Review

New frontiers and emerging applications of 3D printing in ENT surgery: a systematic review of the literature

Nuove frontiere e applicazioni emergenti della stampa 3D in ORL: revisione sistematica della letteratura

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SUMMARY

3D printing systems have revolutionised prototyping in the industrial field by lowering production time from days to hours and costs from thousands to just a few dollars. Today, 3D printers are no more confined to prototyping, but are increasingly employed in medical disciplines with fascinating results, even in many aspects of otorhinolaryngology. All publications on ENT surgery, sourced through updated electronic databases (PubMed, MEDLINE, EMBASE) and published up to March 2017, were examined according to PRISMA guidelines. Overall, 121 studies fulfilled specific inclusion criteria and were included in our systematic review. Studies were classified according to the specific field of application (otologic, rhinologic, head and neck) and area of interest (surgical and preclinical education, customised surgical planning, tissue engineering and implantable prosthesis). Technological aspects, clinical implications and limits of 3D printing processes are discussed focusing on current benefits and future perspectives.

KEY WORDS: 3D printing • Additive manufacturing • Rapid prototyping • Otorhinolaryngology • ENT • Systematic review

RIASSUNTO

Le tecnologie di stampa 3D hanno rivoluzionato la realizzazione di prototipi in ambito industriale, riducendo i tempi ed i costi di produzione rispettivamente da giorni ad ore, da migliaia a pochi dollari. Ad oggi, i sistemi di stampa 3D non sono solamente confinati alla creazione di prototipi, ma hanno trovato un crescente impiego in medicina con risultati affascinanti anche nel campo dell'Otorinolaringoiatria. Applicando le linee guida "PRISMA", abbiamo svolto una revisione sistematica della letteratura al fine di esaminare tutti gli articoli inerenti l'Otorinolaringoiatria, che sono stati riportati sui database elettronici (PubMed, MEDLINE, EMBASE) aggiornati fino a Marzo 2017. Complessivamente, 121 studi scientifici hanno soddisfatto specifici criteri di inclusione e sono stati sottoposti alla nostra revisione sistematica. Le pubblicazioni sono state classificate in relazione al campo di applicazione specifico (otologico, rinologico, testa-collo) e all'area di interesse (formazione chirurgica e preclinica, pianificazione prechirurgica personalizzata, ingegneria tissutale e protesi impiantabile). Gli aspetti tecnologici, le implicazioni cliniche ed i limiti delle tecnologie di stampa 3D sono stati ampiamente discussi in riferimento agli effettivi vantaggi attuali ed alle prospettive future.

PAROLE CHIAVE: *Stampa 3D • Prototipizzazione rapida • Produzione additiva • Otorinolaringoiatria • ORL • Revisione sistematica*

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Introduction

Around 1450, Gutenberg developed a printing system that became a stepping-stone in the timeline of communication technology, and considered as one of the most influential events in the sharing of scientific and medical knowledge. Since its first introduction in the early 1980s, 3D printing (3DP) technology has rapidly caught the interest of the industry, healthcare and media with an overall business of $700 million [1-4]. The nature of all 3D printers is the creation of a wide range of 3D objects obtained from digital data of easy management and available in open-access digital databases, allowing a unique opportunity for information exchange (e.g. 3dprint.nih.gov). Almost anything can be produced by 3DP systems: fuel injectors for rockets, jewels and hearing aid shells [5 6]. One of the most fascinating aspects of this technology concerns the employment of imaging studies. Today, radiology plays a pivotal role in diagnostic and therapeutic decision making. However, scans are still displayed on flat screens, resulting in a 2D representation of reality. Surgeons' experience the difficult task of figuring out a three-dimensional image on a daily basis, by analysing CT or MRI-slices in separate two-dimensional axial, coronal and sagittal projections [7]. 3DP systems allow to restore the third dimension that is lacking during visualisation of radiological image data. Along with the production of anatomical models addressed to customised surgical planning, medical teaching and surgical training, research in 3DP has explored the pioneering world of biologic tissue engineering, patient-specific implantation and ultimately of personalised pharmacoprinting. The increasing impact of 3DP processes in the scientific literature has recently involved many aspects of otorhinolaryngology, often followed by great expectations regarding patient care. Up to now, what are the applications of 3DP technologies in ENT surgery? Does this tool provide any substantial benefits in the ENT field? And what about future perspectives? The present work aims to answer these questions by carrying out a systematic review of the literature on the topic, a task that, to the best of our knowledge, has not undertaken previously.

The technology of 3DP systems

3DP is a subset of additive manufacturing (AM) or rapid prototyping in which objects are achieved by gradually layering material, rather than by subtraction from the raw material as is in the case of conventional technologies [8]. The main advantages of AM are its flexibility, precision and relative quickness in creating customised physical structures of almost any complex shape in a myriad of materials. Historically, 3DP processes were employed by the manufacturing industry to rapidly produce a representation of a system or a part before final release or commercialisation [9]. The 3DP was first conceived by C. Hull in 1986 as an "apparatus for production of three-dimensional objects by stereolithography" [3]. During the same year, he also developed the "Standard Triangulation Language" (.STL) file format, which makes it possible to deconstruct the surface of a three-dimensional object in a series of triangles. The .STL file can be obtained from a 3D "Computer-Aided Design" (CAD) software, a medical scan data (e.g. CT scan, MRI), or from existing objects by using point or laser scanners. This virtual model is subsequently sliced into thin 2D layers, which are then sent to the 3D printer. 3DP methodologies differ from one another in the way that materials are deployed and cured [8]. Recently, the ASTM International Committee F42 classified 3DP technologies in 7 different working process categories [10] (Fig. 1).

I. *Vat photopolymerisation:* in this technique a container gets filled with photopolymeric resin. This resin is then hardened by an UV light source.
II. *Material jetting*: this process resembles inkjet paper printing, since the material is dropped through small diameter nozzles. In this case, the base material is a photopolymeric resin subsequently hardened by a UV lamp.
III. *Binder jetting:* this method employs a powder base material and a liquid binder. In the build chamber, the powder is spread in equal layers and binder is applied through jet nozzles that "glue" the powder particles together in the shape of a programmed 3D object.
IV. *Material extrusion:* the most widespread and popular 3DP technology on the market. These printers are fed a thermo-plastic filament that gets pushed through a heating chamber: the fused material is moulded and then solidified through cooling, allowing the deposition of successive layers.
V. *Powder bed fusion*: this technology uses a high-power laser source to fuse small particles of plastic, metal, ceramic or glass powders into a mass that has the desired three-dimensional shape. The laser selectively fuses the powdered material by scanning the cross-sections generated by the 3D modelling program on the surface of a powder bed.
VI. *Sheet lamination*: in this technique sheets of material are bound together through external force. These processes can be further categorised based on the mechanism employed to achieve bonding between layers: gluing or adhesive bonding, thermal bonding, clamping, or ultrasonic welding.
VII. *Direct energy deposition*: this process, mostly used in the high-tech metal industry, enables the creation of parts by melting material as it is being deposited. The 3DP is usually attached to a multi-axis robotic arm composed of a nozzle that deposits metal powder or wire on a surface and an energy source (laser, electron beam or plasma arc) that melts it, forming a solid object.

