of the study population. The encouraging results of the present review are in accordance with the work of Yampolsky *et al.* (2017), that reported a sensitive functional recovery in 93.75% of cases (15/16 patients) after repair of the trigeminal nerve (lingual and IAN) in the context of iatrogenic injuries, with a mean interval between injury and surgery of 272.2 days ± 248.9 (27).

The functional sensitive outcomes of PNA are similar to those obtained using autograft techniques for the reconstruction of peripheral nerves (38). Ducic *et al.* (2019) concluded there was no significant difference between these two techniques regarding the sensory recovery rate after microsurgical repair of the IAN and lingual nerve injuries, no matter their etiologies (28).

Teams have also started to reconstruct motor nerves using PNA with promising results: Safa *et al* (2019) found a significant motor recovery in 73% of cases. In this study, a reconstruction of branches of the facial nerve was performed and motor recovery was also observed (20).

This is likely due to the fact that PNA allows to preserve the architecture of the nerve and the extracellular matrix, which are key elements for nerve regrowth (28). In addition, the Avance® nerve graft product, which is the only commercial PNA available on the market, is available in several lengths and diameters, in order to best adapt to the clinical situation and the severed nerve. They are stored frozen at less than -40°C for up to 3 years. Before use, it is necessary to completely thawed PNA in either a lactated Ringer or a sterile saline solution for

5 to 10 minutes. Then, they can be implanted using a conventional microsurgery technique (14). Information concerning the length of the allograft required is also an interesting result of the present review. Indeed, care must be taken to avoid any tension on the operating site, and therefore choosing a slightly greater length might be of use. The diameter should also be larger than that of the nerve to be reconstructed. Indeed, if the graft is too narrow, there is a risk of compression of the axon during regeneration (38). However, diameter should not be too large either, this parameter being linked to disappointing results (38). Some authors recommend to remove about 1 cm of the buccal cortex in order to free the nerve on its proximal portion so that the ends are freer and therefore easier to suture (37).

In some studies, the surgeons used AxoGuard ® protector and connector to protect the nerve repair sites (14,15,35,37), but in one study it was not specify whether they used it or not (36).

Complications are very rare. No complication concerning the reconstruction of the trigeminal nerve was reported. Cases with no functional sensory recovery of the upper limp that needed reintervention were reported (16,39). A case of hyperesthesia of the IAN was reported by Yampolsky *et al.* (2017), but the patient already had neuropathic pain before surgery (27).

A major limitation of this study is the small sample size, and the design of the reported studies. Indeed, the 5 studies included are of low level of evidence and considered as level 4 according to the Center of Evidence Based Medicine (40). However, these are the only studies available to date on this subject. Moreover, among these studies, data concerning the sensory recovery were missing for 22% of patients. Nevertheless, consistence with the results found in the literature seems to show that this technique is reliable and safe in the hand of different users and allows good functional sensory recovery. Unlike carcinologic surgery that imposes a loss of sensitivity, nerve reconstruction simultaneous to surgical resection should really be considered in the context of benign mandibular pathologies.

The encouraging results of this review should promote the sensitive repair whenever it is possible. Indeed, the current trend is toward surgical repair of the peripheral nerve to restore function as well as esthetics. The ongoing RANGER study (ClinicalTrials.gov Identifier NCT01526681) concerning all nerve reconstructions performed with PNA in the USA points out the growing interest in this therapeutic approach.

CONCLUSION

PNA are a reliable, safe, and effective alternative to nerve autografts for IAN rehabilitation, with 92% of functional recovery according to the reported literature, without the comorbidity associated with the use of a donor site. Nerve reconstruction, in addition to bone, dental, and soft tissue reconstruction performed in case of benign tumor pathologies, allows complete patient care and optimal functional rehabilitation. Thus, further studies with better level of evidence are needed to widen the use of this technique.

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Figures legends:

