



3D-printed spine surgery implants: a systematic review of the efficacy and clinical safety profile of patient-specific and off-the-shelf devices

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Abstract

Purpose Three-dimensional printing (3DP), or additive manufacturing, is an emergent fabrication technology for surgical devices. As a production method, 3DP enables physical realisation of surgical implants from geometrically complex digital-models in computer-aided design. Spine surgery has been an innovative adopter of 3DP technology for both patient-specific (PS) and market-available ‘Off-The-Shelf’ (OTS) implants. The present study assessed clinical evidence for efficacy and safety of both PS and OTS 3DP spinal implants through review of the published literature. The aim was to evaluate the clinical utility of 3DP devices for spinal surgery.

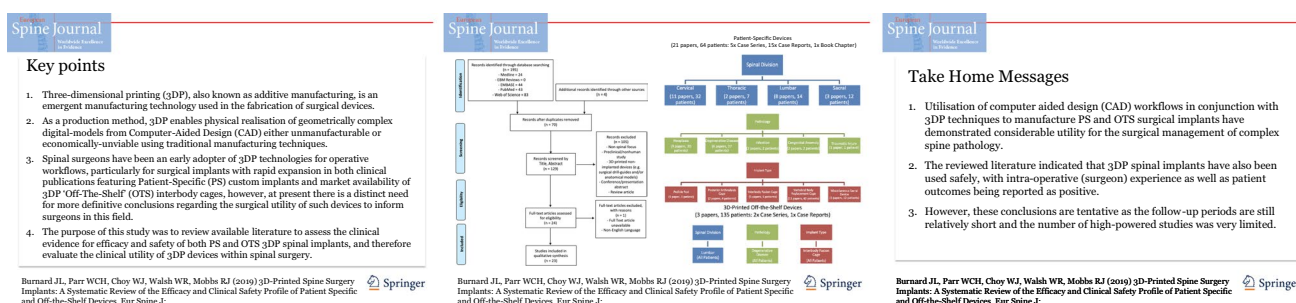
Methods A systematic literature review of peer-reviewed papers featured on online medical databases evidencing the application of 3DP (PS and OTS) surgical spine implants was conducted in accordance with PRISMA guidelines.

Results Twenty-two peer-reviewed articles and one book-chapter were eligible for systematic review. The published literature was limited to case reports and case series, with a predominant focus on PS designs fabricated from titanium alloys for surgical reconstruction in cases where neoplasia, infection, trauma or degenerative processes of the spine have precipitated significant anatomical complexity.

Conclusion PS and 3DP OTS surgical implants have demonstrated considerable utility for the surgical management of complex spine pathology. The reviewed literature indicated that 3DP spinal implants have also been used safely, with positive surgeon- and patient-reported outcomes. However, these conclusions are tentative as the follow-up periods are still relatively short and the number of high-powered studies was limited. Single case and small case series reporting would benefit greatly from more standardised reporting of clinical, radiographic and biomechanical outcomes.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.



Keywords 3D-printing · Additive manufacturing · Spine surgery · Patient specific · Custom made · Implant

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Extended author information available on the last page of the article

Introduction

3DP, also known as additive manufacturing, is a process whereby a three-dimensional (3D) virtual structure, computer-aided design (CAD) file (STereoLithography, or.stl), is sliced to create two-dimensional tool paths for the printer-head. This is then printed layer-by-layer through deposition of a raw material that is polymerised, fused or melted together (via modalities dependant on material/design specifications) to create a 3D-construct [1, 2]. Since the invention of three-dimensional printing (3DP) by Hull [3], advancement of manufacturing methods has expanded the selection of printable raw materials and refined precision/reliability to medical-grade standards. Orthopaedic, maxillofacial and spine surgery have been early adopters of 3DP technology for applications such as anatomical models, surgical instrument guides and implantable devices, both off-the-shelf (OTS) and patient specific (PS) [4–7].

Spine pathology may originate from the spinal cord (myelopathic) or spinal nerve root (radiculopathic). The underlying pathophysiology is more commonly spondylotic (aged-related degeneration). Non-spondylotic disease may occur because of tumour, trauma or infection [8–11]. The objectives of spinal surgery, when indicated, are neural decompression and segment stabilisation preventing further motion-induced neural-compression. Additional goals include excision of diseased intervertebral discs with concomitant nociceptors often accompanied by arthroplasty or arthrodesis of pathological spinal segments to restore vertebral interbody height and alignment [12–14].

Lumbar surgery techniques contemporarily used to accomplish these goals include central/foraminal decompression with/without lumbar interbody fusion (LIF) which involves implanting an intervertebral cage/spacer/structural-graft following discectomy and endplate preparation, chosen surgical approach varies depending on vertebral level, pathology and surgeon preference [12, 13, 15, 16]. In the cervical spine, spondylosis has historically been managed with anterior and posterior approaches; anterior cervical discectomy with fusion (ACDF) and anterior cervical corpectomy with fusion (ACCF) are effective techniques with choice similarly dependant on patient, pathological and surgical factors [12, 17–19].

