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Rapid prototyped patient specific guiding implants in critical mandibular reconstruction☆

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ABSTRACT

Large tumours of the mandible need immediate reconstruction to provide continuity of the mandible, satisfactory function of the jaw, as well as an acceptable aesthetic outcome. In this prospective study we described the immediate reconstruction of the mandible using computer aided design and 15 rapid prototyped patient specific implants (PSI) in 14 patients suffering from benign or malignant tumours demanding continuity resection of the mandible. The scaffold PSI was filled with β-tricalcium phosphate granules and autologous bone. Microvascular reconstruction was additionally needed in 12/15 cases. The clinical follow up was on average 33 months and the radiological follow up was on average 21 months.

In nine cases the healing was uneventful. One patient lost the microvascular flap during the first postoperative week and one patient needed a revision due to perforation of the mucosa at the site of the PSI. Four patients had a major complication due to perforation of the mucosa leading to infection, which resulted in the total or partial removal of the PSI. The PSI seems to be a promising solution for treatment of patients demanding large reconstruction after mandible resection. The benefits are decreased rate of donor site complications and more accurate and prompt surgical procedure.

1. Introduction

Ablative surgery in the maxillofacial area often leads to functional as well as aesthetic complications. A mandibular (continuity) defect may be the result of surgery due to malignant or benign tumours, extensive trauma or other diseases involving bone. Without adequate primary reconstruction loss of mandibular continuity leads to considerable difficulties with regard to form and function and psychosocial issues (Urken et al., 1991; Bak et al., 2010).

Previously, free bone grafting was the most common method for rebuilding the mandible (Devireddy et al., 2015). Today rehabilitation of patients with mandibular defects can be achieved using vascularized bone flaps or bone substitutes (Disa & Cordeiro, 2000; Bak et al., 2010; Gibber et al., 2015). This can be performed either primarily or in a secondary procedure (Urken et al., 1991).

Reconstruction of the maxillofacial area with free grafts or composite microvascular flaps is challenging and needs a team with experienced surgeons. The surgical procedure is time consuming not only because of the microvascular procedure, but also due to the fact that the bone requires shaping to optimize the configuration and symmetry of the mandible. The focus is to obtain and restore the facial contour and the occlusal relationship and masticatory function. The site of harvest is frequently prone to severe morbidity (Kuvat et al., 2012). The patient's general condition might be a contraindication for such a comprehensive reconstructive surgery.

Computer aided design (CAD) and computer aided manufacturing (CAM) are widely used in the engineering. However, the use of CAD/CAM in medicine is still limited (Hassfeld & Mühling, 2001; Schmelzeisen et al., 2002). In medicine, mainly preoperative virtual planning is performed using CAD technique. If the deformed or missing bone should be repaired using solid implants, this is done manually(Schön et al., 2006; Fan et al., 2007; Li et al., 2009; Lieger et al., 2010; Stoetzer et al., 2011; Mustafa et al., 2011).

Using CAD the patient's virtual individual 3D model of the facial skeleton can be obtained. 3D model is beneficial since the surgeon can evaluate, plan, experiment and simulate surgery multiple

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times. Furthermore the virtual implant can be designed if found necessary (Rudman et al., 2011). With CAM the virtual model can then be fabricated into a solid model. The solid models can be manufactured out of several materials including titanium (Klein and Glatzer, 2006; Lopez-Heredia et al., 2008). There is good evidence that RP reproduce solid models with acceptable precision (Ibrahim et al., 2009).

The process from CT data to virtual model and to solid model/implant manufacturing is complex due to conversion of data at several steps (Stoor et al., 2014; Huotilainen et al., 2014) The process itself has been described simply as a four step flow (Mäkitie et al., 2010). One of the main issues is the option of proper CT protocol at the beginning of the process.

The aim of this study was to assess if a clinically usable patient specific mandibular implant with the right anatomic shape can be manufactured utilizing CAD – CAM technique. The second aim was to study if the implant could be designed in such a way that it guides without navigation the surgeon to place the implant in the operative theatre similarly to the CAD design.

2. Materials and methods

2.1. Rapid prototyped implant

The design of the 3D volumetric virtual implant was done using PTC ProEngineer™ 3D CAD software. The shape was obtained using the geometry of the opposite side of the mandibular body, angle and condyle. The 3D modelling with ProEngineer™ was performed first by mirroring the intact mandible and transferring it into the deformed side. The 3D virtual implant was then designed using traditional 3D technique. The implant was a combination of scaffold and reconstruction plate with screw holes (Fig. 1). In surgery, each implant was fixed using 2.0 titanium screws (Synthes, Paoli, USA).