Figure 1: Flow chart

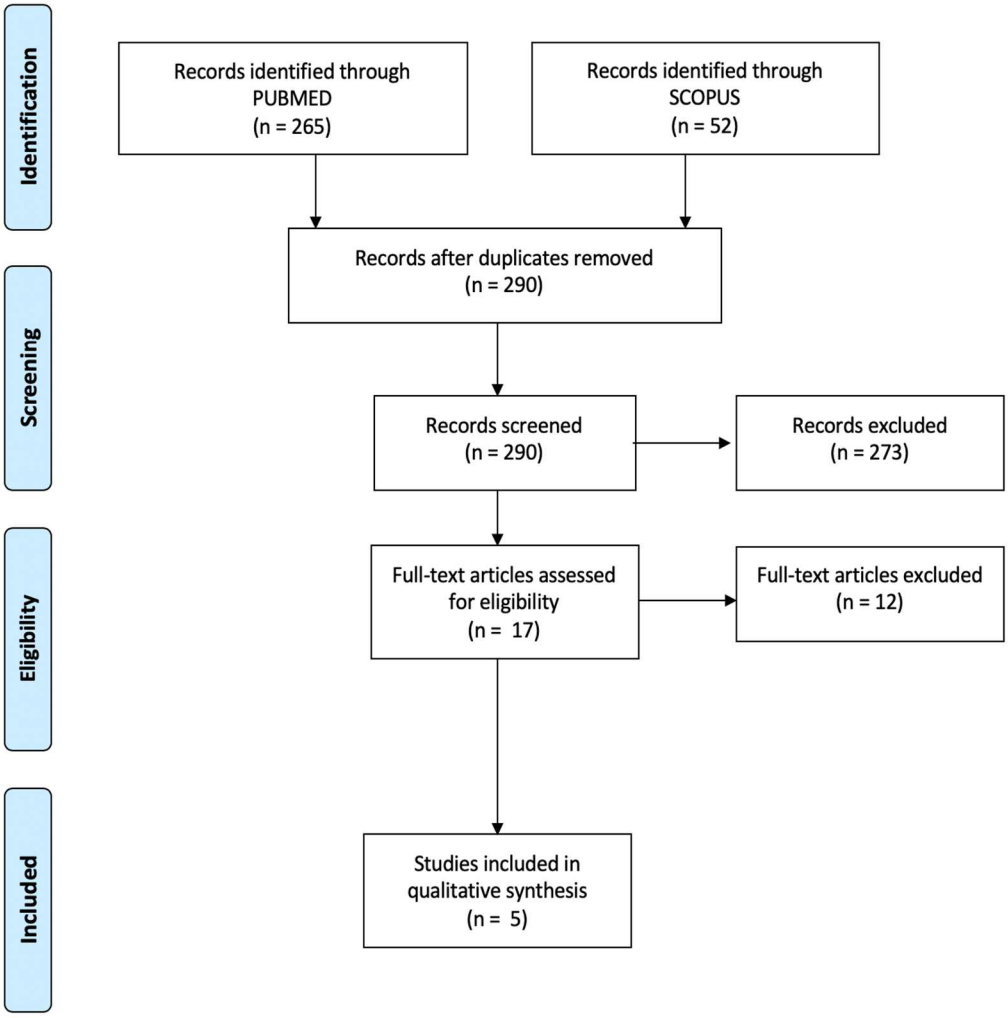

Figure 2: Distribution of grafts' length used during surgery

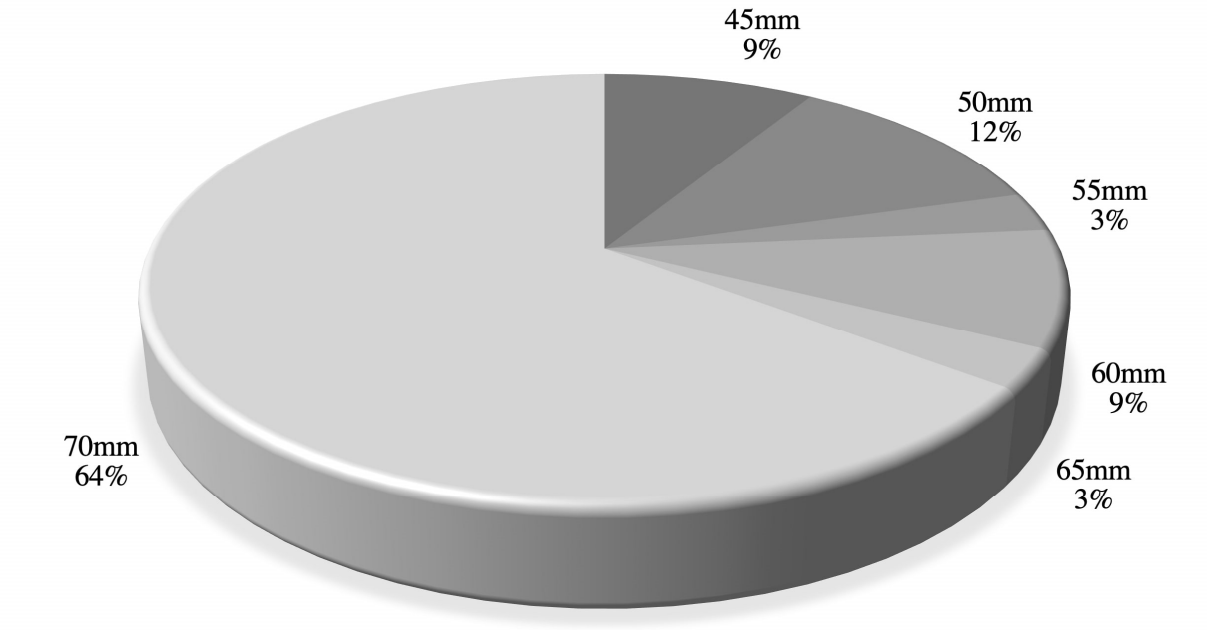

Figure 3 : Distribution of pathologies found in the population requiring resection of the inferior alveolar nerve