The design of spinal interbody fusion devices has changed with time to achieve the surgical objectives of restoring foraminal volume, disc-height, sagittal balance and vertebral alignment and additionally maximise secondary post-operative outcomes such as immediate stability, high fusion, reduced subsidence and low complication rates [20, 21]. A progression of this evolution has been the advent of PS spinal implants, whereby the device may be

custom-designed according to the desired surgical objective. Creation of a custom implant typically includes input of anatomical data collated from patient imaging, commonly computed tomography (CT) or magnetic resonance imaging (MRI), into computer-aided design (CAD). CAD workflows enable accurate 3D modelling of a patient's anatomy and, further, incorporation of device design features customised to the anticipated defect dimensions and intraoperative surgical requirements.

The present study systematically reviewed the clinical applications of 3DP implants for spine surgery, examining current trends in implant design and evaluating the efficacy and safety of 3DP spine devices to determine surgical utility of both additively manufactured ‘Off-The-Shelf’ (OTS) and patient-specific (PS), or custom devices.

Methods

The literature searches were conducted up to 31 July 2019 in accordance with PRISMA guidelines and approach tools [22–24] using online databases: Medline, EMBASE, EBM Reviews, PubMed and Web of Science. Search sensitivity and specificity was maximised by combining terms “3D-printing”, “additive-manufacturing”, “spine”, “spinal fusion”, “implant” and/or “prosthetic” as keywords or MeSH-terms with Boolean operators (AND, OR) in respective databases, as shown in Appendix A. Reference lists of retrieved articles were screened to identify additional relevant studies.

Article titles and abstracts were initially screened, followed by full-text articles for selection criteria. Inclusion criteria were the use of 3DP implants (OTS and PS) in spinal surgery (cervical, thoracic, lumbar and sacral) in clinical (human) cases, and additionally, all device materials/designs use and patient demographics were considered. Exclusion criteria for this review included non-spinal focus, non-implantable 3DP devices (for example anatomical models or drill-guides) and preclinical or non-human studies. Studies in non-English languages or inaccessible full-texts were unable to be evaluated.

Results

The systematic search returned 195 results with an additional 3 publications and 1 book chapter identified through reference list screening. Following removal of 70 duplicates, 128 peer-reviewed journal articles (in addition to the book chapter) were screened by title/abstract for inclusion/exclusion criteria. Of the remaining 24 articles selected for full-reading, 23 were deemed eligible for this review: 22 publications and 1 book chapter. This process is summarised in

Appendix B. A summary of the current clinical literature for 3DP implants used in spinal surgery procedures is provided in Table 1.

The available clinical literature dated the first applications of 3DP implants for spine surgery to 2016 [25]; at the time of the present review, there were 23 papers representing a total of 197 patients (2016: 3, 2017: 7, 2018: 7, 2019: 6). There were no high-powered randomised control clinical trials exploring efficacy of any 3DP spine implant, the 22 published articles were limited to case series (7) and case reports (15), with a further case report featured in a book chapter [26]. Titanium alloy (Ti6Al4V) was the material used to manufacture the spinal implants by 3DP (22/23 studies, 191 patients) in all but one study (Amelot et al. [27]), which used PolyEther-Ketone-Ketone, or PEKK, implants for six patients. PS implant designs were used in 21 of 23 reviewed articles (5 case series, 14 case reports; 64 patients), whereas two case series [28, 29] and a case report [30], respectively, were published on a generic (OTS) devices (135 patients), the Medussa-PL [29], K2M Lamellar Titanium Cage [28] and EIT Cellular Titanium interbody cage [30]. Thayaparan et al. [30] implanted both PS and OTS 3DP devices. One retrospective study, Wei et al. [31], evaluated the comparative post-operative outcomes of a PS reconstructive implant against conventionally manufactured (non-3DP) alternatives.

PS implants were implemented in all spine divisions: sacral (3 papers, 12 patients) [31–33], lumbar (8 papers, 14 patients) [26, 30, 34–39], thoracic (2 papers, 7 patients) [35, 40] and cervical (11 papers, 32 patients) [25–27, 34, 41–47]. The indications for implantation with PS devices were found to be neoplasia (9 papers, 30 patients) [25, 31–36, 40, 43, 46], degenerative disease (6 papers, 27 patients) [27, 30, 41, 42, 44, 45], infection (2 papers, 2 patients) [39, 47], congenital anomaly (2 papers, 2 patients) [34, 38] and one case of traumatic injury [37], and indication was unknown for a further two patients [26]. The application of custom-designed implants was categorised into pedicle fixation rod (1 patient) [30], posterior arthrodesis cage (2 papers, 4 patients) [41, 45], interbody fusion cage (5 papers, 5 patients) [34, 37–39, 42], vertebral body replacement device (11 papers, 42 patients) [25–27, 34–36, 40, 43, 44, 46, 47] and miscellaneous sacral reconstructive device (3 papers, 12 patients) [31–33]. Utilisation of OTS devices manufactured using 3DP was limited to interbody fusion cages for degenerative pathology in the lumbar (3 papers, 134 patients) [28–30].