Materials and methods

All existing articles sourced through updated electronic databases (PubMed, MEDLINE, EMBASE) and published up to March 2017 were examined according to the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) guidelines [11]. The research was conducted using the following keywords: "3D printing OR three di-

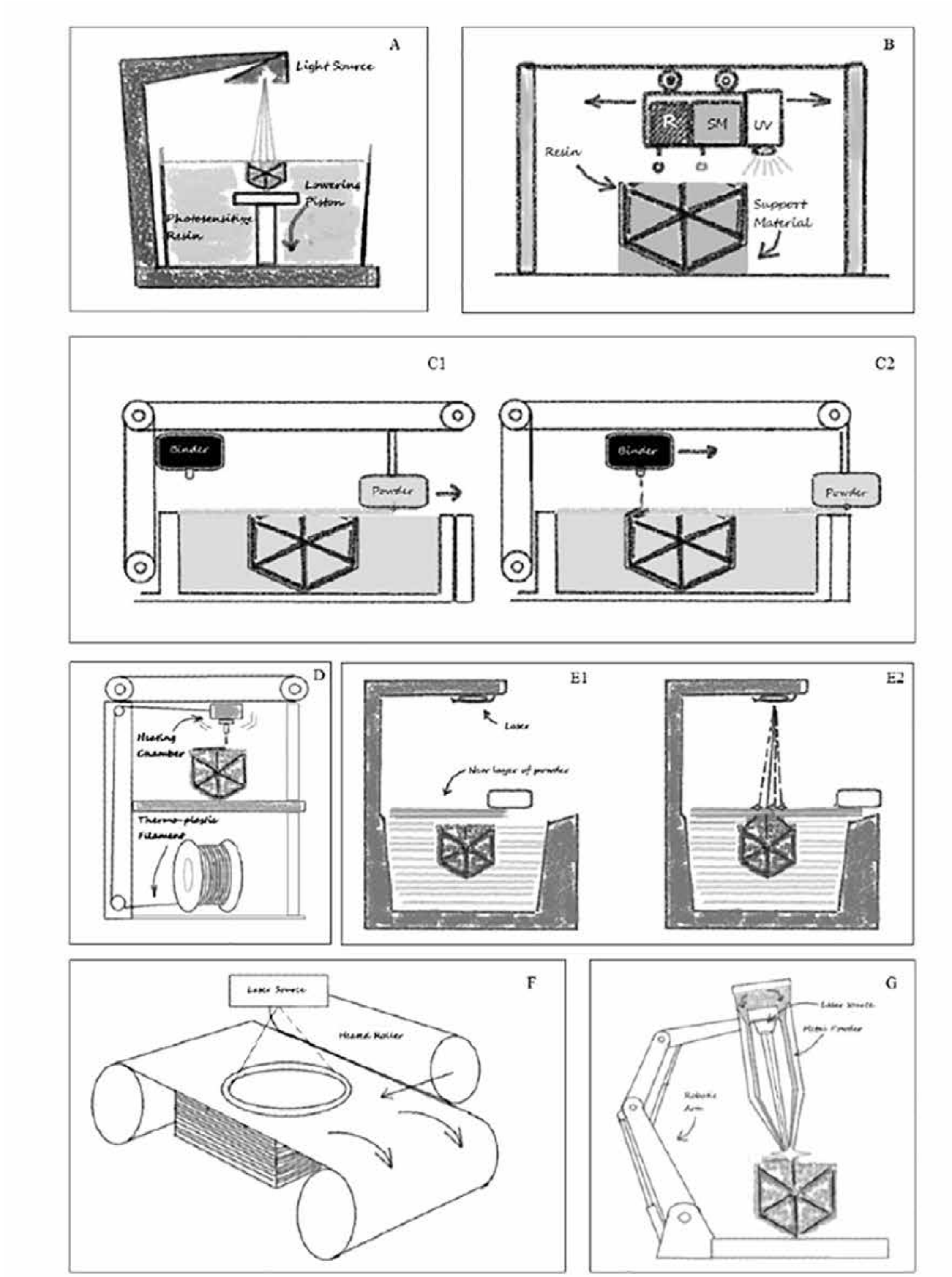

Fig. 1. Schematic representation of AM technologies: (A) vat photopolymerisation, (B) material jetting, (C1, C2) binder jetting (R: resin, SM: supporting material, UV: UV lamp), (D) material extrusion, (E1, E2) powder bed fusion, (F) sheet lamination, (G) direct energy deposition.

mensional printing AND otorhinolaryngology NOT plastic surgery", "3D printing OR three dimensional printing AND ENT NOT plastic surgery", "3D printing OR three dimensional printing AND otology NOT plastic surgery", "3D printing OR three dimensional printing AND rhinology NOT plastic surgery", "3D printing OR three dimensional printing AND head neck NOT plastic surgery", "3D Printing OR three-dimensional printing AND mandible NOT plastic surgery". Other sources analysed for additional relevant trials were reference lists of previous systematic reviews and evaluated works, journal homepages and publications citing included trials. Furthermore, experts in the field of 3D printing and engineering were contacted to ensure that all relevant studies had been included. Searches were done at all stages, from the initial drafting of the paper to submission of the revised and final version. Works lacking clinical or surgical relevance, such as engineering and bio-engineering publications and those regarding the evaluation of accuracy of the 3DP models were excluded since these are out of the expertise of ENT surgeons. Moreover, papers primarily addressing maxillofacial surgery, plastic surgery, thoracic surgery, neurosurgery and dentistry were also excluded. Exclusion criteria also applied to animal research and studies with ambiguous information regarding the modalities of production and employment of the 3DP methodology. Articles not written in English, review articles, letters, editorials and congress abstracts were omitted as well. All the considered studies were classified according to the specific field of application (otologic, rhinologic, head and neck). Each field was furthermore categorised into three distinct areas of interest: surgical and preclinical education, customised surgical planning and tissue engineering and implantable prostheses.