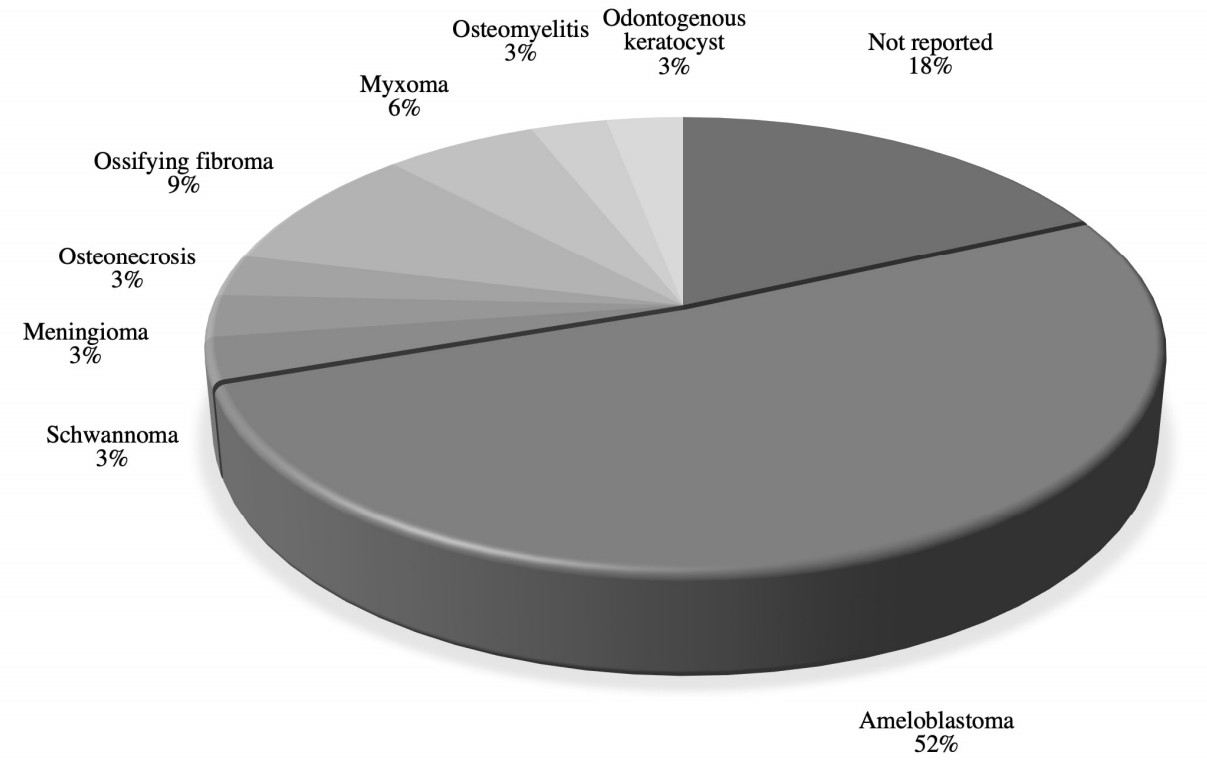

Figure 4: Distribution of functional sensory recovery (grade S3, S3+, and S4 from the MRC classification)