The manufacturing of the solid implant was done through Planmeca (Helsinki, Finland) using ArCAM's Electron Beam Melting (EBM) technology. The technology is based on layer-by-layer melting, in this case, the titanium powder into solid form by blasting the powder with electron beams. Titanium raw material was Ti6Al4V ELI titanium powder (Grade 23), particle size: 45–105 μm with the density of 2.30 gr/cm^3. The PSI is considered as a medical device identified in Medical Devices Directive 93/42/EEC/Article 1(2)(a). The chemical composition must thus meet specific criteria. The implants were tested for chemical impurities at Fruth Innovative Technologien GmbH, Eichenbuhl, Parsenberg, Germany.

2.2. Patient material

14 patients with a total of 15 PSIs were included into this study, 10 males and 4 females suffering from squamous cell carcinoma (10), ameloblastoma (3) or drug induced osteonecrosis (1). One of the patients (No 4) needed two PSIs, one on the left side and one on the right side of the mandible due to metastasis of squamous cell carcinoma. The average age of the patients was 63 years (39–77). The indication for PSI aided surgery was a large continuity defect of the mandible, which normally would have needed a microvascular composite flap for reconstruction (Table 1).

Fig. 1. Patient specific implant.

The mandibulotomy was carried out through combined intraoral and extraoral incision or through an intraoral approach. A special CAD–CAM patient specific guiding splint was used for exact cutting of the mandible (Fig. 2). Neck dissections were performed according to normal standard. The PSIs were placed under direct vision and fixed with bicortical 2.0 mm screws (Synthes, Oberdorf, Switzerland) (Fig. 3).

All PSIs were filled with beta-tricalciumphosphate (β-TCP) granules (chronOS granules 1.4–2.8 mm, Synthes, Oberdorf, Switzerland). In 12 cases the PSIs were additionally filled with autologous cancellous bone chips harvested from the iliac crest and in one case with bone harvested from the mandible. Bone morphogenic protein 2 (BMP-2, Inductos®, Medtronic, Hertfordshire, UK) soaked in the absorbable sponge or in a collagen membrane (Bio-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland) placed to cover the cage was additionally used in the patients with ameloblastomas and drug induced osteonecrosis of the mandible to improve the bone formation. In most of the cases the scaffold was covered with a collagen membrane (Bio-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland). The PSIs were finally covered with a radial forearm (RFA) flap in 5 cases and with an anterior lateral thigh (ALT) flap in 7 cases. One patient (No 10) suffering from a residual SCC had an abdominal rectus flap from earlier surgery and needed no further flap for wound closure. Additionally 2 implants did not need any free flap reconstruction for sufficient closure.

Seven patients did not receive any additional therapy. Three patients received postoperatively radiation therapy only. Five patients received both radiotherapy and chemotherapy postoperatively (Table 1).

3. Results

The clinical results are presented in Table 1. The follow up was on average 33 months (6–49). Five patients died during the follow up. Three patients died due to spreading of the tumour into to the scull. One patient died due to bladder carcinoma (No 4) and one due to pulmonary carcinoma (No 11). The healing of 8 RP-implants (53%) was uneventful. Minor complication occurred in two (13%) cases. One of these patients had a perforation in the lingual mucosa due to the RP-implant being too high at that region. After revision and shortening of the lingual implant foil the healing was uneventful. The second patient with a minor complication had a slight disturbance in the occlusion, which was corrected with dental ceramic inserts and on-lays.

One patient (6%) lost the anterior and lateral thigh microvascular flap during the first postoperative week due to venous difficulty. Re-reconstruction with radial forearm microvascular flap was uneventful.

Four patients (27%) had a major complication due to perforation of the lingual mucosa leading to infection. Despite wound revision and lowering of the implant's lingual foil, the bone substitute β-TCP was infected resulting in removal of the PSI in three patients, which were finally treated with a deep circumflex iliac artery composite microvascular flap (DCIA). In one patient (No 12) only the scaffold part of the PSI had to be removed, and the inferior rigid plate part was left with uneventful healing.

Table 1
Diagnosis and treatment of patients with mandibular patient specific implants.