Results

The electronic database search yielded 258 citations and a further 123 articles were identified from additional sources, but after removing duplicates the total number of articles decreased to 278. A total of 157 records were removed as they did not fulfil inclusion criteria. Overall, 121 studies were included in the systematic review (Fig. 2). Figure 3 shows the studies according to the spe-

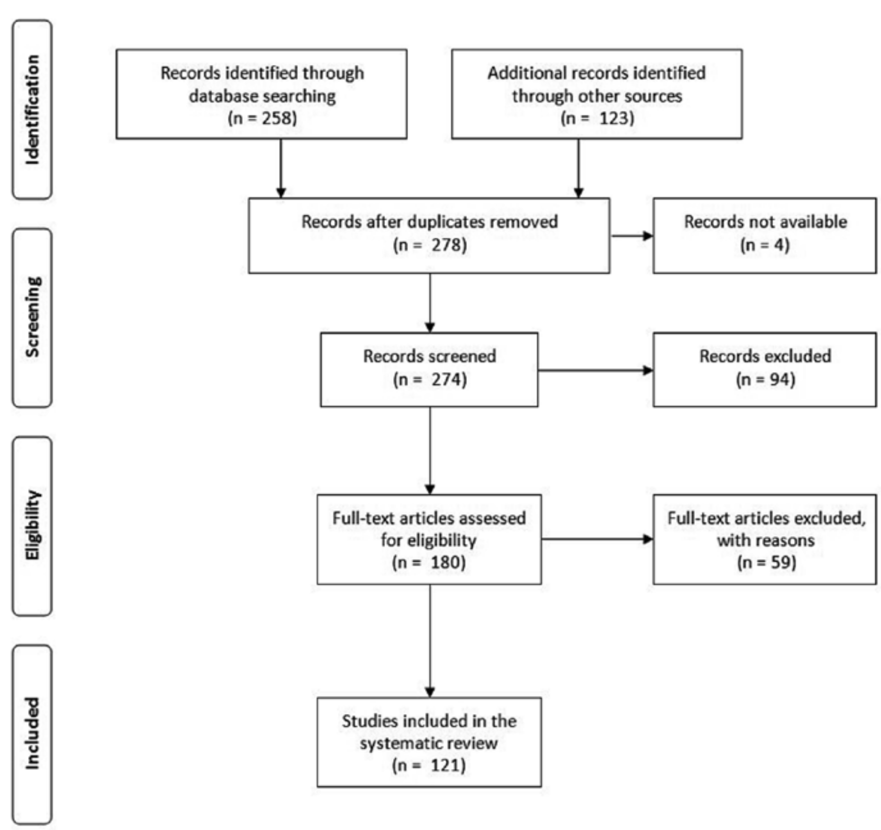

Fig. 2. PRISMA flowchart showing the study selection process.

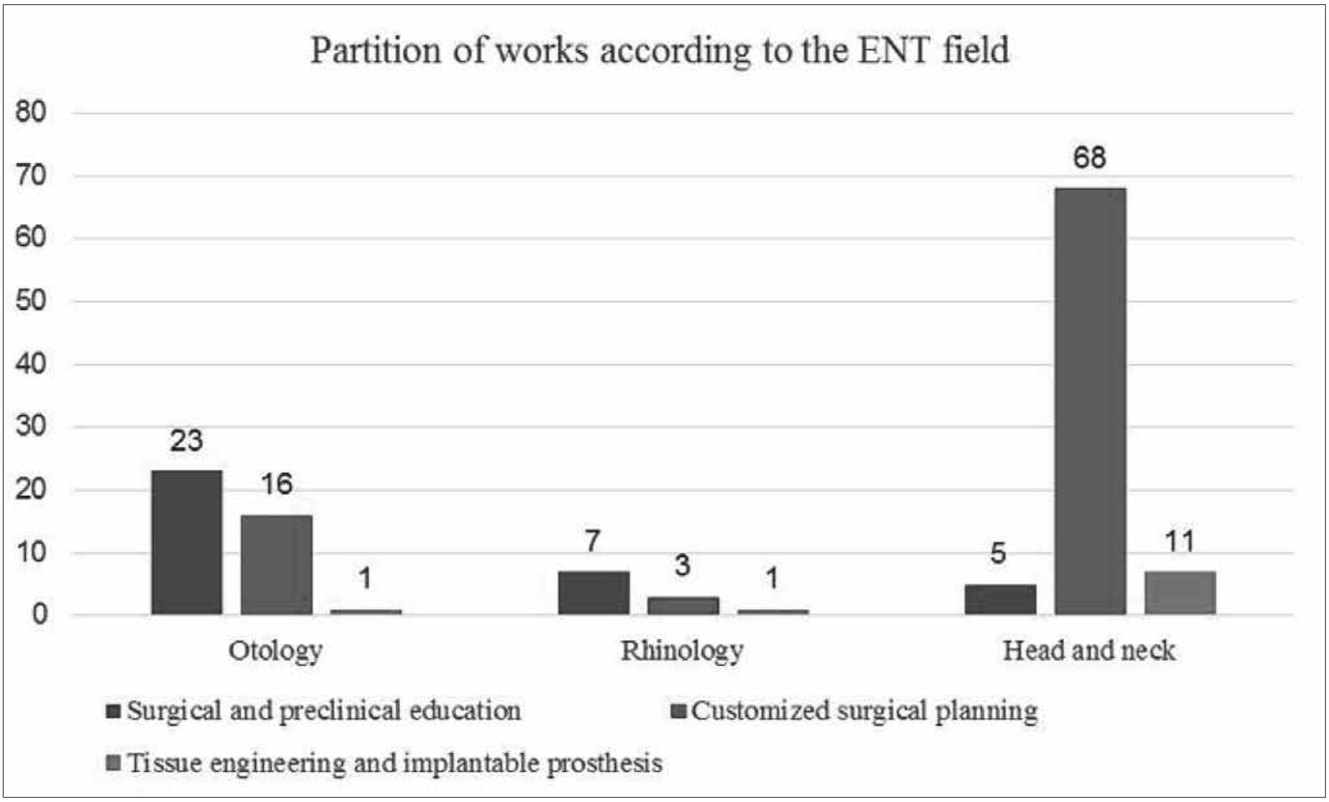

Fig. 3. Number of studies according to ENT field.

cific field of application (otologic, rhinologic, head and neck) and area of interest (surgical and preclinical education, customised surgical planning, tissue engineering and implantable prostheses). The total number of articles in Figure 3 is 135, and not 121, since 14 articles belong to more than one field of application and/or area of interest. Employed AM technology is summarised in Figure 4 considering the three areas of interest.