Review of the literature found variable reporting of clinical outcome measures, when reported the following scoring methodologies were used; Visual Analogue Scale, Neck/Oswestry Disability Index, Japanese Orthopaedic Association, SF-36, EuroQOL-5D and European Myelopathy Score. All papers reporting clinical outcomes demonstrated significant mean post-operative score improvements compared to the preoperative baseline (11 papers, 162 patients) [25,

27–30, 32, 34, 43–46]. The biomechanical and radiographic outcomes implants reported in the literature were restoration of sagittal lordotic alignment (5 papers, 36 patients) [27, 35, 37, 43, 44] and intervertebral height (4 papers, 23 patients) [27, 37, 42, 44], minimal subsidence (8 papers, 161 patients) [25, 27–29, 34, 35, 44, 46] or device migration (13 papers, 169 patients) [25, 28–30, 34, 35, 38–40, 43, 44, 46, 47], bone on-growth (4 papers, 12 patients) [25, 31, 33, 40] and bony fusion (9 papers, 158 patients) [27–29, 32, 34, 37–39, 44]. There were two reported incidences of titanium hardware failure [31, 33] and nine cases of clinically severe device subsidence (> 3 mm) [27, 28, 35]; this was asymptomatic in 8/9 patients; however, one case required surgical revision. Interbody fusion cages were retrieved in one case, and specimens were histologically analysed by Girolami et al. [35], with reported bone ingrowth into the device lattice (osseointegration), with no evidence of inflammatory response cells or adverse host tissue response. One patient [39] exhibited clinically asymptomatic eosinophilia for 19 days immediately post-operative due to a suspected allergic hypersensitivity response to titanium powder particles.

Discussion

Device material

A trend of the reviewed literature was the predominant use of Ti6Al4V (22/23 studies). This is likely due to its load-carrying capacity, cellular-adhesion, low-density (for a metal), surface TiO₂ formation resulting in corrosion resistance attributed to Ti6Al4V alloy [20, 48]. Noted shortcomings of titanium alloys are high radio-opacity, risk of metal allergy and relative modulus mismatch (110 GPa) compared to spinal bone. There were no confirmed adverse reactions attributed to in situ 3DP titanium implants, which was as expected with the biocompatibility of additively manufactured titanium alloy (Ti6Al4V) devices well established [49–53]. Similarly, histological examination of retrieved interbody cages failed to elucidate characteristics indicative of cytotoxicity or non-cytocompatibility [35]. However, Chung et al. [39] reported post-operative eosinophilia uncomplicated by further clinical symptomology, which was postulated to be an allergic-type hypersensitivity response to titanium powder particles [54]. Hence, post-print processing to ensure removal of powder particles may be important for manufacturers of 3DP implants to consider, as suggested by the Food and Drug Administration (FDA) [55].

The radio-opacity of titanium alloy made post-operative assessment of fusion progress challenging, occasionally resulting in serial CT imaging of the patient throughout follow-up [56–58]. The only study (1/22) in which the 3DP implants were manufactured in a material alternative to

