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A Systematic Review on 3D-Printed Imaging and Dosimetry Phantoms in Radiation Therapy

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Abstract

Introduction: Additive manufacturing or 3-dimensional printing has become a widespread technology with many applications in medicine. We have conducted a systematic review of its application in radiation oncology with a particular emphasis on the creation of phantoms for image quality assessment and radiation dosimetry. Traditionally used phantoms for quality assurance in radiotherapy are often constraint by simplified geometry and homogenous nature to perform imaging analysis or pretreatment dosimetric verification. Such phantoms are limited due to their ability in only representing the average human body, not only in proportion and radiation properties but also do not accommodate pathological features. These limiting factors restrict the patient-specific quality assurance process to verify image-guided positioning accuracy and/or dose accuracy in "water-like" condition. **Methods and Results:** English speaking manuscripts published since 2008 were searched in 5 databases (Google Scholar, Scopus, PubMed, IEEE Xplore, and Web of Science). A significant increase in publications over the 10 years was observed with imaging and dosimetry phantoms about the same total number (52 vs 50). Key features of additive manufacturing are the customization with creation of realistic pathology as well as the ability to vary density and as such contrast. Commonly used printing materials, such as polylactic acid, acrylonitrile butadiene styrene, high-impact polystyrene and many more, are utilized to achieve a wide range of achievable X-ray attenuation values from −1000 HU to 500 HU and higher. Not surprisingly, multimaterial printing using the polymer jetting technology is emerging as an important printing process with its ability to create heterogeneous phantoms for dosimetry in radiotherapy. **Conclusion:** Given the flexibility and increasing availability and low cost of additive manufacturing, it can be expected that its applications for radiation medicine will continue to increase.

Keywords

additive manufacturing, radiation, imaging, dosimetry, radiopacity, heterogeneity

Abbreviations

3DP, 3-dimensional printing (powder bed fusion); AM, additive manufacturing; ABS, acrylonitrile butadiene styrene; AM-CIP, additive manufacturing of patient-specific contrast imaging phantoms; AM-RDP, additive manufacturing of patient-specific radiation dosimetry phantoms; AM-RPs, AM-radiotherapy phantoms; CT, computed tomography; DMD, digital micromirror device; FDM, Fused Deposition Modelling; HIPS, high-impact polystyrene; HU, Hounsfield units; MMAM, multiple material additive manufacturing; MRI, magnetic resonance imaging; PBP, pixel-by-pixel; PET, positron emission tomography; PJT, polymer jetting; PLA, polylactic acid; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QA, quality assurance; RP, radiotherapy phantoms; SLA, stereolithography; SPECT, single-photon emission computed tomography.

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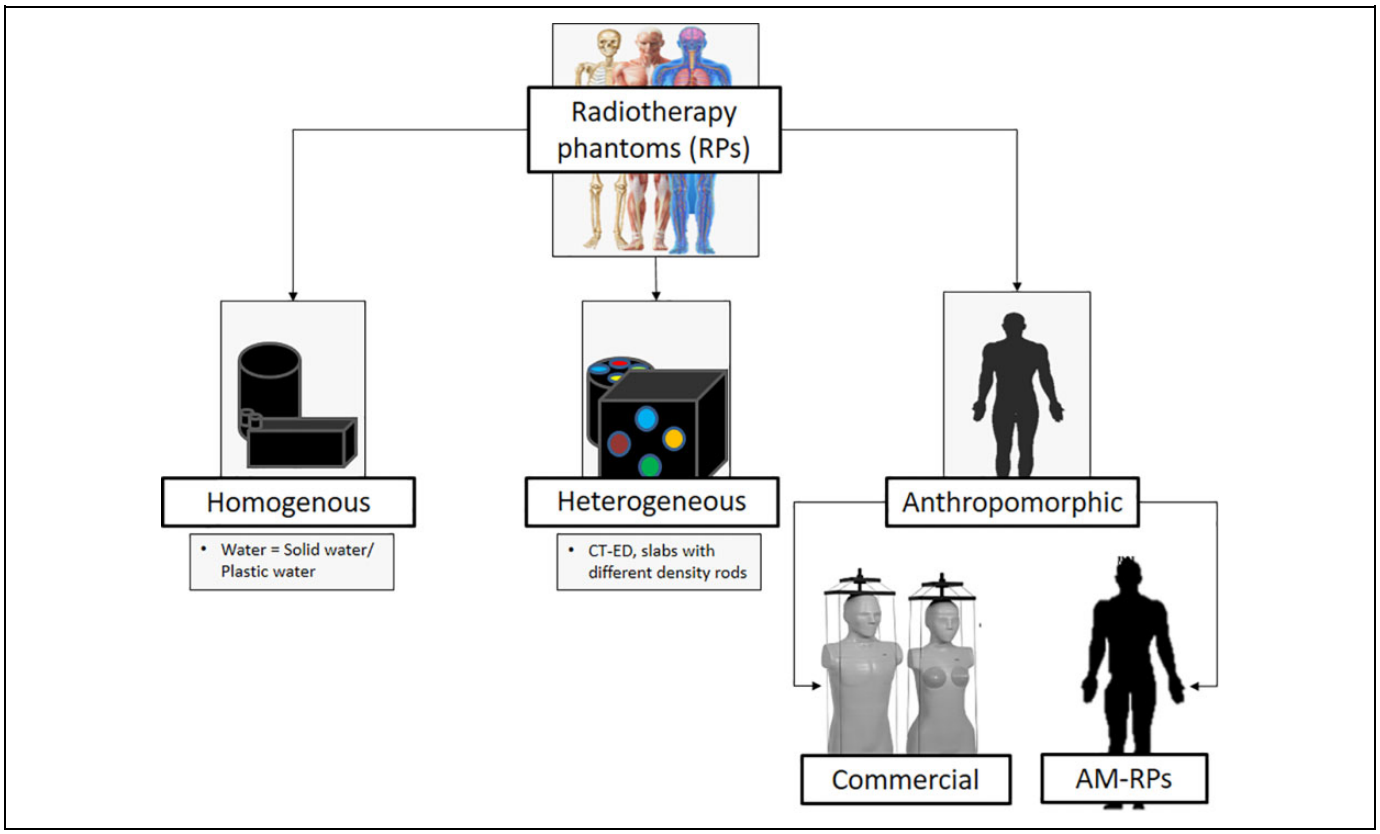

Figure 1. Types of radiation dosimetry phantoms for quality assurance applications.