Otologic applications (Table I)

Surgical and preclinical education [12–34]

Twenty-three studies of the otologic ones (n = 39) involved the surgical and preclinical education area (59.0%) and mostly concerned the field of temporal bone dissection. Since the first report in 1998[31], technological efforts aimed to overcome the restrictions of the initial 3DP models. These first models, which employed a sole material and a single colour, allowed acceptable anatomical results, but limited haptic and drilling features. The evolution of 3DP systems (e.g. binder jetting) led to greater anatomical fidelity thanks to the employment of multiple colours and materials that are able to reproduce the mechanical properties of trabecular mastoid bone with realistic drilling experience. Moreover, the development of printed models coupled with electronic simulators provided a real-time alert in case of injury to vital structures during dissecting practice [28].

Customised surgical planning [29 35-49]

The production of patient-specific 3DP temporal bones based on preoperative CT was considered suitable for surgical planning and simulation in five cases of challenging anatomy (e.g. congenital aural atresia, acquired subverted anatomy) and in one case of cochlear implant surgery [29, 35-38]. Four papers dealt with the creation of 3DP operative templates to assist surgical positioning of a transcutaneous bone-conduction hearing device [39-42.] Finally, six studies were on the combined use of surgical navigation and 3DP technology [43-48]. In particular, a Japanese publication described the development of a registration method based on bone-anchored fiducial markers using 3DP templates without requiring a preoperative invasive marking process or additional CT. Since its first publication, this process has been simplified and further improved.

Tissue engineering and implantable prosthetics [50]

Kozin et al. tested a customised 3DP prosthesis for repair of bony superior canal defects on cadaveric temporal bones, even if clinical uses were not yet reported [50].

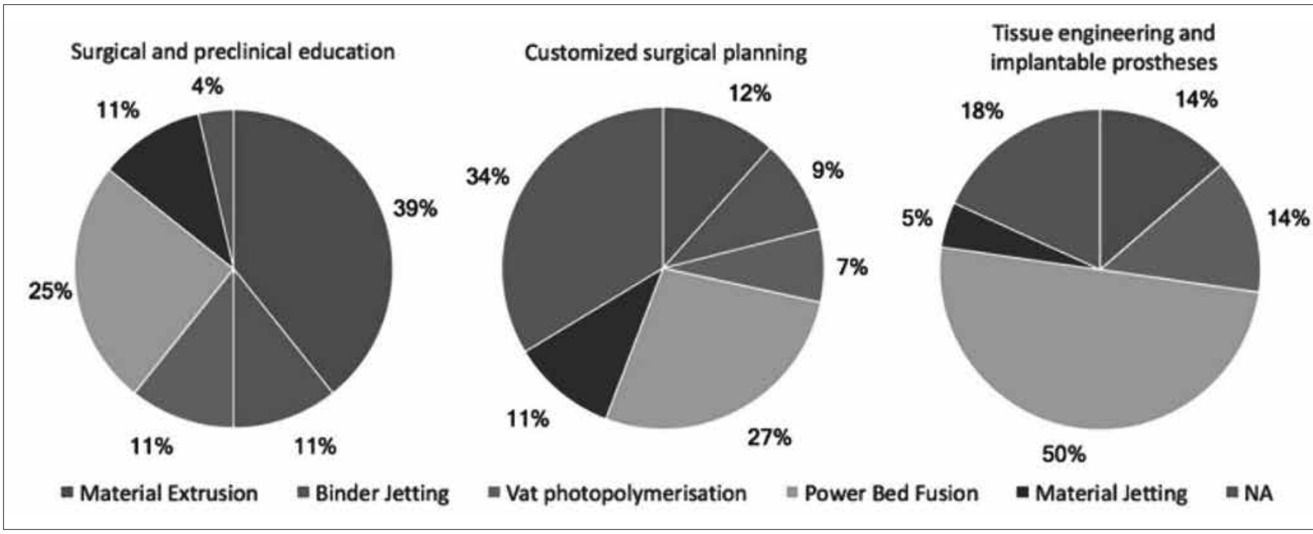

Fig. 4. Employed AM technology considering the area of interest.

Table I. Otologic studies classified according to each area of interest.

SURGICAL AND PRECLINICAL EDUCATION				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Temporal bone dissection training model	Cohen J et al., 2015 [12]	Material extrusion	Dimensions SST 1200es	Abs + resin (support material)
	Da Cruz MJ et al., 2015 [13]	Binder jetting	Spectrum Z510	Chalk-like powder + binder + colors
	Hochman JB et al., 2015 (1) [14]	Binder jetting	ZPrinter 650	Chalk-like powder + binder + colors
	Hochman JB et al., 2015 (2) [15]	Binder jetting	ZPrinter 650	Chalk-like powder + binder + colors
	Longfield EA et al., 2015 [16]	Binder jetting	Spectrum Z510	Chalk-like powder + binder + colors
	Mowry SE et al., 2015 [17]	Material extrusion	MakerBot 2x	ABS + HIPS
	Rose AS et al., 2015 [18]	Vat photopolymerisation	Objet Connex 350	Photo-polymer resins with different mechanical properties
	Hochman JB et al., 2014 [19]	Binder jetting	ZPrinter 650	Chalk-like powder + binder + colors
	Unger BJ et al., 2014 [20]	Binder jetting	ZPrinter 650	Chalk-like powder + binder + colors
	Mick PT et al., 2013 [21]	Binder jetting	ZPrinter 650	Zp®131 powder binder(Zb®7) + colors
	Roosli C et al., 2013 [22]	Binder jetting	Spectrum Z510	Chalk-like powder + binder + colors
	Bakhos D et al., 2010 [23]	Vat photopolymerisation	SLA® 5000	Somos® 14120
	Mori K, 2009 [24]	Powder bed fusion	NA (commercial available prototype)	Polyamide nylon and glass beads
	Mori K et al., 2009 [25]	Powder bed fusion	NA (commercial available prototype)	Polyamide nylon and glass beads
	Mori K et al., 2008 [26]	Powder bed fusion	NA (commercial available prototype)	Polyamide nylon and glass beads
	Suzuki M et al., 2007 [27]	Powder bed fusion	NA	Polyamide nylon and glass beads
	Grunert S et al., 2006 [28]	Binder jetting	Spectrum Z510	Plaster + post-processing with polyurethane and acetone
	Suzuki M et al., 2004 (1) [29]	Powder bed fusion	NA	Polyamide nylon and glass beads
	Suzuki M et al., 2004 (2) [30]	Powder bed fusion	NA	Polyamide nylon and glass beads
	Begall K et al., 1998 [31]	Vat photopolymerisation	Laser Model stereolithographic System by Fockele & Schwarze GmbH	Photosensitive; expoxy resins