Table 1 Summary of the clinical literature on 3DP spinal implants

Article	Indication	Implant design (PSI/OTS)	Material, manufacturing method	Clinical and radiological outcomes
Phan et al. [41] (case report)	C1/C2 arthrodesis	Implant-overlaid C2 spinous process/lamina, pre-calculated screw holes (PSI)	Titanium, unknown	Satisfactory radiographic outcomes at 1, 3 (X-ray) and 6 (CT) month FU. Significant pain reduction by 7-month FU
Spetzger et al. [42] (case report)	C6/C7 ACDF	EIT Cellular Titanium Cervical Cage shaped to match patient end-plate. 3 implant-heights made (PSI)	Titanium alloy (Ti6Al4V), SLM	Immediate press-fit with 'self-location' during implantation, excellent primary stability
Xu et al. [25] (case report)	C2 Spondylectomy for Ewing Sarcoma	C2 SSAVB with customised proximal wings (PSI)	Titanium Alloy, EBM	12-month FU; Improved neurological (JOA 16/17) with evidence of implant osseointegration, no implant subsidence/displacement
Choy et al. [40] (case report)	T9 VBR for primary bone tumour	T9 vertebral body implant with inbuilt pedicle screw fixation holes, multiple cage heights (PSI)	Titanium, unknown	Early mobilisation and return to normal daily living, 6-month FU scans indicate implant integration with endplates, no displacement
Chung et al. [29] (case series)	1–2 level L3-S1 PLIF; 40 patients (53 segments) for spondylotic disease	Medussa-PL Implant (2 per segment) (OTS)	Titanium alloy (Ti6Al4V), EBM	Significant improvements at 12-month FU in VAS (lower back and extremities), Oswestry Disability Index and SF-36 scores. X-Ray at 3/6-months and 12-month CT indicate maintained increased anterior/posterior interbody height, small segmental motion at 6/12-month FU (none > 5 degrees), minimal subsidence, segmental bone fusion bilaterally (94.3%) and unilaterally (5.7%), no pseudarthrosis, epi-cage translucency or device migration
Kim et al. [32] (case report)	Sacral osteosarcoma requiring hemi-sacral reconstruction	Hemisacrum with high-density at contact surfaces, inbuilt fixation screw holes (PSI)	Titanium alloy (Ti6Al4V), EBM	PSI eliminated dead-space with no plastic reconstruction required. S1-root neuropathy with VAS 3 at 12-month FU. 12-month X-ray/CT confirm bone ingrowth/fusion with right hemisacrum
Li et al. [43] (case report)	Metastatic papillary thyroid carcinoma requiring C2–C4 spondylectomy	C2–C4 SSAVB, 32 implant variations printed (PSI)	Titanium Alloy (Ti6Al4V), EBM	12-month FU; JOA 16/17 with independent functioning, X-ray/CT indicate good implant position and vertebral sequencing

Table 1 (continued)

Article	Indication	Implant design (PSI/OTS)	Material, manufacturing method	Clinical and radiological outcomes
Lu et al. [44] (case series)	Single level ACCF for spondylotic myelopathy; 4 × C4, 9 × C5, 2 × C6	Anatomic-Adaptive Titanium Mesh Cage, 8 size variants printed (PSI)	Titanium alloy (Ti6Al4V), SLM	Mean final FU 13.2 ± 1.4-months; VAS decreased to mean 1.67 ± 1.18, JOA increased to mean 14.9 ± 1.39. Radiography indicates solid fusion in all patient by 6-months, final FU all patient implant in optimal position with no significant subsidence (> 3 mm)
Mobbs et al. [34] (case report)	Case 1: Vertebral reconstruction following C1–C2 chordoma Case 2: L4/L5 ALIF with congenital anomaly	Case 1: Inbuilt fixation screw trajectories (PSI) Case 2: Design Criteria—maximal strength with large graft volume, minimal support material, maximum sparseness (post-operative imaging) (PSI)	Titanium, EBM	Case 1: 9-month FU radiograph probable fusion with no implant movement in flexion/extension Case 2: 12-month FU VAS scores 0 (axial back, right/left leg), Oswestry Disability Index 0%. 10-month FU radiograph indicates solid fusion with no subsidence or fixation failure.
Wei et al. [33] (case report)	Sacral chordoma en bloc resection	Porous bone contacting surfaces (inferior L5 endplate and bilateral iliac plates). Pre-planned screw holes. 3 size variants printed (PSI)	Titanium alloy, EBM	Uneventful wound-healing with no perioperative complications, asymptomatic by 8-month FU. Evidence of implant loosening and screw fracture in 3/8-month FU, new bone-formation at implant-ileum interface on CT
Amelot et al. [27] (case series)	VBR ACCF for spondylotic myelopathy; 3 × C4, 3 × C4–C6	Coverage of vertebral endplate delimited by uncus, embedded Tantalum markers for imaging. 2-sizes per patient. (PSI)	PEKK, unknown	Mean improvement in JOA, EMS, NDI and VAS (neck/arm) at last FU (mean 21-months). At final FU mean C2–C7 Cobb Angle Constant 11 degrees (without hyper-lordosis or kyphotic sliding). Corpectomy Cobb Angle 6.1 degrees, beck index approximately 1. All patients developed bone fusion. Restoration/main-tenance of vertebral height with no sever subsidence (> 3 mm)
Girolami et al. [35] (case series)	Anterior column reconstruction after spinal tumour en bloc resection; 13 patients: 7 × Lumbar, 6 × Thoracic	Attachment to posterior pedicle screw rod via adjustable connector (PSI)	Titanium alloy (Ti6Al4V), EBM	Correction of segmental kyphosis 97% corrected at 14-month FU. Mean subsidence 2.8 ± 1.8 mm proximal, 4.3 ± 5.7 mm distal, clinically irrelevant in 11/12 cases, 1 case requiring revision. No implant failure/migration

Table 1 (continued)