Introduction

Radiotherapy aims to deliver curable radiation dose to tumors while sparing surrounding healthy tissue, which is achieved by the accurate conformal delivery of ionizing radiation via external beam using linear accelerators or internal beam using sealed radiation source (called brachytherapy). Modern radiotherapy involves computed tomography (CT) simulation, 3-dimensional (3D)-treatment planning, and its quality assurance (QA) processes prior to patient treatment, in order to produce highly conformal dose distributions and to ensure its safe and accurate delivery. It is common to build phantoms that mimic radiation properties of humans as radiation dose cannot be directly measured in patients. As part of QA of patient treatment plans, patient-specific dose measurements are often performed using radiotherapy phantoms (RPs) combined with various dosimeters. Unfortunately, commercially available phantoms are not always anatomically correct and typically represent healthy "standard" persons (Figure 1). However, the manufacturing process of these phantoms is high in costs and is often limited to accommodate individual patient's pathological features. Such phantoms consist of homogenous materials simulating some form of tissue such as bone, muscle, and lung. The uniformity in contrast within these homogenous materials do not mimic the inhomogeneity found in human tissues. This limitation results to dose inaccuracies hence, in particular, when commercially available dosimetry phantoms are used. With the advancing research in additive manufacturing-RPs (AM-RPs), there exist significant opportunities in developing accurate and reliable phantoms to improve patient treatment.

Apart from the standard fabrication of RPs through moulding and casting, a current trend involves the use of patient imaging data to design and manufacture phantoms through a process called additive manufacturing (AM), commonly known as 3D printing.[1-3] The AM process follows a layer-by-layer method of printing from simple to complex geometries. This process enables us to develop "viable" patient-specific and low-cost RPs. There is an increasing number of studies to demonstrate various applications of AM technology[4] and its significant utility in manufacturing radiotherapy devices, not only for imaging and dosimetry phantoms but also for bolus,[5-8] immobilization tools,[9-12], brachytherapy moulds,[13-17] electron beam cutouts,[18-21] and compensator devices.[22-24] Other medical applications for AM also include pharmaceutical[25] and surgical applications.[26,27]

Within the last decade, a number of studies have investigated the use of AM technologies to produce customized patient-specific RPs using different types of in-house and commercially available AM materials including thermoplastics and photopolymer resins.[28-32] To emulate patient-like geometry, it is essential to achieve heterogeneity in terms of electron

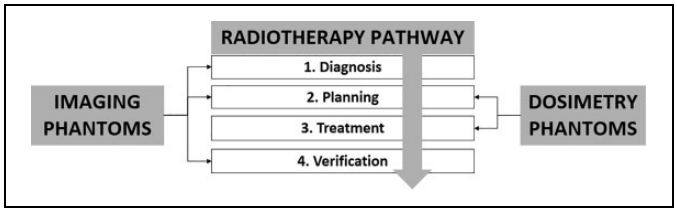

Figure 2. Applications for imaging and dosimetry phantoms within the radiotherapy treatment pathway: (1) the use of various imaging modalities, (2) utilizing available treatment planning software systems, (3) irradiation—fractionation, and (4) comparison of planned dose to actual dose.

density, which is often defined by Hounsfield units (HU) in CT imaging[33]; common methods to vary the density during AM process include controlling the standard Fused Deposition Modelling (FDM) printing parameters such as infilling percentage, infilling pattern, printing temperature, and material extrusion rate.[34] Other methods to increase achievable HU values involve AM material content doping.[35,36]

The ability of AM in fabricating imaging phantoms is concisely summarized by Filipou *et al*,[37] showing a collection of recent studies in AM applications for various imaging modalities, such as CT, magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound. Despite this, there is no systematic review, till now, to explore various application methods of the emerging AM technologies to manufacture imaging and dosimetric phantoms, which are both a primary interest in radiotherapy. In this context, our study focuses on a comprehensive review of recent studies in relation to patient-specific RPs using AM technologies for imaging and dosimetry applications. Within the radiotherapy process, imaging phantoms are utilized for (1) diagnosis, (2) planning, and (4) verification, whereas dosimetry phantoms are only utilized for (2) planning and (3) treatment (Figure 2). Various 3D printing workflows, printing materials, and dosimetric characteristics are summarized along with its relevance to different radiotherapy applications and tasks to highlight the current literature status and existing significant research opportunities.

Search Methodology

Systematic Search Strategy

This review was initiated using the following electronic research databases: Google Scholar, Scopus, National Center for Biotechnology Information (NCBI; PubMed), IEEE Xplore, and Web of Science (Clarivate analysis) until August 31, 2018. A search string containing key search terms including "additive manufacturing," "3D printing," "three-dimensional printing," "rapid prototyping," "radiation therapy," "dosimetry phantoms," "dosimetric phantoms," "phantoms," "quality assurance phantoms," "anthropomorphic," "patient-specific," "human-like," "lung," and "bone."

Study Selection

Published papers in the last 10 years were considered (2008-2018), and *Alert* option was activated until the final submission date. Selected publications highlight the following inclusion criteria: (1) full text papers and written in English language; (2) studies linking AM with medical applications, especially with radiotherapy applications; and (3) imaging modalities implemented (CT, MRI, and/or PET). Duplicate findings were discarded to ensure that no data overlap occurred. Further study selection follows exclusion criteria including: (1) did not implement imaging and/or dosimetry analysis on the printed phantoms; (2) other radiotherapy applications including bolus, immobilizers, molds, and compensators; (3) books and case reports; and (4) expert opinion papers. Screening process was documented systematically using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to illustrate selection of studies for this intended review.[38]

Data Extraction

A comprehensive systematic literature search and outcome extraction was performed by the corresponding author (R.T.). Summary of the selected publications were tabulated (study description, focus of study, the AM workflow used [process, machine details, and materials], publication year, and corresponding author). Furthermore, selected publications for data analysis extraction were categorized into various segmentations of the human body and are tabulated focusing on CT imaging outcomes and the manufactured phantom-associated dosimetric evaluations.

Results

Current Trend of AM for Radiotherapy Applications

In summary, a total of 10 266 publications were identified until July 31, 2018, using the previously defined search terms, from which n = 4116 in Google scholar, n = 2693 in NCBI (PubMed central), n = 2285 in IEEExplore, n = 896 in Scopus, n = 45 in Web of Science, and n = 231 from other sources (ie, recent journals, review, reference lists). After removing non-English (n = 13) and duplicate findings (n = 3317), a total of 6891 publications remained. Selection was implemented by going through the remaining publications, reading titles, and applying the inclusion criteria, leaving 564 articles. These articles were further assessed for full text articles and relevant studies taking into account the specified exclusion criteria for this systematic review. A total of 268 potentially eligible studies were included while 296 studies were excluded due to insufficient data linking AM to radiotherapy applications.

For eligibility, the remaining 268 studies were analyzed carefully through reading abstracts. This process resulted in a total of 53 studies included and a total of 215 studies excluded: n = 28 for bolus applications, n = 16 for immobilizers, n = 9 for compensators, n = 20 for brachytherapy moulds, n = 7 for electron beam cutouts, n = 24 for other

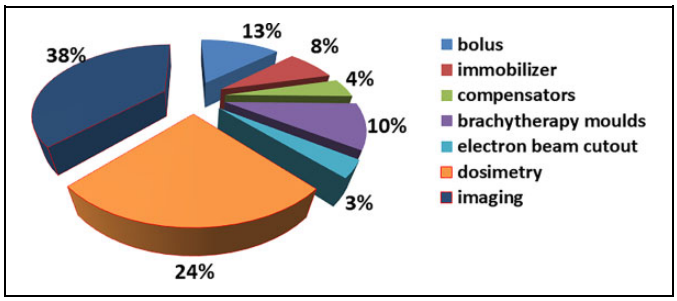

Figure 3. Current trend of AM applications for radiation therapy as of 2018. AM indicates additive manufacturing.

imaging applications involving optical and ultrasound, and n = 111 for the lack of data.