continues

Table I. follows

SURGICAL AND PRECLINICAL EDUCATION				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Surgical middle ear training model	Monfared A et al., 2012 [32]	Material jetting	Objet Polyjet printer	Combination of 2 photosensitive resins
Endoscopic ear surgery training model	Barber SR et al., 2016 [33]	Binder jetting	ZPrinter 650	Zp® 151 composite material + binder (ColorBond zbond® 90) + colors
Functioning anatomical middle ear model	Kuru I et al., 2016 [34]	Powder bed fusion	EOS Formiga P100	Polyamide powder PA2200
CUSTOMISED SURGICAL PLANNING				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Temporal bone surgical simulation	Rose AS et al., 2015 [35]	Material jetting	Objet Connex 350	Photo-polymers with different mechanical properties
	Suzuki M et al., 2005 [36]	Powder bed fusion	NA	Polyamide nylon and glass beads
	Suzuki M et al., 2004 (1) [29]	Powder bed fusion	NA	Polyamide nylon and glass beads
	Lopponen H et al., 1997 [37]	Vat photopolymerisation	NA	Acrylic solution
	Andrews JC et al., 1994 [38]	Vat photopolymerisation	3D Systems SLA 250	Liquid plastic
Template-guided surgery	Pai I et al., 2016[39]	Material jetting	Objet Eden 250	Transparent photo-polymer
	Matsumoto N et al., 2015[40]	Vat photopolymerisation	NA	Transparent photo-polymer
	Cho B et al., 2014[41]”	Material jetting	Objet Connex 500	Transparent photo-polymer
	Takumi Y et al., 2014[42]	Vat photopolymerisation	NA	Transparent photo-polymer
Navigation for otoneurosurgery	Yamashita M et al., 2016 [43]	Material jetting	Objet Connex 500	Phantom: TangoPlus FLX930, VeroWhitePlus RGD835 Template: VeroWhitePlus RGD835
	Ritacco LE et al., 2015 [44]	NA	NA	NA
	Oka M et al., 2014 [45]	NA	NA	NA
	Cho B et al., 2013 [46]	Powder bed fusion	NA	NA
	Matsumoto N et al., 2012 [47]	Powder bed fusion	NA	NA
	Matsumoto N et al., 2009 [48]	Powder bed fusion	NA	NA
Lateral skull base approaches	Muelleman TJ et al., 2016 [49]	Material extrusion	uPrint SE Plus	Thermo-plastic material
TISSUE ENGINEERING AND IMPLANTABLE PROSTHESIS				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Prosthesis for superior canal dehiscence	Kozin ED et al., 2015 [50]	Vat photopolymerisation	FormLabs Form 1+	Photo-polymer
		Powder bed fusion	EOS Formiga	Plastic-based material; Aluminium-based material

ABS: Acrylonitrile Butadiene Styrene; PLA: PolyLactic Acid; HIPS: High Impact PolyStyrene; NA: not available.

Rhinologic applications (Table II)

Surgical and preclinical education [51-57]

Four studies focused on the development of 3DP training models for endoscopic sinonasal and skull base surgery [51-54]. Medium-high fidelity simulators allowed developing surgical skills in the main endoscopic procedures, including drilling techniques and skull base exposure. Low-cost models were primary limited by the materials employed to mimic human bone as much as possible.

Customised surgical planning [58–60]

Two studies took advantage of the versatility of 3DP systems to fabricate operative templates tailored on the patient’s anatomy. Daniel et al. produced 3DP cutting guides to design an osteoplastic flap during frontal surgery [59]; Onerci Altunay et al. used 3DP templates to fashion septal prosthesis for large irregular septal perforations [58]. 3DP endoscopic sinus surgery simulation was carried out in two patients with chronic rhinosinusitis to obtain safer and faster procedures [60].

Table II. Rhinologic studies classified according to each area of interest.

SURGICAL AND PRECLINICAL EDUCATION				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Endoscopic sinonasal and skull base training models	Chang DR et al., 2017 [51]	Material extrusion	Airwolf 3D HD2X	ABS + molding with Aquasil Ultra XLV silicone
	Tai BL et al., 2016 [52]	Material extrusion	NA	Thermo-plastic material
	Narayanan V et al., 2015 [53]	Material jetting	Objet Connex 500	Photo-polymers with different mechanical properties
	Chan HHL et al., 2015 [54] – Paranasal sinus phantom	Material extrusion	Vantage - Stratasys	ABS
	Chan HHL et al., 2015 [54] – Skull base phantom	Binder jetting	ZPrinter 310 - ZCorp	ZP-130 plaster powder + CA101 cyanoacrylate; ZP-15 plaster powder + infiltrant elastomeric
	Chan HHL et al., 2015 [54] – Mandible templates	Material extrusion	Vantage - Stratasys	Polycarbonate
Septoplasty training model	AlReefi MA et al., 2017 [55]	Material jetting	Objet Connex 500	VeroWhitePlus, Tango-Plus and their combination to simulate different mechanical properties
Nosebleed training model	Estomba C et al., 2016 [56]	NA	NA	PLA + Polyurethane
Anatomical models	Sander IM et al., 2017 [57]	Material extrusion	LulzBot TAZ 5	PLA
CUSTOMISED SURGICAL PLANNING				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Template-guided surgery	Onerci Altunay Z et al., 2016 [58]	Binder jetting	Spectrum Z510	Z131 powder
	Daniel M et al., 2011 [59]	Binder jetting	ZPrinter 310 plus	NA
Endoscopic sinus surgery simulation	Raos P et al., 2015 [60]	Binder jetting	ZPrint 310	NA
TISSUE ENGINEERING AND IMPLANTABLE PROSTHESIS				
Field of work	**Authors, year**	**AM category**	**3D printer**	**3DP material**
Customised prosthesis	Nahumi N et al., 2015 [61]	NA	NA	PolyEtherEtherKetone

ABS: Acrylonitrile Butadiene Styrene; PLA: PolyLactic Acid; HIPS: High Impact PolyStyrene; NA: not available.