Article	Indication	Implant design (PSI/OTS)	Material, manufacturing method	Clinical and radiological outcomes
Mobbs et al. [36] (case report)	L5 vertebral reconstruction in metastatic renal-cell carcinoma. [Intraoperative trial]	Screw holes with pre-planned trajectories. (PSI)	Titanium Alloy (Ti6Al4V), Unknown	Immediate press-fit, intraoperative time < 90-s compared to 46-min for OTS
Siu et al. [37] (case report)	Previous traumatic L2/L3 osteoporotic fracture requiring L2–L3 and L3–L4 LLIF	Two implant heights printed for each level, overall lordosis 10 degrees. Biconvex contouring to match end-plates, large graft window. (PSI)	Titanium alloy (Ti6Al4V), EBM	Recovery uneventful, no neurological sequelae. Post-operative CT indicates restoration of lost disc space and segmental lordosis with improved coronal deformity, excellent match between cage and depressed endplates. Bone fusion evidenced at 6-month FU
Thayaparan et al. [45] (case series)	Posterior atlantoaxial arthrodysis for unilateral osteoarthritis; 3 patients	Posterior atlantoaxial fixation implant with C1/C2 trans-articular and posterior C1 arch screws. (PSI)	Titanium alloy (Ti6Al4V), EBM	6-month FU VAS score (0, 0, 2) with no intraoperative complications, < 50 ml blood loss and no neurological deterioration at 6-months. Radiography at 1/2/6-months satisfactory, no implant failure at 12-months
Thayaparan et al. [30] (case report)	L5-S1 TLIF revision of L2-S1 fixation in degenerative scoliosis	EIT Cellular Titanium lumbar interbody cage (OTS) with PS fixation-rods (PSI)	Titanium alloy (Ti6Al4V), EBM	6-month FU: VAS 5 with symptom resolution, and no radiographic evidence of implant dysfunction
Mobbs et al. [38] (case report)	L5/S1 ALIF for segmental congenital anomaly causing spondylotic disease	Pre-angled screw holes and corrective implant angulation to restore lumbar lordosis. 3 height-variants printed. (PSI)	Titanium alloy (Ti6Al4V), DMLS	Easy prosthetic insertion with firm press-fit, no intraoperative/post-operative complications, 3-month FU; relief of radiculopathy pain maintained and radiographic indication of good implant position and early osseointegration.
Chung et al. [39] (case report)	L1-L4 PLIF for revision surgery due to recurrent infectious spondylitis	PLIF cage (2 segments) with inbuilt arms for pedicle screw fixation. (PSI)	Titanium alloy (Ti6Al4V), EBM	Paraplegic, therefore no specific neurologic changes immediately post-operative, wheelchair ambulation and tolerable pain at 2-week FU. FU over 3-years yield no further infection, mechanical complication or novel neurological symptoms. CT/XR show stable bony fusion with no evidence of implant failure/migration.

Table 1 (continued)

Article	Indication	Implant design (PSI/OTS)	Material, manufacturing method	Clinical and radiological outcomes
He et al. [46] (case report)	C2–C7 VBR for primary cervical chondrosarcoma	Porous titanium cervical vertebrectomy cage (PSI)	Titanium alloy, unknown	No significant perioperative complications, VAS score reduced from 8–9 to 0–1. JOA score upgraded to 13 (60% improvement), muscle strength grade 4 (nil hand/forearm weakness) at 6-month FU. Patient ambulatory at 3 weeks post-operative. 12-month FU radiography/CT indicate good implant position, no signs of subsidence/failure. Patient back to work at 14 months
Zhang et al. [47] (case report)	C5–C6 VBR for cervical tuberculolysis	Porous titanium cervical vertebrectomy cage with integrated anterior plate with screw holes (PSI)	Titanium alloy, unknown	Upper/lower limb numbness resolved and preoperative neck pain/stiffness alleviated. 2-year FU: tuberculolysis cured and radiography showing appropriate hardware placement, no screw loosening
Mokawem et al. [28] (case series)	Single/multilevel LLIF/TLIF; 93 patients (150 segments) for degenerative lumbar disease or deformity	K2M Lamellar Titanium Cage (LLIF/TLIF) packed with silicate-substituted calcium phosphate graft (OTS)	Titanium alloy, unknown	Significant mean reduction in VAS for TLIF (–5.5 back, –6.7 leg) and PLIF (–5.9 back, –6.9 leg) cohort and ODI (–43% TLIF, –41.2% LLIF) at 1-year FU. Bony fusion in 92/93 patients, complications in 9/93 patients (no direct relation to interbody cage/graft)
Wei et al. [31] (case series)	En bloc tumour resection requiring total sacral reconstruction: Retrospective comparative study of 3DP device (10 patients) and conventional pedicle SPF ± ASCF (22 patients)	Porous titanium sacral endo-prosthesis, manufactured in 3 × sizes with preset screw holes (PSI)	Titanium alloy, unknown	Pelvic stability (pain/motor scores) of 3DP-group significantly less than SPF and similar to combined SPF/ASCF cohort. Radiological evidence of bone on-growth and osseointegration. Hardware failure (1/10) was comparable to combined reconstruction (1/14) but significantly less than SPF (5/8)
Tang et al. [26] (case report) [book chapter]	Case 1: C2–C4 ACCF Case 2: Lumbar-Sacral Fusion with VBR	Porous titanium implants; cervical and sacral vertebral fusion cage (PSI)	Titanium Alloy (Ti6Al4V), EBM	Normal cage function and patient remaining in good condition through final FU for both cases