Aside from AM of imaging (ultrasound, optical, and radiopacity studies) and dosimetry phantoms, there is an observed demand for AM in other radiotherapy tools such as bolus, immobilization, compensators, brachytherapy moulds, electron beam shielding, and other radiotherapy accessories (Figure 3). These neighboring applications illustrate an increasing interest for research as it requires a low-cost and efficient printing workflow using Fused Filament Fabrication, now commonly known as FDM where thermoplastics such as polylactic acid (PLA), a water-equivalent AM material is melted and extruded through a nozzle.

Fifty-two studies were extracted regarding contrast imaging phantoms (additive manufacturing of patient-specific contrast imaging phantoms [AM-CIPs]); however, 25 studies were excluded due to lack of data and the focus of study involves the optical and ultrasound applications rather than radiopacity analysis. Fifty studies regarding printed dosimetry phantoms (additive manufacturing of patient-specific dosimetry phantoms [AM-RDPs]) were extracted, however, 24 of them were excluded due to the lack of data in terms of the applied material imaging and dosimetry evaluation, leaving 26 studies. A total of 53 publications have been selected for this review: AM-CIPs for material radiopacity studies, in particular the investigation of observed electron density in CT imaging (n = 27) and the irradiation of AM-RDPs involving CT and dose evaluations (n = 26; Figure 4).

The PRISMA flowchart implemented for this review is provided in Figure 5. As a result, a directed review has been conducted regarding the manufacture of AM-RPs, showcasing their importance in high-precision radiotherapy using stereotactic[39-41] or proton therapy.[42] The AM-RPs are categorized into AM-CIPs and AM-RDPs.

Manufacture of AM-CIPs

The AM-CIPs are printed phantoms aiming to evaluate imaging quality of current imaging modalities. Table 1 summarizes the selected studies in terms of body sites, implemented AM processes and materials, and imaging modalities. Current AM-CIPs in the literature revolve around mimicking the upper region of the target medical patient data. Simulated regions

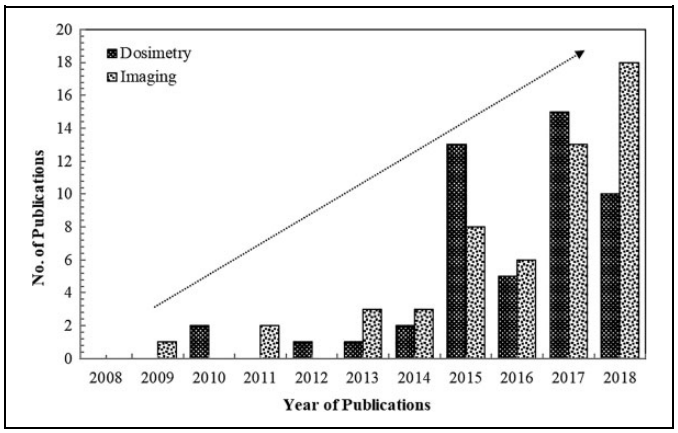

Figure 4. Number of publications for AM of imaging and dosimetry radiation therapy phantoms. The ascending arrow indicates an observed linear trend for both imaging and dosimetry applications of manufactured radiotherapy phantoms using AM. AM indicates additive manufacturing.

range from the head and chest sections (bone, soft tissue, and lung tissue)[43,46,48,53,55,58] to the abdominal section (liver, spleen, and kidney).[44,49,56]

Manufacture of AM-RDPs

In characterizing AM materials for RPs, it is important to consider the photoelectric and Compton effects when comparing printed materials to human tissues. Photoelectric effect serves as the dominant phenomena at low X-ray energies ranging below 200 keV, hence, for imaging modalities (CT, MRI, PET), suited for AM-CIPs. At higher X-ray energies up to 10 MeV, Compton effects can be considered as the dominant phenomena, where material attenuation differs depending on their elemental composition. Compton effects signify how radiation doses are distributed, hence explored by AM-RDPs. Ideally, AM-RDPs aim to simulate not only the patient's proportion and pathological features but also both the imaging attenuation of human tissues, the photoelectric effect, and the dose attenuation of tissues, the Compton effect.[60]

When compared to current AM-CIPs, AM-RDPs are identically derived from patient CT data, however, they are further utilized for the clinical aspect of the radiotherapy process involving dose measurements and treatment planning. Commonly used dose evaluations for AM-RDPs involve percentage depth dose evaluation and measurements of dose distributions through thermoluminiscent dosimeters,[61,62] ionization chambers,[63,64] and film dosimetry. [65-69] More recently, studies also utilize motor actuators[67,70] and readily available motion platforms[40] in combination with the printed imaging and dosimetry phantoms to evaluate tumor tracking (fiducials).

The AM thermoplastics used for manufacturing AM-RDPs, such as PLA, acrylonitrile butadiene styrene (ABS), and high-impact polystyrene (HIPS) were observed to achieve tissue-like imaging attenuations through varying their printing parameters and achieve similar dose distributions from human tissues. As