Patient No	Gender	Age at surgery	DG	Radiotherapy	PSI	Microvascular flap	Cancellous bone from the iliac crest	Growth factors	Membrane	Major complications	Minor complication	Histology post operatively	Follow up (months)
1	Female	66	Ameloblastoma	No	Left mandibular body	RFA	Yes	BMP	No membrane		Perforation of lingual mucosa	9 months: bone formation, strong chronic inflammation	44
2	Male	39	Ameloblastoma	No	Left mandibular body	RFA	No	BMP	No membrane			22 months: mature bone	49
3	Male	73	Squamous cell carcinoma	No	Left mandibular body	RFA	Yes	No	No membrane		Slight disturbance of the occlusion		48
4	Male	55	Squamous cell carcinoma metastasis	Yes & chemotherapy	Right mandibular body	ALT	Yes	No	Collagen membrane	Removal of PSI 18 months post op and DCIA, Exitus		11 months: bone formation, mild chronic inflammation	30
			Squamous cell carcinoma metastasis	Yes & chemotherapy	Lower rim of left mandibular body	No	Yes	No	No membrane				27
5	Female	67	Ameloblastoma	No	Right mandibular angle, body & TMJ	No	Yes	BMP	Collage sponge				43
6	Female	63	Squamous cell carcinoma	No	Right mandibular angle	RFA	Yes	No	Collagen membrane	Removal of PSI 11 months post op and DCIA			42
7	Male	46	Squamous cell carcinoma	Yes & chemotherapy	Right mandibular angle	RFA	Yes	No	Collagen membrane				43
8	Male	59	Squamous cell carcinoma	Yes & chemotherapy	Right mandibular body	ALT	Yes	No	No membrane	Exitus		15 months: bone formation & TCP granules	24
9	Male	64	Squamous cell carcinoma	Yes	Right and left mandibular symphyses	ALT	Bone from mandible	No	Collagen membrane				39
10	Male	66	Squamous cell carcinoma recurrence	Yes & chemotherapy	Left mandibular angle, body & TMJ	ReA from before	No	No	Collagen membrane	Exitus			24
11	Male	73	Osteonecrosis of mandible	No	Right and left mandibular bodies & symphyses	ALT	Yes	BMP	Collagen membrane	ALT lost during first postop week; replaced by RFA. Exitus			6
12	Male	77	Squamous cell carcinoma	No	Mandibular symphyses & parasymphyses	ALT	Yes	No	Collagen membrane	Removal of PSI partly 25 months post op			37
13	Male	66	Squamous cell carcinoma	Yes	Right mandibular angle & body	ALT	Yes	No	Collagen membrane	Exitus			7
14	Female	59	Squamous cell carcinoma	Yes	Left mandibular angle & body	ALT	Yes	No	Collagen membrane	Removal of PSI 6 months post op and DCIA			39

PSI: patient specific implant.
ALT: anterior and lateral thigh microvascular flap.
RFA: radial forearm flap.
DCIA: deep circumflex iliac artery composite microvascular flap.
ReA: abdominal rectus microvascular flap.
BMP: bone morphogenic protein.
TCP: tricalcium phosphate.

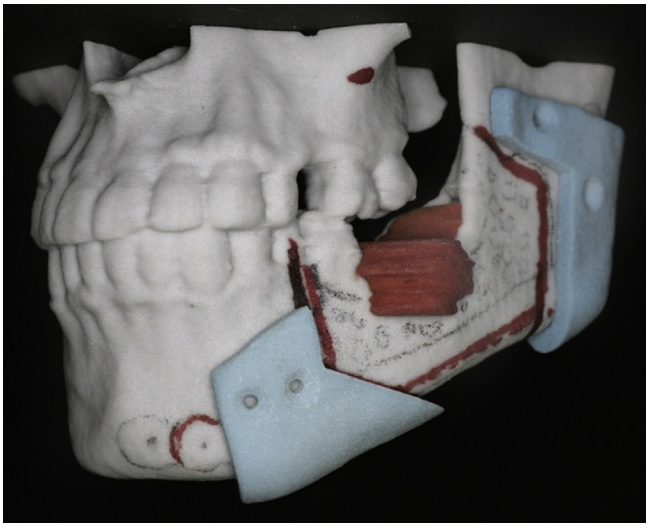

Fig. 2. 3-D skull model with surgical patient specific guiding splint for left border of the mandibular corpus designed for a patient suffering from ameloblastoma (Patient No 2).