PSI patient-specific implant, *FU* follow-up, *SLM* selective laser melting, *SSAVB* self-stabilising artificial vertebral body, *JOA* Japanese Orthopaedic Association score, *VBR* vertebral body replacement, *VAS* Visual Analogue Scale, *PEKK* PolyEther-Ketone, *EMS* European Myelopathy Score, *NDI* Neck Dysfunction Index, *DMLS* Direct Metal Laser Sintering, *SPF* Spinal Pelvic Fixation, *ASCF* Anterior Spinal Column Fixation

titanium alloy featured devices 3DP in PolyEther-Ketone-Ketone (PEKK) is a polymer closely related to PolyEther-Ether-Ketone (PEEK) [33]. Amelot et al. [27] implanted cervical vertebral body replacement cages manufactured from radiolucent PEKK, and this enabled post-operative imaging without artefact obscuring the fusion bone within the cage.

Class of device: ‘off-the-shelf’ (OTS) versus patient-specific (PS) custom-made implants

Of 23 papers, 21 reviewed feature patient-specific (PS) custom-made implants, 3/23 papers featured OTS implants with 1/22 paper featuring both OTS and PS implants [35]. The overrepresentation of papers reporting on the use of PS devices was unexpected. Regulatory approval and marketing of a medical implant can frequently be achieved without a clinical trial, for example through a predicate pathway (for example a 510 k in the US). The majority of OTS 3DP interbody spinal device manufacturers have received FDA 510 k clearance for the production of OTS 3DP implants. The result of this is, despite the numerous 3DP OTS interbody fusion cages approved for market release, there are a lack of case series and high-powered clinical trials to support their comparative efficacy over traditionally manufactured alternatives. Only one randomised control clinical trial focussed on 3DP spinal interbody devices is currently registered on the World Health Organization International Clinical Trials Registry [59], with results not expected until 2022.

Pathology treated

The use of PS implants has thus far been limited to anatomically challenging cases where neoplasia, degenerative disease, infection, trauma or congenital anomaly have caused significant structural deformity and therefore an anatomy-specific prosthesis has been deemed necessary by the clinician to improve prognosis. Significant anatomical and surgical complexity in the cervical spine may explain why the majority of PS devices have been implemented for this division, the unique osteology of the atlantoaxial joint (C1–C2) and neurovascular complexities at the cranio-cervical junction can determine that generic OTS cervical cages indicated for vertebrectomy caudal to C2 are inadequate for atlantoaxial surgery [17, 34, 41, 45].

Reported outcomes

A commonality of reviewed articles was the lack of standardised framework for reporting clinical scores and radiographic outcomes, although some papers [27–29, 35, 44] used quantitative measures to analyse outcomes using endpoints clearly defined in the methodology elsewhere extractable data were typically qualitative or anecdotal in nature.

For this reason, in conjunction with the inherent heterogeneity of pathologies and implant designs across the PS cohort, a statistically significant meta-analysis of patient clinical and/or radiographic was not viable. To date, there are no OTS studies and only one PS study [31] comparing the post-operative clinical and/or radiographic endpoint of a 3DP device to conventionally manufactured alternatives. Similarly, no clinical studies compare different 3DP biomaterials and only one had follow-up period greater than 2-years (3-years in Chung et al. [39]). Furthermore, small sample sizes and reliance on largely qualitative/anecdotal evidence represent potential reporting bias. Thus, the sparsity of the literature and unavailability of long-term studies complicates extrapolation of results regarding efficacy and safety of 3DP spinal implants. Further, long-term high-power evaluation is required to adequately assess the efficacy/safety of 3DP OTS and PS implants against the current alternatives. Having said this, here we have attempted to collate and assess patterns that were reported.

Fusion

Achievement of bony fusion correlates with clinical outcomes of interbody fusion. Stable arthrodesis of titanium implants as adjudicated by the presence of a solid fusion mass with trabecular continuity bridging adjacent endplates through the graft volume was noted by seven PS papers [29, 32, 34, 37–39, 44]. The present review application of radiolucent polymer biomaterials was limited to one PS study [27], and the remainder of PS implants and all current 3DP OTS interbody fusion cages evidenced in the literature were manufactured in Ti6Al4V. Due to the radio-opacity (x-ray) and imaging artefact (CT and MRI), it may be difficult to assess fusion bone from imaging when Ti6Al4V is used as the material for device manufacture.