Tissue engineering and implantable prosthetics [61]

One child with a craniofacial fibrous dysplasia was submitted to resection and reconstruction of the fronto-orbital region by means of a custom 3DP polyetheretherketone implant resulting in good aesthetical and safe outcomes.

Head and neck applications (Table III)

Surgical and preclinical education [62–66]:

Two studies focused on resident training for laryngeal surgical procedures. In 2014, Ainsworth et al. created a laryngeal model, including the extra-laryngeal soft tissues, to simulate trans-cervical injection of vocal folds [64]. More recently, Kavanagh et al. developed a 3DP paediatric laryngeal model reproducing several challenging surgical conditions (e.g. subglottic cysts, laryngomalacia, subglottic stenosis and laryngeal clefts) [62].

Customised surgical planning [54 65 67-132]

This was the most frequent ENT application of 3DP technology and mentioned in 68 of the 121 papers (56.2%). Among these, 95.6% of studies (65 out of 68) [54 67-130] concerned surgical management of head and neck tumours requiring mandibular resection and/or reconstruction. The first date to the ’90s and dealt with creation of 3DP mandibles to allow a direct handling of the neoplastic lesion, leading to the early surgical resection simulators. However, the most relevant contribution concerned the reconstructive aspects of oncologic surgery, guiding the employment of plates or autografts. Patient-specific 3DP mandibles were developed to “pre-bent” plates preoperatively. More recently, the introduction of image-guide systems used to plan the harvest and positioning of autografts (e.g. fibula flap, iliac crest bone flap) has led to the production of self-fabricated

Table III. Head and neck studies classified according to each area of interest.

SURGICAL AND PRECLINICAL EDUCATION					
Field of work	**Authors, year**		**AM category**	**3D printer**	**3DP material**
Laryngeal model	Kavanagh KR et al., 2017 [62]		Material extrusion	MakerBot	ABS, PLA, HIPS
	Johnson CM et al., 2016 [63]		Material extrusion	MakerBot 2XL	ABS (best performance), HIPS, PLA; Dragon Skin Fast silicon casting in a 3D printed mold
	Ainsworth TA et al., 2014 [64]		Material extrusion	Dimension Elite - Stratasys	ABSplus + silicone casting
Carotid artery model	Govsa F et al., 2017 [65]		Material extrusion	MakerBot	PLA
Tracheostoma model	Grolman W et al., 1995 [66]		Vat photopolimerisation	NA	Synthetic liquid resin
CUSTOMISED SURGICAL PLANNING					
Field of work	**Authors, year**		**AM category**	**3D printer**	**3DP material**
Guided surgery for oro-mandibular resection and reconstruction	Bosc R et al., 2017 [67]		Material jetting Material extrusion	Objet 30Pro – Stratasys Zortrax M200 - Zortrax SARL	Biocompatible photopolymer ABS
	Rachmiel A et al., 2017 [68]	Skull	Material jetting	Objet260 Dental - Stratasys	Photopolimer resin
		Template	Powder bed fusion	EOS	Titanium
	Shah S et al., 2017 [69]		Binder jetting	ZPrinter 310 plus	Gypsum-based material
	Lee UL et al., 2016 [70]		Powder bed fusion	Arcam A1 (Electron Beam Melting)	Ti-6Al-4 V-ELI medical grade powder
	Lim SH et al., 2016 [71]	Mandible	Binder jetting	ProJet 360 - 3D Systems	NA
		Cutting/ position-ing guides	Material jetting	ProJet 3500 HDMax - 3D Systems	Biocompatible materials
	Numajiri T et al., 2016 [72]		Material extrusion	MakerBot	PLA
	Yamada H et al., 2016 [73]		NA	NA	NA
	Chan HHL et al., 2015 [54]	Paranasal sinus phantom	Material extrusion	Vantage - Stratasys	ABS
		Skull base phantom	Binder jetting	ZPrinter 310 - ZCorp	ZP-130 plaster powder + CA101 cyanoacrylate; ZP-15 plaster powder + infiltrant elastomeric
		Mandible templates	Material extrusion	Vantage - Stratasys	Polycarbonate
	Man QW et al., 2015 [74]		NA	NA	NA
	Modabber A et al., 2015 [75]		Powder bed fusion	NA	Polyamide Powder
	Reiser V et al., 2015 [76]		Material jetting	A Objet – Stratasys machine (Model NA)	Biocompatible plastic polymers
	Schepers RH et al., 2015 [77]		NA	NA	Polyamide (for the cutting guides)
	Shan XF et al., 2015 [78]	Residual skull	Material extrusion	Stratasys FDM 400-mc	NA
		Mesh	NA	NA	Titanium
	Steinbacher DM et al., 2015 [79]		NA		
	Succo G et al., 2015 [80]		NA	NA	NA
	Wilde F et al., 2015 [81]		Powder bed fusion	NA	Polyamide
	Ayoub N et al., 2014 [82]		Powder bed fusion	NA	NA
	Azuma M et al., 2014 [83]		Binder jetting	ZPrinter 310 plus	NA

continues

Table III. follows

CUSTOMISED SURGICAL PLANNING					
Field of work	**Authors, year**		**AM category**	**3D printer**	**3DP material**
	de Farias TP et al., 2014 [84]		Binder jetting	Z-Corp Spectrum Z510	Gypsum, cyanoacrylate, and ZP150
	Liu YF et al., 2014 [85]		Powder bed fusion	Sinterstation HiQ +HiSTM - 3D Systems	DuraForm - biocompatible nylon
	Modabber A et al., 2014 [86]		Powder bed fusion	NA	Polyamide
	Tsai MJ et al., 2014 [87]		NA	NA	NA
	Watson J et al., 2014 [88]		Powder bed fusion	Direct metal Powder bed fusion (Model NA)	Medical-grade titanium alloy Ti6AL4V - 3TRPD
	Wilde F et al., 2014 [89]		Powder bed fusion	NA	Biocompatible Polyamide
	Yamada H et al., 2014 [90]		NA	NA	NA
	Coppen C et al., 2013 [91]		Powder bed fusion	NA	DuraForm PA - 3DWorknet
	Foley BD et al., 2013 [92]		NA	NA	NA
	Hanasono MM et al., 2013 [93]		NA	NA	NA
	Mazzoni S et al., 2013 [94]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	NA	Stratasys machine	Resin
	Zheng GS et al., 2013 [95]		Vat photopolymerisation	SLA-3500 3D Systems	NA
	Ciocca L et al., 2012 (1) [96]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	Material extrusion	Stratasys machine	ABS
	Ciocca L et al., 2012 (2) [97]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	Material extrusion	Stratasys machine	ABS
	Dérand P et al., 2012 [98]		Powder bed fusion	ARCAM EBM A2	Ti6Al64V ELI powder
	Hou JS et al., 2012 [99]		NA	NA	Photopolymer
	Lethaus B et al., 2012 [100]		Material extrusion	Maastricht Instruments	NA
	Modabber A et al., 2012 (1) [101]	Guide	Powder bed fusion	NA	Polyamide
		Skull	NA	NA	Acrylic Resin
	Modabber A et al., 2012 (2) [102]	Guide	Powder bed fusion	NA	Polyamide
		Skull	NA	NA	NA
	Patel A et al., 2012 [103]		NA	NA	NA
	Sink J et al., 2012 [104]		NA	NA	NA
	Wilde F et al., 2012 [105]		Binder jetting	ZTM 510 - 4D Concepts	NA
	Zheng GS et al., 2012 [106]		Vat photopolymerisation	SLA-3500 3D Systems	NA
	Abou-ElFetouh A et al., 2011 [107]		Vat photopolymerisation Binder jetting	3D Systems InVision Si2 3D Systems VisiJet SR 200	NA NA
	Antony AK et al., 2011 [108]		NA	NA	NA
	Bell RB et al., 2011 [109]		NA	NA	Acrylic resin
	Hou JS et al., 2011 [110]		NA	NA	Polybutadiene-styrene resin
	Mehra Pet al., 2011 [111]		Vat photopolymerisation Material extrusion	NA	Acrylic, Epoxy Starch