The overall primary recovery of the patients was favourable. The facial appearance with respect to symmetry and continuity of the mandible border was obtained (Fig. 4). Only the patient who required a new microvascular flap was hospitalised longer.

The patients were radiologically followed (Tables 2 and 3). The fit of the RP-implants was excellent in nine cases (56%) (Fig. 5). In the remaining six cases only minor fitting defects, maximally 1–2 mm, were detected. In addition, in one patient, the condylar part of the RP-implant was located somewhat laterocaudal in comparison to the contralateral side. The bone and bone substitute was in good contact to the resection lines in 14 out of 15 implants. Typically there were bone (substitute) surplus in the first postoperative radiological examination and it typically resorbed during the follow up (Fig. 6). In one patient major lack of the bone (substitute) was found. In two patients the plate was exposed and in one patient air connection to the plate was suspected. In one patient abscess or tumour recurrence was radiologically suspected.

Bone biopsies were taken from four patients 9–22 months after surgery. Two of these patients had received the growth factor treatment, and the histological analysis showed lamellar bone formation after 9 months and mature bone after 22 months (Fig. 7). The histological samples of the two patients that had not received growth factor treatment, also showed bone formation at 11 and 15 months after surgery.

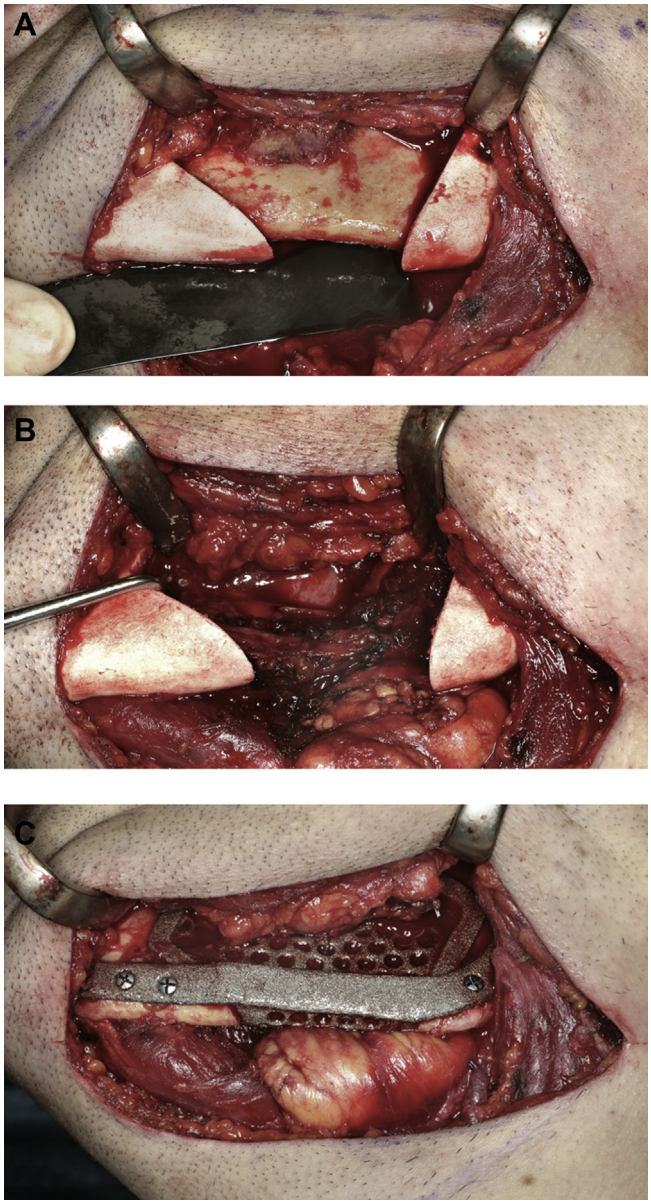

Fig. 3. A) Patient specific guiding splint in place during surgery. B) Osteotomy according to the guiding splint. C) PSI in place, osteosynthesis with screws (Patient No 2).