Xu et al. [25] reported bony fusion achieved with no evidence of implant displacement at 1-year without utilising bone grafting. The authors suggested that enhancement of 3DP biomaterials and inclusion of lattices for bone ingrowth could facilitate stable arthrodesis such that the need for bone grafting is obviated, although this proposition is not widely accepted in the literature.

Subsidence and anatomy conforming devices

Preservation of cortical end-plate bone structural integrity has been suggested to lower subsidence risk [38, 60]. Geometrical conformity of the implant to the contours of adjacent endplates was repeatedly identified as a design characteristic of PS devices, with the suggestion that this design feature increases the cage footprint surface area, which should reduce cage subsidence, and maintains endplate integrity by reducing requirements for endplate milling/

burring. Finite element analyses performed by Mobbs et al. [38] and Zhang et al. [47] comparing the mechanical performance of respective PS designs to generic OTS designs indicate geometrical conformity of the bone–implant interface minimises point-loading and resulting stress risers through more even load distribution. The reduction in stress risers may reduce the risk of subsidence or hardware failure [61–63], which may contextualise the discrepancy between the rate of significant subsidence (> 3 mm) of PS vertebrectomy implants, approximately 15% (8/54 patients), and the subsidence rates of OTS vertebrectomy cages reported elsewhere (19–52%) [64–66]. Of the eight patients for which significant subsidence was documented [27, 35], one case required surgical revision to restore anterior column stability [35]. None of these cases progressed to hardware failure or bone fracture.

Common design features

Anatomy-adaptive topography

A significant component of the efficacy of PS implants was attributed to the customisation of the interbody cage surface topography to mimic the morphology of adjacent vertebral endplates, as it was found to contribute immediate primary stability with instantaneous device ‘press-fit’ and self-location to correct position [27, 32–37, 42]. The intraoperative trial comparing the surgical insertion of PS 3DP cage and OTS device [36] demonstrated significant reduction in operative time for the PS implant (< 90 -s) as the generic (46-min) required multiple iterations of endplate preparation and attempts at insertion of the OTS implant.

Device customisation according to the unique anatomical and/or surgical case demands enhanced patient-reported post-operative outcomes, for example Xu et al. [25] developed a C2 vertebral body with zero anterior profile to minimise compression of adjacent sensitive laryngeal structures responsible for vocalisation/swallowing and thus mitigate potential post-operative dysphagia/dysphonia. However, implant designs failing to accommodate anatomical obstructions during insertion or variable intraoperative defect dimensions yielded problematic implantation. Chung et al. [39] failed to achieve midline union of the two-piece interbody cage due to impediment of insertion by approach-anatomy (e.g. spinous process) and intraoperative discrepancy to the anticipated defect geometry and relative positioning of the posterior rods. Therefore, multiple implant height/sizes can be required to accommodate for variable resection defect and dimensions of the surgical insertion-window mandate consideration during design-rendering, attributing further layers of complexity to the preoperative design/planning workflows [43].

Constraints of large-scale production-processes inherent to traditional OTS surgical devices are prohibitive to the manufacturing of one-off customised implants in a cost-effective manner, championing the use of 3DP in this domain [34, 44]. However, despite cost-offsets provided by perpetual advancement of 3DP technology and augmented intraoperative ergonomics (reduced operative time and consumption of medical equipment), several authors cited an unavoidable commitment to burdensome preoperative workflows and requirement for specialised design/manufacturing equipment and personnel [35, 38]. The consensus being current commercial comparative advantage over generic devices is yet to be achieved for cases of typical anatomy/pathology [38].

Micro-architecture: porosity and pore-size

Numerous OTS and PS devices incorporated a lattice architecture with the aims of enhancing: device performance with respect to device stiffness; osseointegration through bone on-growth (direct opposition of bone–implant interfaces) and ingrowth (interlocking bone formation within a three-dimensional lattice); and post-operative imaging parameters [25, 28, 29, 31–33, 35, 37, 38, 41–44, 46]. The thematic rationale was that structural mimicry of trabecular bone would function as a scaffold, facilitating osseointegration through the interconnected porous domains of the implant. Ingrowth of bone into lattice designs was reported in four cases [25, 31, 32, 38], and cautioned interpretation is advised as the radio-opacity of titanium constructs and resultant imaging artefact on CT and MRI was a noted challenge for post-operative clinical assessment of bone ingrowth and fusion status elsewhere [43]. For this reason, true determination of osseointegration could only be achieved where the interbody cage was retrieved and subsequently examined histologically [35]. These findings indicated new bone formation through the lattice with direct apposition (uninterrupted by a fibrous tissue interface) to the titanium scaffold. However, without provision of the histological slide, the current authors were unable to determine whether this was homogenous throughout the lattice or if heterogeneously distributed with regions of soft/fibrous tissue interspersed.