continues

Table III. follows

CUSTOMISED SURGICAL PLANNING					
Field of work	**Authors, year**		**AM category**	**3D printer**	**3DP material**
	Yamanaka Y et al., 2010 [112]		NA	NA	Acrylic plastic
	Zhou LB et al., 2010 [113]		Vat photopolymerisation	LPS 600 laser prototyping	Resin
	Cohen A et al., 2009 [114]		Material jetting	Eden 500 V	Photo-polymer
	Farina R et al., 2009 [115]		Vat photopolymerisation Binder jetting	3D Systems SLA-250/30 Z-Corporation Z406	8110 resin (DSM Somos) Starch-cellulose material
	Juergens P et al., 2009 [116]		NA	NA	NA
	Leiggener C et al., 2009 [117]		Powder bed fusion	NA	Medical grade polyamide
	Liu XJ et al., 2009 [118]		NA	NA	Resin
	Chow LK et al., 2007 [119]		NA	NA	Starch, epoxy resin, acrylic
	Lee JW et al., 2007 [120]		NA	NA	NA
	Ro EY et al., 2007 [121]		NA	NA	Epoxy
	Toro C et al., 2007 [122]		Vat photopolymerisation	SLA 3500 – 3D Systems	Epoxy resin Watershed 11120
	Yeung RWK et al,. 2007 [123]		NA	NA	NA
	Hallermann W et al., 2006 [124]		Powder bed fusion	NA	Duraform PA12 - 3D Systems
	Hannen EJM et al., 2006 [125]		NA	NA	Resin
	Cunningham LL et al., 2005 [126]		Vat photopolymerisation Binder jetting	3D Systems SLA-250/30 Z-Corporation Z406	8110 resin (DSM Somos) Starch-cellulose material
	Wong TY et al., 2005 [127]		NA	NA	NA
	Singare S et al., 2004 [128]		Vat photopolymerisation	LPS 600	Photo-polymer
	Kernan BT et al., 2000 [129]		NA	NA	NA
	Komori T et al., 1994 [130]		Vat photopolymerisation	Solid Creation System (D-MEC Ltd, Tokyo, Japan),	Desolight SCR- 100, D-MEC Ltd)
Guided surgery for cranio-cervicofacial teratoma	Wiedermann JP et al., 2017 [131]		NA	NA	NA
Carotid artery model	Govsa F et al., 2017 [65]		Material extrusion	MakerBot	PLA
MRI compatible laryngoscope	Paydarfar JA et al., 2016 [132]		Material jetting	Objet Eden250 - Stratasys	MED610 (Stratasys) biocompatible photopolymer
TISSUE ENGINEERING AND IMPLANTABLE PROSTHESIS					
Field of work	**Authors, year**		**AM category**	**3D printer**	**3DP material**
Customised prosthesis for mandibular reconstruction	Rachmiel A et al., 2017 [68]	Skull	Material jetting	Objet260 Dental - Stratasys	Photopolymer resin
		Template	Powder bed fusion	EOS	Titanium
	Lee UL et al., 2016 [70]		Powder bed fusion	Arcam A1 (Electron Beam Melting)	Ti-6Al-4 V-ELI medical grade powder
	Schepers RH et al., 2015 [77]		NA	NA	Polyamide (for the cutting guides)
	Shan XF et al., 2015 [78]	Residual Skull	Material extrusion	Stratasys FDM 400-mc	NA
		Mesh	NA	NA	Titanium
	Watson J et al., 2014 [88]		Powder bed fusion	Direct metal Powder bed fusion (Model NA)	Medical-grade titanium alloy Ti6AL4V - 3TRPD
	Mazzoni S et al., 2013 [94]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	NA	Stratasys machine	Resin

continues

Table III. follows

TISSUE ENGINEERING AND IMPLANTABLE PROSTHESIS					
Field of work	Authors, year		AM category	3D printer	3DP material
	Ciocca L et al., 2012 (1) [96]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	Material Extrusion	Stratasys machine	ABS
	Ciocca L et al., 2012 (2) [97]	Plate	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Titanium Ti64
		Guide	Powder bed fusion	EOSINT M270 - Electro-Optical Systems	EOS Cobalt-Chrome MP1
		Mandible	Material extrusion	Stratasys machine	ABS
	Dérand P et al., 2012 [98]		Powder bed fusion	ARCAM EBM A2	Ti6Al64V ELI powder
	Zhou LB et al., 2010 [113]		Vat photopolymerisation	LPS 600 laser prototyping	Resin
	Singare S et al., 2004 [128]		Vat photopolymerisation	LPS 600	Photopolymer

ABS: Acrylonitrile Butadiene Styrene; PLA: PolyLactic Acid; HIPS: High Impact PolyStyrene; NA: not available.

customised 3DP cutting guides. Many authors experienced a decrease in surgical time and the risk of undesirable events during reconstructive approaches, which resulted in a proper mandibular function. Concerning AM technology, in 38.2% of the studies (26 of 68) the AM category was not specified, mainly due to the outsourcing of all 3D printing operations to external services, which are becoming more common in recent years.