4. Discussion

The immediate rehabilitation of patients with mandibular continuity defects has always been a challenging problem. Immediate reconstruction is the treatment of choice to ensure rehabilitation with moderate or good life quality postoperatively. The reconstruction after tumour resection of the mandible can be performed with or without free bone graft or flap. Small defects can be repaired using local flaps but larger defects often need distant soft tissue or composite flaps. However, the free flap surgery, particularly composite flap transfer, includes a clear risks for complications (Urken et al., 1991, 1994; Goyal et al., 2016; Bak et al., 2010; Markiewicz et al., 2015; Wilkman et al., 2016) New 3D-methods and innovations are of interest for the development of advances in tumour surgery (Rana et al., 2012; Yu et al., 2016).

In this study we have shown the promising use of PSIs in combination with bone substitutes with or without vascularized flaps instead of using microvascular composite flaps. The treatment diminishes donor site morbidity and improves facial symmetry. If the mandibular condyle is lost the patient often suffers from major functional problems, such as restricted mouth opening and asymmetry. With RP-implants patient specific temporomandibular joint-prosthesis can be made as a part of the implant.

One of the complications related to the PSI was the perforation of the lingual mucosa. The lingual foil of the implant scaffold is designed easily too high, thus perforating the lingual mucosa during the postoperative healing. It has to be considered during the planning of the PSI that extraction of teeth in the osteotomy line will further lead to resorbtion and remodelling of the marginal alveolar crest and thus lower the lingual and buccal border during healing. In two patients a shortening of the lingual foil of the PSI led to uneventful healing. However, in three patients despite revision

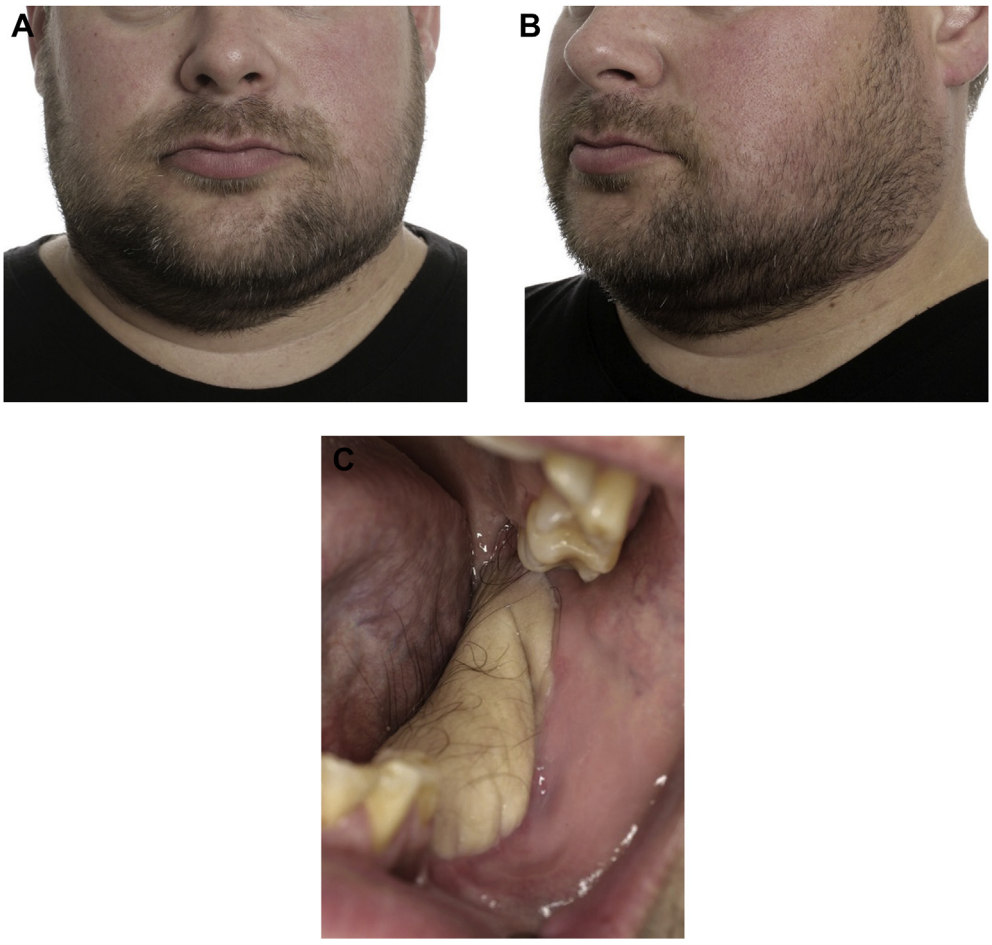

Fig. 4. Two months postoperative clinical A) anterior, B) lateral and C) intraoral view of patient treated with PSI and a radial forearm flap (Patient No 2).