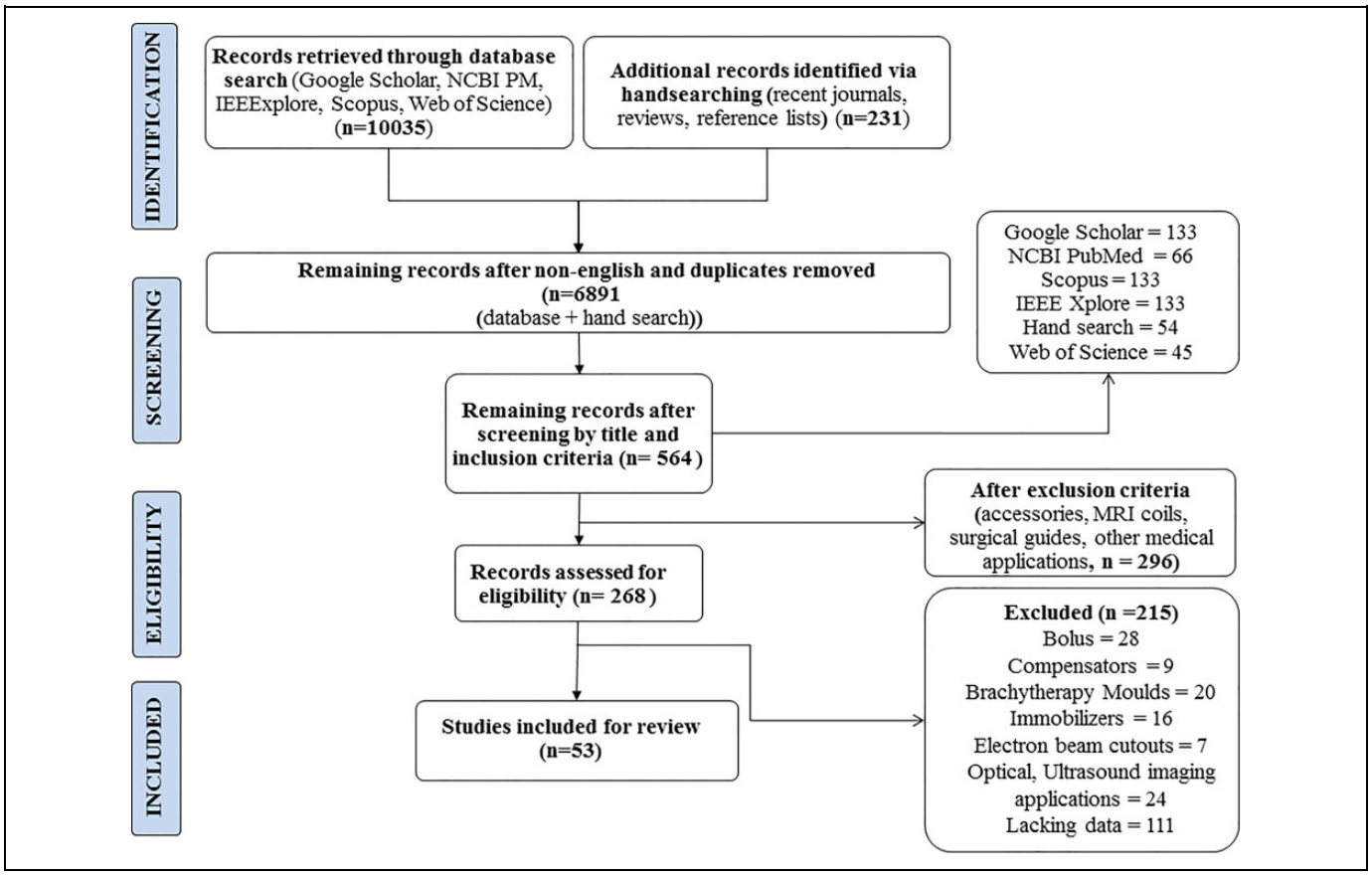

Figure 5. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart process for paper selection.

found in the literature, the PLA material was demonstrated to show good agreements with the human thyroid in terms of elemental composition characterized using an energy-dispersive X-ray spectroscopy machine.[62] Especially for ABS and HIPS, both materials were observed to show good agreements in terms of measured and planned doses for printed patient-specific phantoms.[66,68,71] Elastic filaments known as thermoplastic Polyurethane (TPU; ie Ninjaflex and Cheetah) have been investigated to show HU results similar to the white and gray matter of the head (Figure 6).[72] However, current research interests for TPU lean toward the fabrication of skin bolus applications due to their excellent conformity and elasticity.[73,74] Other non-FDM materials, such as photopolymer and nylon powder were also investigated for their dose attenuation and their deformability, which were observed to produce reasonably good results for fiducial tracking.[39,46,63]

The key in selecting AM materials for printing AM-RDPs do revolve around their elemental and atomic composition, hence, careful characterization of printing materials is important to minimize dose errors and improve treatment planning outcomes. It is also important to consider the changes within each material's imaging and dose attenuations over time after printing.[75] Table 2 summarizes the selected studies for this review of AM-RDPs in terms of body sites, implemented AM processes and materials, imaging modalities, and dose evaluation.

A range of achievable HU via AM processes could be extracted from Tables 1 and 2, illustrating that nearly air (eg, −1000 HU) to compact bone density (eg, +500 HU) could be precisely controlled. A summary of achievable HU range with utilized AM materials is illustrated in Figures 6 and 7 for FDM and non-FDM processes, respectively.

Discussion

The current literature illustrates a growing field regarding AM-RPs for imaging and dosimetry applications (Figure 4). Additive manufacturing's relatively low-cost and iterative fabrication process compared to the standard moulding and casting process proves to be experimentally advantageous. Most importantly, as highlighted by Figures 6 and 7, AM materials, polymers in particular, can have a wide range of HU with different densities in different body parts, which can be precisely controlled via AM processes. This results in AM methods as a strong alternative in the near future to potentially replace the current method of producing commercially available phantoms.[86]

Table 1. Summary of Manufactured Contrast Imaging Phantoms Using AM.

Segment	AM Process and Model	AM Material(s)	Country	Year	Evaluation	Reference
Glandular and adipose tissues	Bioplotter Pneumatic dispensing printer (EnvisionTEC, GmbH)	Gelatine-based material	United States	2018	X-ray spectroscopy, micro-CT	Dahal *et al*[43]
Abdomen (liver, spleen, kidney)	Polymer jetting, Objet EDEN 500 V (Stratasys)	VeroClear	United Kingdom	2014	CT, PET, SPECT	Gear *et al*[44]
Pelvis	FDM, Lulzbot TAZ and TAZ 6 (Aleph Objects)	ABS-barium sulfate	United States	2018	CT, micro-CT	Hamedani *et al*[36]
N/a	DLP, n/a	Silicon-based material	Canada	2017	CT, MRI, ultrasound	In *et al*[45]
Breast	FDM and polymer jetting, n/a	ABS, brick, hybrid, nylon, PET-G, PLA, PVA, black, Clear, Flex, Gray, NDBase, NDC + B, NDCast, NDSG, Tough, white	Bulgaria	2018	CT, attenuation coefficients and elemental composition	Ivanov *et al*[46]
Lung	MJP, Projet 3D (3D systems)	VisiJet EX200	Netherlands	2017	CT, structural similarity (SSIM)	Joemai *et al*[47]
Head	Polymer jetting, Objet Connex 350 (Stratasys)	VeroClear, VeroBlack, VeroWhite	Australia	2015	CT	REDACTED *et al*[48]
Liver	Polymer jetting, Objet Connex 350 (Stratasys)	Photopolymer resin (unknown)	United States	2016	CT, Channelized Hotelling model observer (CHO)	Leng *et al*[49]
N/a	FDM and MJP, n/a	PLA, RCL-ENT 300	Canada	2018	Micro-CT, scanning electron microscope (SEM)	Low *et al*[50]
Head	FDM, Mendel Printer (RepRapPro)	PLA	United Kingdom	2016	CT	Negus *et al*[51]
Pelvis	Polymer jetting, Objet 30 pro (Stratasys)	VeroClear	Germany	2016	Dual-energy CT (DECT), MRI	Niebuhr *et al*[52]
Head	Binder jetting, Spectrum 510 printer (ZCorp)	zp15e—Iodine	United States	2011	CT	Yoo *et al*[53]
Heart	FDM, DM plus model (Creatbot)	ABS	Australia	2018	CT	Abdullah *et al*[54]
Thryoid	FDM, n/a	ABS	United Kingdom	2017	CT, SPECT, SFOV hybrid gamma imaging,	Alqahtani *et al*[55]
Liver	Polymer jetting, Objet 260 (Stratasys)	TangoBlack Plus, VeroClear	United States	2018	CT	Berman *et al*[56]
N/a	FDM, Finebot Z420 (Anyworks)	PLA	Korea	2017	CT	Oh *et al*[57]
Thorax	FDM, T-Rex 2 (Formbot) FDM, Prusa i2 (Mendel)	ABS-Ca, PLA, PLA-Cu, Flex, PLA-wood, PEDG, ABS, HIPS, ABS-carbon	Greece	2017	CT	Okkalidis *et al*[58]
Thorax and head	FDM, T-Rex 2 (Formbot)	PLA	Greece	2018	CT	Okkalidis *et al*[34]
N/a	MJP, ProJet HD3500 (3D systems)	VisiJet M3 Crystal	United States	2015	CT, PET, MRI	Bieniosek *et al*[59]