Three papers [25, 35, 43] additionally utilised porosity manipulation to adjust the devices mechanical properties, namely elasticity and density. Additive manufacturing has substantial potential utility for OTS interbody cage manufacturers as 3DP facilitates complex internal lattice geometries, unmanufacturable by conventional methods, with predefined reticulated (regular) scaffold architectures that have replicable homogenous microstructural and therefore mechanical properties [49, 67, 68]. Numerous authors discussed augmentation of implant performance with respect to compromises associated with porosity (elasticity and bone ingrowth

vs. compressive strength) and pore-size (vascular permeability vs. bone ingrowth). The thematic rationale across these papers was that reduction in cage modulus through manipulation of device porosity and/or pore-morphology/size would permit greater micro-movements within the lattice that are more conducive to bone growth [49]. Porosity and pore-diameters of clinically implanted devices were reported by: Chung et al. [29] (87.5%, 535 µm); Wei et al. [33] (50–80%, 800 µm); Tang et al. [26] (80%, 450 µm); Spetzger et al. [42] (80%, 650 µm). These reported porosities were comparable to specifications defined by preclinical modelling to optimise the trade-offs in device performance (40–85%, ~300–600 µm) [49, 67, 69]. However, as noted by Walsh et al. [70], the causation of bone in-growth is multifactorial and is significantly influenced by biological implantation site and technical skill of the surgeon, indicating that optimisation of micro-architecture is not a guarantee of bone ingrowth and that further publications featuring histological examination of 3DP cages implanted in patients are necessary for further conclusions regarding the clinical bone ingrowth potential in a 3DP lattice. Mobbs et al. [38] and Lu et al. [44] designed devices without porous domains, stating that the native irregularity of 3DP titanium's surface topography at micro/submicro-scales provided sufficient increased surface area at the bone–implant interface to facilitate cell and tissue attachment. Two studies indicated a limitation of radiographic assessment was impediment by titanium imaging artefact [37, 43], and implant porosity has been suggested as a means to reduce internal titanium content and thus net radio-density of the device [71].

Preoperative planning

CAD planning can be thematically categorised into: (i) interactive visualisation and real-time manipulation of device designs to identify necessary design modifications (for example, plan/alter screw trajectories); (ii) anatomy modelling to plan potential operative approaches, navigate complex neurovascular anatomy and identify appropriate pathology resection margins; and (iii) facilitating training/rehearsal of critical/challenging procedural events, such as implant-insertion, to streamline surgical workflows. Inclusion of inbuilt pedicle or integral fixation screw holes with planned trajectories was suggested to reduce the risks of neurovascular compromise and operative time due to procedural simplification [41, 45] and was found in 11/22 papers [31–36, 38, 40, 41, 45, 47]. Pre-surgical planning on the basis of CAD virtual models and 3DP prototypes in conjunction with utilisation of PS implants was found to improve intraoperative ergonomics by shifting time-consuming intraoperative planning/decision-making tasks to the preoperative phase, resulting in reduced intraoperative time, blood loss, fluoroscopy time (and thus patient radiation exposure)

and consumption of sterilised medical equipment [30, 32, 38, 45]. Additional to cost-offsets, reduced operative time may also mitigate perioperative risks such as surgical-site infection [33, 38, 40].

Conclusion

When accurate fit of the reconstructive defect is unavailable and the associated implant-failure risk increases, use of PS spinal implants may be indicated to optimise clinical prognosis. Many studies reviewed here stated that by enabling the manufacture of PS customised devices, 3DP has good potential in reconstructive spinal surgery. Tumours, trauma or infection can potentiate significant anatomical abnormality, which may mean that a generic OTS spinal implant will not fit well, extending surgery times and trauma caused to the patient as the surrounding tissues are removed to accommodate the implant. In such cases, the literature noted that PS, or custom, devices may hold particular benefits. From the literature reviewed, the use of PS approach can also hold particular significance in cervical surgery where the intricacy, inter-patient variability and variable course of sensitive neurovascular structures such as the vertebral arteries compound operative difficulty.

However, despite the provisional evidence, shortcomings in the availability/quality of the literature complicate judgements on efficacy and safety of 3DP spinal implants. The variation in clinical, radiographic and biomechanical reporting is particularly apparent in the case studies of PS (custom) implants. Further high-powered studies (case series, trials) with more complete and/or standardised outcome reporting are required for more conclusive evaluations. Although there were no reported surgical complications, caution should be taken with consideration to the small available sample-size. There is a distinct need for further publication of case series in which the outcomes (clinical and radiological) for patients receiving generic, or 'off-the-shelf' 3DP spinal devices are reported.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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