and shortening of the implant the β-TCP was infected and the PSI was removed. This has to be taken into consideration in the future in the CAD–CAM. Reconstruction with a DCIA-flap was the treatment of choice for these three patients. The design of the implant's lingual foil has to be shorter than the opposite healthy side's border to avoid problems with perforations. No clear difference was seen in results regarding the use of a membrane or not. However, the surgeons felt that it was preferable to use the membrane to protect the biomaterial and implant during the primary wound healing. No clear differences in the results were seen regarding the

Table 2
The imaging methods used in the postoperative follow up with timetables. The time of the examinations is presented as days after surgery and the number of each examination is presented in parenthesis (if more than one). Patient number 4 had two separate operations.

Patient No	Ptg	Towne view	CT	CBCT	CT scan for planning of radiation therapy	PET–CT
1	4–224 (2)	–	–	–	–	–
2	4–634 (4)	–	350	929	–	–
3	7–878 (3)	7	179–940 (4)	–	–	–
4a	8–569 (2)	8	87–718 (4)	–	157	349
4b	474	–	159–623 (3)	–	62	254
5	1–503 (4)	1	–	421	–	–
6	–	–	121	–	–	–
7	309–747 (2)	–	524–747 (2)	–	42	193–331 (2)
8	12–441 (3)	12	177–695 (4)	379	39–708 (2)	–
9	264–514 (2)	–	155–702 (4)	–	–	–
10	3	–	6	–	180	107
11	9–75 (2)	–	167	–	–	–
12	5	–	–	10	–	–
13	–	–	152	–	47	134
14	7	–	–	7	45	–

Ptg = panoramic tomography.
CT = computed tomography.
CBCT = cone beam CT.
PET–CT = positron emission tomography CT.

Table 3
The radiological findings including: plate fitting, bone or bone substitute location in the resection line (in contact or not), bone or bone substitute surplus or deficiency, and possible radiological complications. Patient number 4 had two separate operations.

Patient No	Plate fitting	Bone or bone substitute in contact	Bone or bone substitute surplus [s] or deficiency [d]		Radiological complications
			1st X-ray examination	follow up (≥152 days)	
1	Good	Yes	No	No	No
2	Good	Yes	s	No	No
3	Good	No	d (major)	d (major)	Defect in plate fitting at follow up[a]
4a	Excellent	Yes	d	d	Abscess or recidive suspicion
4b	Excellent	Yes	No	No	No
5	Excellent	Yes	s	No	No
6	Excellent	Yes	d	NA	Plate exposed
7	Good	Yes	d	d	No
8	Excellent	Yes	s	s + d (minor)	Defect in plate fitting at follow up[a]
9	Excellent	Yes	No	No	No
10	Good[b]	Yes	s	No	Suspected air connection of the plate
11	Excellent	Yes	s	s + d (minor)	No
12	Excellent	Yes	s	NA	Plate exposed
13	Excellent	Yes	d (minor)	d (minor)	No
14	Good	Yes	s	NA	No

Excellent = perfect fitting.
Good = a minor defect of no more than 1–2 mm.
s = surplus.
d = deficiency.
NA = not assessed.
[a] Defect in plate fitting at follow up because of the bone or bone substitute resorption.
[b] The condylar part of the custom made plate laterocaudally in comparison to contralateral side.

postoperative treatment with chemotherapy or radiotherapy or no additional treatment. The size of the PSI did not correlate to the outcome.

Permanent reconstruction of the mandible requires bone continuity to allow rehabilitation of the masticatory function with dental implants and/or dental prostheses. In the case of benign disease, benign tumours or traumatic defects, immediate bone grafting is often indicated. For malignant tumours the timing of the bone transplantation varies. Today most surgeons reconstruct the defect with a vascularized bone flap during primary surgery (Mehta and Deschler, 2004). Others prefer a secondary procedure using a strictly extra oral approach after primary wound healing (Markowitz et al., 1994). It has also been advocated to wait up to 1–2 years before carrying out the bony reconstruction to facilitate the early detection of recurrence. Whichever procedure is preferred, the rigid plate reconstruction can and must successfully bridge the defect during bony healing and can later be used for fixation of the graft in an appropriate position.