Abbreviations: AM, Additive manufacturing; CT, computed tomography; FDM, Fused Deposition Modelling; MRI, magnetic resonance imaging; n/a, not applicable; PET, positron emission tomography; PLA, polylactic acid; SFOV, small field of view; SPECT, single-photon emission computed tomography.

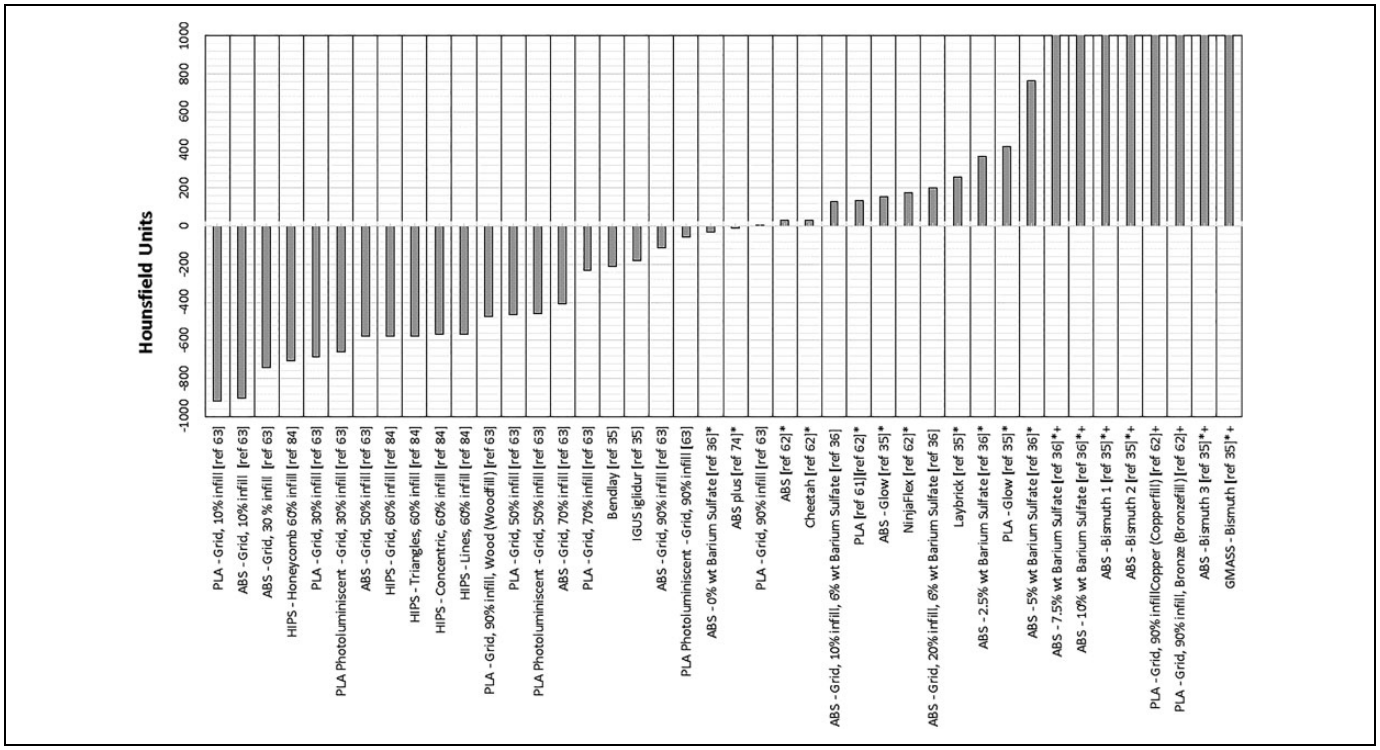

Figure 6. Different fused deposition AM materials, their achievable hounsfield units, and their corresponding references. * indicates materials with 100% infilling and + indicates materials with greater than 1000 hounsfield units (Tables 1 and 2). AM indicates additive manufacturing.

Additive Manufacture of Polymers

The AM of polymers is the additive process of materials in a layer-by-layer fashion creating simple to complex 3D part geometries as opposed to removing materials (subtractive manufacturing) to generate parts.[87] During the 1980s, the very first rapid prototyping technique, known as Stereolithography (SLA) was introduced by Japanese doctor, Dr Hideo Kodama.[88] Since then, AM has branched out into different kinds of processes and techniques: Binder jetting; directed energy deposition; material extrusion; powder bed fusion; sheet lamination; and vat photopolymerization (Table 3).

Additive Manufacture Printing Workflow for the Manufacture of Radiotherapy Phantoms

Various studies have specified the standard workflows for manufacturing patient-specific imaging and dosimetry phantoms.[75,80,82,83] From the observed literature, standard AM workflow for fabricating these patient-specific phantoms consists of 4 major processes: imaging, segmentation, slicing, and the printing stage. Post-processing is optional for phantoms with significant manufacturing defects requiring further cleaning (Figure 8).

Classification of Manufactured AM Radiotherapy Phantoms

Additively manufactured patient-specific imaging and dosimetry phantom models are commonly derived from CT data as they are easily accessible and they provide reasonable results in a short amount of time. Only a few studies investigated the use of other imaging modalities such as MRI, PET, PET/SPECT, and ultrasound.[37,44,51,52] Although CT provides limited contrast detail between soft tissues and bone compared to other modalities, the short time interval is desired, especially for the rapid prototyping of patient-specific phantoms for urgent treatment planning.