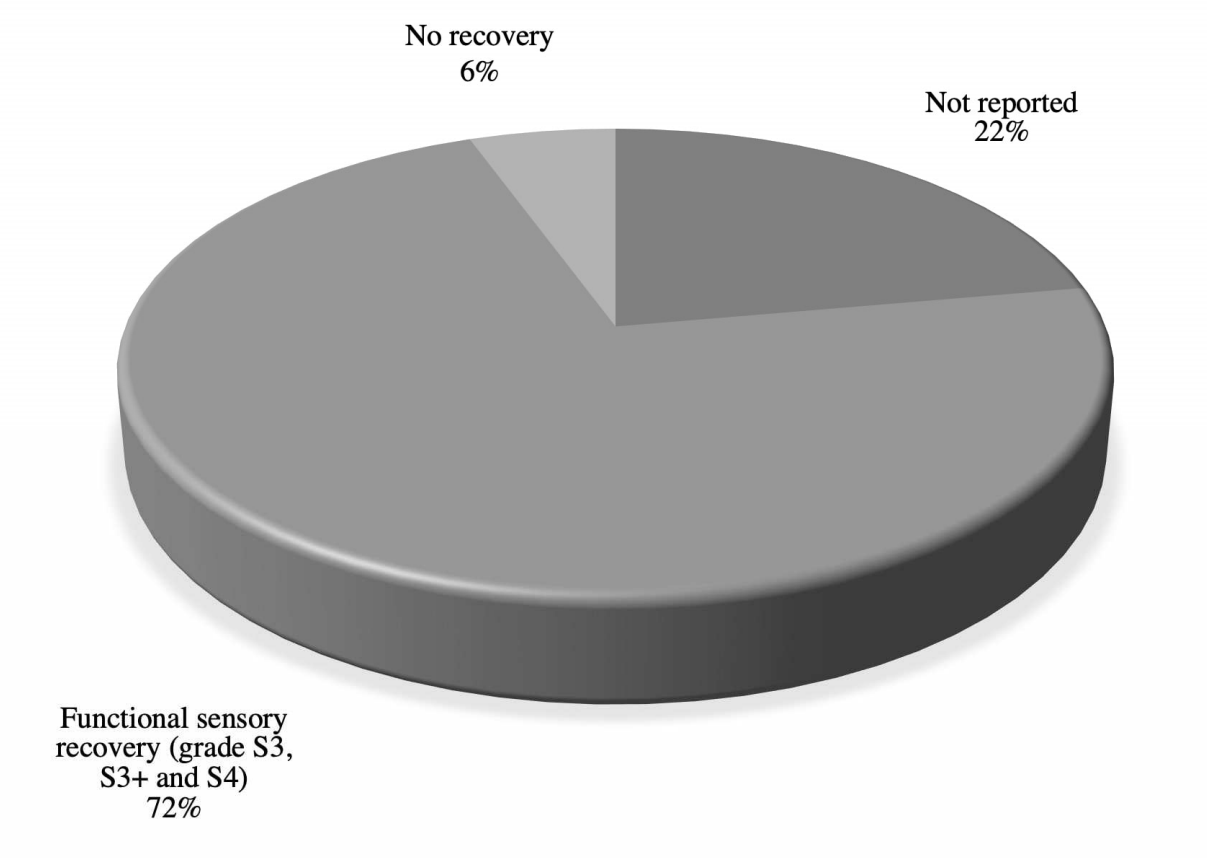

Table 1: Data extracted from the studies included in the systematic review

	PATIENT	AGE	GENDER	PATHOLOGY	GRAFT LENGHT (MM)	SENSORY RECOVERY (MRCS SCALE)
ZUNIGA ET AL. (2015)	1	67	M	Not specified	50	Functional
	2	35	M	Not specified	70	Functional
	3	9	M	Not specified	70	Functional
	4	37	M	Not specified	70	Functional
	5	11	M	Not specified	70	Functional
	6	50	F	Not specified	70	Functional
SALOMON ET AL (2016)	7	25	M	Ameloblastoma	70	Functional

	8	61	M	Ameloblastoma	70	Functional
	9	35	M	Schwannoma	50	Functional
	10	27	F	Ameloblastoma	70	Non functional
	11	20	M	Ameloblastoma	70	Functional
	12	18	M	Meningioma	70	Functional
TURSUN ET AL. (2017)	13	79	M	Osteonecrosis	70	Functional
ZUNIGA ET AL. (2017)	14	35	M	Ameloblastoma	70	Functional
	15	11	M	Ossifying fibroma	70	Functional
	16	37	M	Ameloblastoma	70	Functional
	17	29	M	Ameloblastoma	60	Functional
	18	28	F	Ameloblastoma	70	Functional
	19	36	F	Ameloblastoma	65	Functional
	20	28	F	Ameloblastoma	55	Functional
	21	22	F	Myxoma	70	Functional
	22	10	F	Ossifying fibroma	60	Functional
	23	60	F	Osteomyelitis	60	Functional
	24	12	F	Ameloblastoma	50	Functional
	25 (right)	25	M	Ossifying fibroma	50	Functional
	25 (left)				70	Functional
	26	18	F	Ameloblastoma	45	Not specified
	27 (right)	14	F	Ameloblastoma	45	Not specified
	27 (left)				45	Not specified
	28 (right)	18	F	Ameloblastoma	70	Not specified
	28 (left)				70	Not specified

	29	64	F	Ameloblastoma	70	Not specified
	30	25	M	Odontogenous keratocyst	70	Not specified
	31	12	M	Myxoma	70	Not specified
SARLABOUS ET AL. (2018)	32	22	F	Ameloblastoma	Not specified	Functional
	33	20	M	Ameloblastoma	Not specified	Non functional
MEAN		**30**			**64,0**	