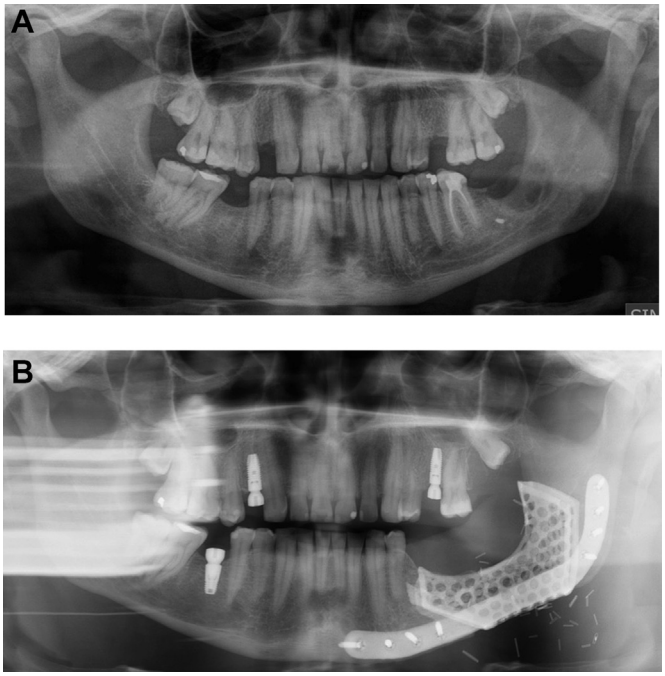

Fig. 5. A) Preoperative and B) 45 months postoperative panoramic radiographs with the PSI in place (Patient no 2).

As the hard tissue framework is successfully restored in the mandible, good function is often achieved. However, bridging of even restricted continuity defects in the anterior part of the mandible is still prone to poor outcome. This is due to the delicate soft tissue equilibrium between the floor of the mouth and lower lip, which is often disrupted due to the loss of the anterior insertion for muscles of the floor of the mouth and tongue. Despite successful contouring of the hard tissue frame deficient lip support will cause major functional problems for the patient.

In this study we showed a new alternative to provide the patient with an immediate reconstruction using PSI without the need of composite microvascular flaps. PSIs seem to be easy to fit and are stable. To achieve a good bone formation, β-TCP mixed with autologous bone showed promising results, especially when used together with the growth factor BMP-2. However, no dental rehabilitation was planned in the reconstructed area for these patients. The titanium cage implant with high borders reshaping the alveolar ridge is not a suitable base for over denture due to risk of perforation of the mucosa leading to potential infection of the implant. Dental rehabilitation with implants on the other hand was not executed in any patient in this study due to uncertainty of the bone quality. Further studies are needed to improve the optimal bone substitute in cases where the use of growth factors is contraindicated. The most challenging issue seemed to be the estimation of the right height of the lingual foil to avoid perforation of the mucosa, which may lead to infection of the bone substitutes and PSI failure.

5. Conclusion

In conclusion, the PSI seems to be a promising solution for treatment of patients requiring large reconstruction of the