Early versions of printed imaging and dosimetry phantoms were manufactured as-shell phantoms, which are hollowed phantoms filled with various tissue-equivalent materials (sawdust, silicone gels, cork, etc). The emergence of better AM technologies hasattracted interests in exploring the simulation of the human tissue heterogeneity[54], classified as as-printed phantoms. Heterogeneity in printed phantoms can be achieved using modified FDM printing parameters such infilling patterns and percentage, printing nozzle size, temperature, and, more recently, the modification of material extrusion rate using the pixel-by-pixel method.[34,57] Furthermore, contrast variations can also be achieved by constructing phantoms with 2 or more different AM materials (multiple material

Table 2. Summary of Manufactured Radiation Dosimetry Phantoms Using AM.

Segment	AM Process and Model	AM Material(s)	Country	Year	Evaluation	Reference
Thyroid gland	FDM, Prusa i3 3D printer (Prusa research)	PLA	Malaysia	2017	SEM-EDS, CT, dose evaluation using TLDs	Alssabbagh *et al*[62]
N/a	FDM, uPrint SE Plus (Stratasys)	ABS-P430	United States	2017	4D PET/CT, dosimetry and cell irradiation assay, end-to-end test[a]	Cerviño *et al*[76]
N/a	Polymer jetting, n/a (Stratasys)	FullCure930 TangoBlack Plus	United States	2010	End-to-end test[a] (Conformal, VMAT, and IMRT)	Court *et al*[77]
Thorax	FDM, Gigabot 2.0 (re:3d)	PLA	United States	2017	CT, percentage depth dose (PDD) evaluation	Craft *et al*[75]
N/a	FDM, Gigabot 3.0 (red:3d)	PLA, NinjaFlex, ABS, Cheetah	United States	2018	CT, PDD evaluation	Craft *et al*[72]
Head	FDM, MakerBot (MakerBot Industries)	ABS-Bismuth, ABS—Glow, PLA—Glow, Woodfill, Copperfill, Bronzefill	United States	2017	CT, radiation attenuation	Ceh *et al*[35]
N/a	FDM, 3D Touch (3D systems), FDM, Replicator 2 (Makerbot), FDM, TAZ 5 (Lulzbot), SLA, Form 1+ (Formlabs)	ABS, PLA, Bronzefill, Copperfill, Woodfill, photoluminiscent PLA, photopolymer resins[b]	Australia	2017	CT, dose evaluation using ionizing chamber	Dancewicz *et al*[63]
N/a	FDM, Prusa i3 MK2 (Prusa Research)	PLA	Greece	2018	Density evaluation, CT, PDD	Diamantopoulos *et al*[21]
Head	FDM, Replicator 2x (Makerbot)	ABS	United States	2014	CT, end-to-end test[a] (IMRT)	Ehler *et al*[78]
Head	n/a	Epoxy resin[d]	Germany	2015	CT, DECT, end-to-end test[a]	Gallas *et al*[79]
Thorax	Polymer jetting, Objet Connex3 (Stratasys)	VeroWhite Plus FullCure835, FullCure980 TangoBlack Plus, VeroClear FullCure810	United Kingdom	2016	CT, SPECT, dose-volume evaluation	Gear *et al*[80]
Thorac ribs, lung, and tumor	Inkjet, ZCorp 650 (3D Systems), SLS, EOS (GmbH)	Gypsum, nylon (Polyamide 12)	Netherlands	2018	CT, dose-volume evaluation	Hazelaar *et al*[81]
Head + eye	Polymer jetting, Objet Eden 350 (Stratasys)	FullCure720	Austria	2017	CT, dose evaluation using TLDs	Homolka *et al*[61]
N/a	FDM, Replicator 5 (Makerbot)	PLA	Korea	2015	CT, dose evaluation using array detectors and EBT3 films	Jeong *et al*[65]
Lung	FDM, Da Vinci 3D	ABS	Australia	2015	CT, end-to-end test[a]	Kairn *et al*[69]
Head	FDM, FDM-200 W (Ninjabot)	PLA	Japan	2017	CT, end-to-end test[a] (VMAT)	Kamomae *et al* [82]
Spine	Polymer jetting, Objet Connex (Stratasys), DLP[c], Titan1 (Kudo 3D)	Acrylic polymer[d]	Korea	2017	CT, end-to-end test[a] (SBRT)	Kim *et al*[83]
Abdomen	SLA, Uniontech RS4500 (Shanhai Luen Thai 3D Technology Co, Ltd)	ABS	China	2017	CT, dose evaluation using ionization chamber, deformable image registration evaluation (DIR)	Liao *et al*[64]
N/a	FDM, ORION Delta 3D (SeeMeCNC)	High-Impact polystyrene (HIPS)	Canada	2016	CT, dose evaluation using EBT3 film with associated TPS (using anisotropic analytical algorithm, AAA)	Madamesila *et al*[66]
Thorax	Polymer jetting, Objet500 (Stratasys)	TangoPlus, VeroWhite	United States	2015	CT, 4D-CT, dose evaluation using EBT3 films with associated TPS (photon treatment plan)	Mayer *et al*[67]
Thorax	FDM, n/a	ABS	Italy	2017	CT, CBCT, TPS, tumor-to-surface motion correlation	Pallotta *et al*[70]
Spine, external body	Polymer jetting, Projet5000 (3Dsystems), Powder Bed, Z printer (3Dsystems)	UV-curable acrylic plastic[d], plastic powder[d]	Korea	2017	CT, TPS	Oh *et al*[39]
Spleen, pancreas, liver, kidney	FDM, Dimension Elite (Stratasys)	ABS plus	United Kingdom	2016	CT, absorbed dose evaluation	Robinson *et al* [71]
Lung	FDM, Edison Printer (Lokit)	PLA	Korea	2015	4D-CT, end-to-end test (SABR)	Jung *et al*[40]
Kidney	FDM, Renkforce RF1000 (Conrad Electronic SE)	PLA	Germany	2016	SPECT/CT, absorbed dose evaluation	Tran-Gia *et al*[84]
Head	FDM, Dimension 1200 Series SST (Stratasys)	ABS plus	Korea	2017	CT, dose evaluation using EBT2 film	Yea *et al*[68]
Thorax	FDM and polymer jetting	ABS (Fat and chest wall), modified resin polymer (ribs, sternum angle, and scapula)	China	2018	CT, end-to-end test (PBC, CCC, and montecarlo algorithms)	Zhang *et al*[85]

Abbreviations: AM, additive manufacturing; CT, computed tomography; DECT; dual-energy CT; EDS, energy-dispersive X-ray spectroscopy machine; FDM, Fused Deposition Modelling; IMRT, Intensity Modulated Radiation Therapy; PET, positron emission tomography; PLA, polylactic acid; SEM, scanning electron microscopy TLDs, thermoluminiscent dosimeters; TPS, Treatment Planning System; VMAT, Volumetric Modulated Arc Therapy; 4D, 4-dimensional.

[a]End-to-end test includes imaging, planning, delivery, and measurement tests (dose films, TLDs, ionization chamber, etc).

[b]Standard and flexible photopolymer resin.

[c]Digital light processing.

[d]Specific AM material name not specified.