Tissue engineering and implantable prosthetics [68 70 77 78 88 94 96-98 113 128]

This area included 9.1% of all studies (11 of 121). All these investigations dealt with mandibular reconstruction following tumour resection in a total of 33 patients. The authors employed 3DP technology to develop patient-specific reconstruction plates, trays, meshes and mandibular implants. Titanium alloys (e.g. Ti6Al4V) were used in all cases due to their suitable physical and mechanical properties: low specific weight, corrosion resistance and good biocompatibility [96]. 3DP reconstruction plates, tray and meshes were associated with a bone autograft in 9 studies: 66.6% opted for a fibula free flap [77 78 94 96-98] and 33.3% for an iliac crest free flap [68 113 128]. Differently, Lee et al. made use of a mandibular implant without the support of a bone autograft, proving an acceptable alternative in cases of unsuitable free flap surgery [70]. A total of 27 patients (81.9%) showed good aesthetical and occlusion outcomes and thus correct oral rehabilitation [68 70 77 78 88 94 96 97 113 128]. Complications were observed in 2 subjects (6%): one patient experienced bone resorption and infection, while the other had flap necrosis [77 113]. The authors reported a reduction of the operating time between 30 [98] and 120 minutes [94], enabling economic benefits at the expense of the additional cost of the 3DP prosthesis.

Discussion

Personalised medicine, minimally-invasive surgery, tissue engineering and regenerative medicine are the watchwords of third millennium healthcare. The arising popularity around the world of 3DP systems may be explained through the opportunities offered by this new technology to support new trends in modern medicine. Since its first applications in the early 1990s, researchers have explored the advantages of 3D printers, publishing 121 studies in otorhinolaryngology (Fig. 2). Customised surgical planning was evaluated in 71.9% of studies, proving to be the main direction of investigation (Fig. 3). The manufacture of anatomical models before surgery allowed both the understanding of specific anomalies and guidance for the operative strategy. The first and most frequently explored clinical application was resection and reconstruction of oro-mandibular tumours due to their easier medical image processing in comparison with other fields. The development of 3DP operative templates for cutting and/or reconstruction guides minimised the surgeon's fatigue and complication rates, and optimised the operating room time, which led to lower morbidity. Similar approaches have been employed for complex cases of temporal bone and sinonasal surgery.

Clinical benefits were advocated by the authors to justify the main limitations of AM technology: costs, necessity for technical skills and technological availability. Cost-effectiveness was widely debated in literature: the decreased surgical time and employment of self-fabricated 3DP models or guides (instead of outsourced manufacturing) appeared to counter balance the price of the starting technological investments and the technical skills required for pre- and postprocessing printing activity [94]. Interestingly, for 34% of studies on customised surgical planning, a specific description of the technology adopted was not available (Fig. 4): this arises from the choice of externalization of the 3D printing process, as often declared by authors themselves [45 77 80 93 110 121]. To date, the rapid expansion of AM machines and materials has significantly lowered costs, making this technology more accessible. The most employed technology in this field of application was power bed fusion (27%), which offers medical grade materials (like titanium, or biocompatible polyamide) to be used as intra-operative templates, followed by material extrusion (12%), which also offers biocompatible materials, even if with lower printing resolution. Surgical and preclinical education represents the second most studied 3DP application. Surgical training traditionally made use of physical models, animals, or human cadavers. The adoption of both fixed and fresh human specimens in labs has long been and still is a core component in training for ENT surgery, but it has certain limitations such as transmission of infectious agents, exposure to potentially carcinogenic formaldehyde and excessive costs. More recently, 3DP models were used in the teaching of complex anatomy and to simulate critical surgical procedures with particular regard to temporal bone and skull base dissection. The most employed AM technology for this application (Fig. 4) was material extrusion (39%): this is not surprising, since this is the most affordable technology, especially in terms of printing materials. Material extrusion is actually the most suited to apply for teaching and training, where models are usually subjected to damage and need to be produced in high numbers. 25% of studies used power bed fusion machines, thanks to the availability of materials (e.g. polyamide) with mechanical properties that are suitable for drilling and dissection operations. The complexity of temporal bone anatomy and related surgical procedures, essentially based on bone drilling and removal, explain the extensive research on this issue.

The evolution of 3DP systems and materials has enabled the reproduction of even the finest chromatic details and mechanical properties of the object resulting in highly representative 3DP simulators. These solutions are unfortunately still expensive, and consequently less employed for the production of didactic devices, as confirmed by the limited use of technologies with high chromatic resolution (binder jetting, 11%) and with tuneable mechanical properties (material jetting, 11%).

Tissue engineering and implantable prostheses is discussed in fewer reports since it represents the most recent 3DP application, but it also entails more exciting future perspectives. The current literature reported the application of 3DP customised titanium alloy prostheses in 33 cases of mandibular reconstruction after tumour resection. Power bed fusion is confirmed as the most widely employed technology in the field, used in 50% of studies: the most common materials are titanium and cobalt-chrome, which are also widely employed in implant standard manufacturing. Preliminary data have provided encouraging results in terms of safety and effectiveness, opening new frontiers of investigation.

Nowadays, AM technology has been involved in the production of biocompatible matrices aimed to be cellularised (scaffold), hence forming a new functional tissue. ENT scaffold research is at present confined to a preclinical stage (in vitro and animal testing), with relevant applications in the reconstruction of the upper aerodigestive tract [133 134], replacement of tympanic membrane [135] and plastic rebuilding of auricular and nasal cartilages [136 137]. Even though scaffold research is in its infancy, it represents a future direction of high interest. New perspectives will concern the microstructure of 3DP scaffolds to overcome many currently unsolved questions as well as proper vascularisation to avoid cell degeneration and adequate stem cell proliferation/specialisation. The final goal would entail functional aspects to produce functional tissues and organs by involvement of multiple types of cells and biomaterials.

Moreover, in the foreseeable future, technical advancements will possibly provide a better solution to issues involving biocompatibility and sterilisation protocols of 3DP materials.

Conclusions

3DP systems have revolutionised prototyping in the industrial field by lowering production time from days to hours and costs from thousands to only a few dollars. Today, 3D printers are no longer confined to prototyping, but are increasingly employed in the medical discipline with fascinating results, even in many aspects of otorhinolaryngology. Nevertheless, current reports are still limited to small case-series of patients and lack of comparative objective data to validate 3DP technology in daily clinical practice. 3DP bioengineering is at the beginning of an exciting research field, and the positive results to date are far from what it will be possible to achieve in forthcoming clinical applications.

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