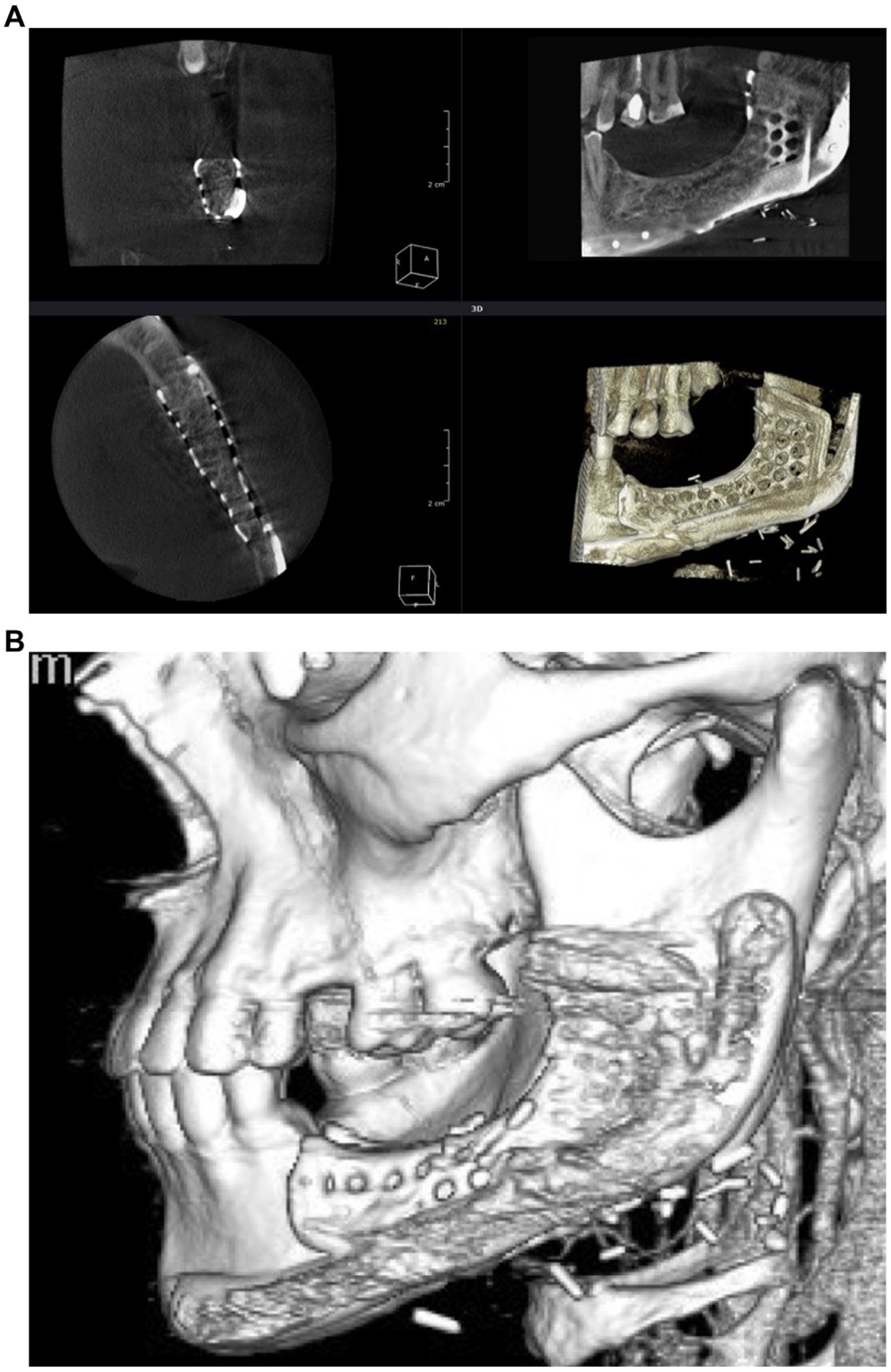

Fig. 6. 12 months postoperative A) cone beam computed tomography radiographs with B) 3D format (Patient No 2).

mandible due to resection surgery. The benefits are decreased rate of donor site complications and more accurate and more prompt surgical procedure.

Guideline

Observational retrospective study (STROBE).

Disclaimer

The views expressed in the submitted manuscript are our own, not official statements of the institutions or of the funders.

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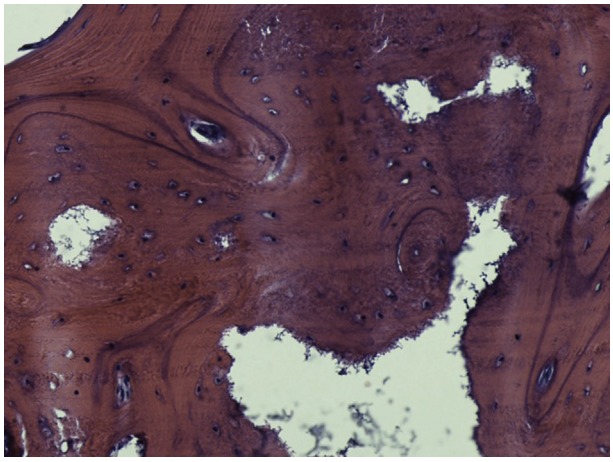

Fig. 7. Histological analysis of bone biopsy at 22 months postoperatively showing lamellar bone formation (Patient No 2).

Conflict of interest

No one of the authors has received any funding for this study. No one of the authors has any commercial associations or financial disclosures that might pose or create a conflict of interest with information presented in this submitted manuscript.

Disclosure

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