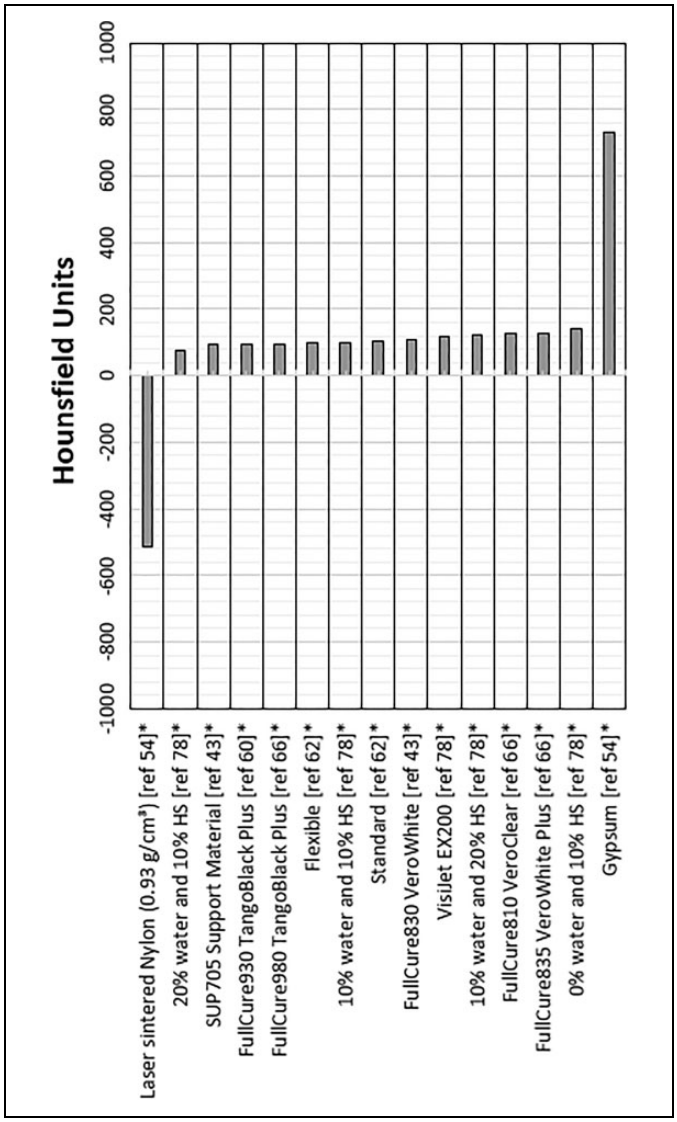

Figure 7. Additive Manufacturing materials manufactured with other AM technologies [Polymer Jetting technology (PJT), Digital Laser printing (DLP), Selective laser sintering (SLS), Stererolithography (SLA), Multijet Printing (MJP)], their achievable hounsfield units, and their corresponding references. * indicates materials with 100% infilling (Tables 1 and 2). SLA indicates stereolithography; SLS, Selective Laser Sintering.

printing), doping filaments with high density materials such as bismuth[35] and barium sulfate[36] to increase HU range, and the use of controlled voided structures within the manufactured phantoms to precisely control HU values. Recent studies have illustrated the combination of these manufactured phantoms with commercially available motion platforms and in-house motion devices to further simulate body movements, in particular the thorax's respiratory movements (classified as 4D AM phantoms).[40,41] These classifications of AM-RPs are illustrated in Figure 9.

Other manufacturing technologies such as SLA and polymer jetting technology (PJT) with their corresponding materials (photopolymers and resins) have also been explored due to their better capabilities in terms of printing resolution and quality, especially for complex structures such manufacturing phantoms with small voided structures in producing heterogeneous CT imaging results.[48,59] These technologies are ideal for manufacturing dosimetry phantoms (AM-RDPs) to verify treatment plans and assess dose accuracy due to better printing accuracy and resolution. This brings us to the multimaterial printing capabilities of the PJT (Current Limitations of FDM Printing Process section).

Table 3. Selected AM Processes That Enables the Manufacture of AM-RPs.[88,a]

AM Process	Technique (s)	Description
Photopolymer vat	Scanning SLA, DMD-based SLA	SLA is the process of curing a vat of photopolymeric resins via ultraviolet light.
Material extrusion	FDM	FDM is the process of extruding thermoplastics through a nozzle via melting.
Powder Bed Fusion	SLS	SLS is the process of sintering polymer and metal powders in a layer-by-layer process.
Directed energy deposition	LENS	LENS uses high-powered lasers to fuse powder in a layer-by-layer process.
Sheet lamination	LOM	LOM is the process of laminating polymers or metal sheets into multiple number of layers and are then cut to shape via knife or laser cutters.
Material jetting	Inkjet printing, PJT	Inkjet and PJT are both jetting processes where droplets of digital and photopolymeric materials are jetted onto a substrate which are cured layer-by-layer via UV light.
Binder jetting	3DP	The 3DP process consists of liquid binding agents jetted in droplet form on to a bed of polymer powder.

Abbreviations: AM, additive manufacturing; DMD, digital micromirror device; FDM, Fused Deposition Modelling; LENS, laser engineering net shape; LOM, laminated object material; PJT, polymer jetting technology; SLA, stereolithography; SLS, selective laser sintering; 3D, three-dimensional printing.

[a]The heterogeneity found in the human body is becoming more important as more sophisticated radiotherapy techniques are employed such as stereotactic radiotherapy.[89] Therefore, simulating patient-specific tissue contrast requires the utilization of available standard AM printing parameters and AM polymers to manufacture clinically usefull imaging and dosimetry phantoms.

Current Limitations of FDM Printing Process

Despite the adaptive capabilities of 3D printed patient-specific radiotherapy devices, there exists limitations from AM technologies, in particular FDM machines. For example, as the majority of printed RPs utilizes this layer-by-layer printing process, it is important to consider manufacturability and reproducibility especially for long-term usage. A recent paper

by Gordeev *et al*[90] has investigated the inherent defects observed from FDM printed geometries and has shown that internal and external void defects, depending on their size and distribution, affect the mechanical properties of the associated geometry. These limitations can be minimized by simply optimizing the printing toolpaths.[91,92]

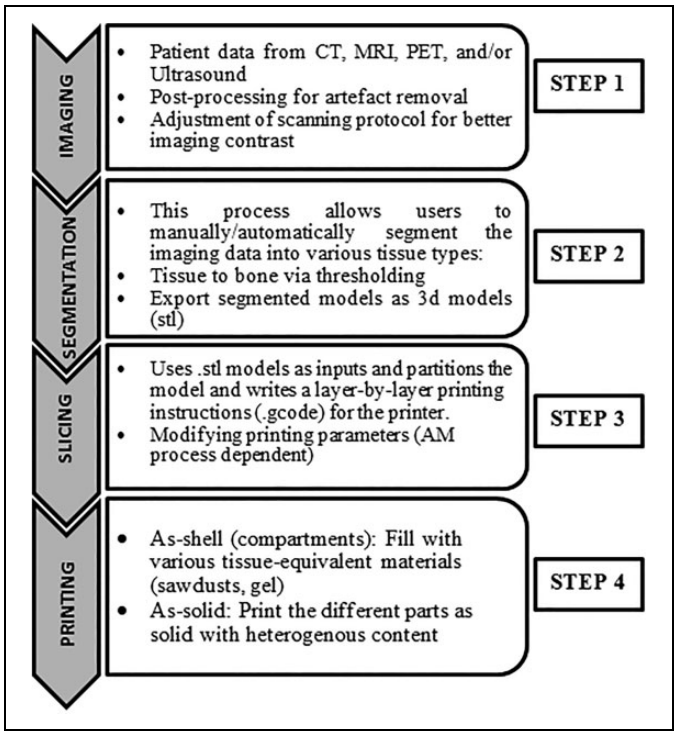

Figure 8. The standard manufacturing workflow for manufacturing patient-specific AM-RPs. AM-RPs indicates additive manufacturing-radiotherapy phantoms.

In translation to radiotherapy applications, not only the robustness of the radiotherapy device is a requirement but also their content uniformity and reliability. Unfortunately, current 3D printed radiotherapy devices through FDM printing are yet to be experimentally validated in terms of these limitations and their effects to radiotherapy imaging and dosimetry. Therefore, these void defects will need to be considered during the printing process, imaging, and dosimetry.

Multiple material printing using AM. Observed from recent publications, both classifications of manufactured RPs do provide reasonable imaging and dosimetry results. Especially with phantoms involving a combination of AM and non-AM materials, they show better imaging contrast results compared to phantoms only consisting of 1 or 2 AM materials.

With the advancing AM technology, 2 or more materials can now be printed within one printing session, classified as multiple-material additive manufacturing (MMAM). This printing capability significantly reduces the overall printing time and the inherent boundary gaps observed from printed phantoms consisting of separately printed segments and eliminates void defects due to the photopolymerization process.

Vaezi *et al*[93] investigated the currently used AM processes and compared them in terms of material resolution and multimaterial printing capabilities. As a result, the AM processes including Selective Laser Sintering, Laminated Object Material, and Shape Deposition Modelling were shown to print low resolution materials and have a fair capability of multimaterial printing. In contrast, polyjet printing was highly regarded to be the superior printing process due its ability in printing high resolution materials and has an excellent multimaterial printing capability. Polymer jetting technology simply uses the process of resin polymerization via UV light. Its neighboring process, called inkjet printing which uses inks instead of resins, also

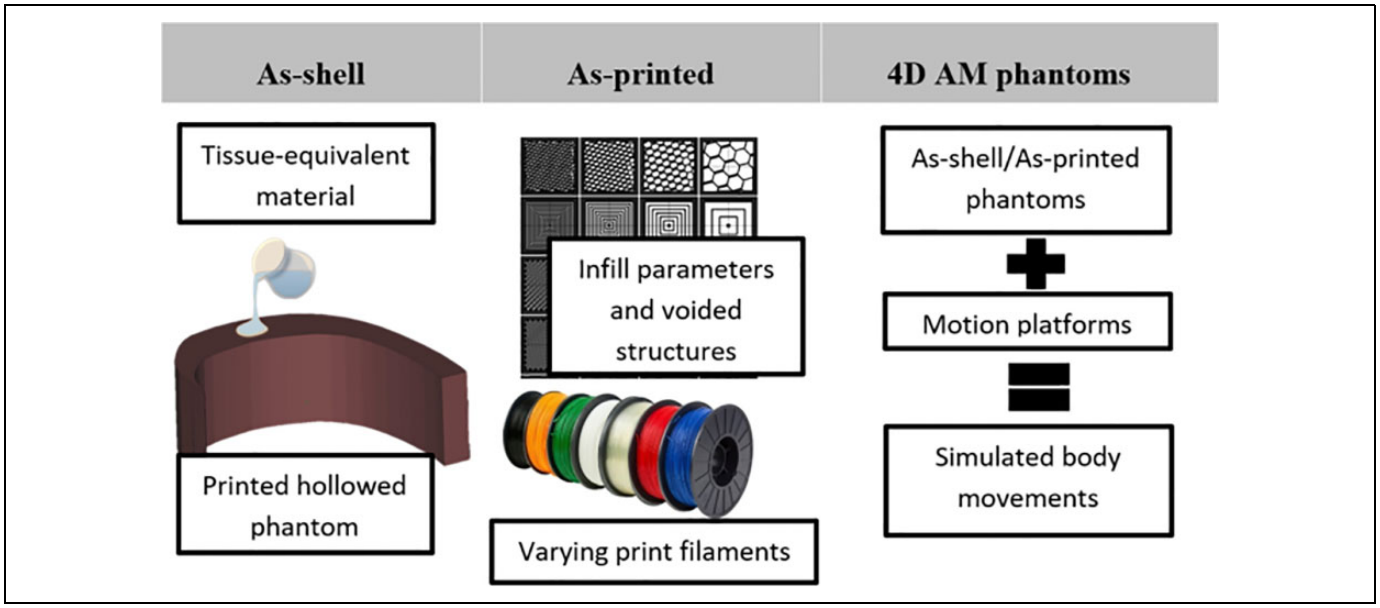

Figure 9. Types of additively manufactured radiotherapy phantoms.

uses material jetting process however came second due to a slightly lower multimaterial printing capability.

The PJT process appears to be the best option for high material resolution and multimaterial polymer printing. This was further demonstrated by a group of researchers from Harvard University and Massachusetts Institute of Technology where they recently published each of their work in *3D-Printing and Additive Manufacturing* journal[94] and *Science Advances* journal,[95] respectively. Compared to existing segmentation-based 3D printing workflows and processes, both printing approaches provided a faster and more accurate printing result involving multiple colors and materials.

Overall, the MMAM process is an excellent manufacturing substitute in developing patient-specific or anthropomorphic imaging and dosimetry phantoms other than the FDM process. Multiple-material additive manufacturing highlights reduced void defects and improved tissue inhomogeneity. However, more research is required to validate MMAM printing materials and workflows suitable for clinical radiotherapy use.

Conclusion

Additive manufacturing is one of the most rapidly emerging and fast adapted technologies for manufacturing customized objects for various applications in radiotherapy. Studies available in electronic search database show obviously arising trend in use of AM technologies for radiotherapy over the last decade including customized bolus, immobilization device, compensators, brachytherapy moulds, electron beam shield cutouts, and RPs. This review article particularly highlights the advances and significance of AM in manufacturing RPs, for both AM-CIPs and AM-RDPs. Additive Manufacturing has a great potential to improve current practice of using different types of phantoms, simply due to low-cost material and extremely adaptive fabrication abilities of complex geometries, emulating patient condition. A range of HU can be produced through different polymers and metallic AM materials for different radiotherapy applications in precisely controlled manner where different printing technologies and workflows are being developed and streamlined in order to meet demand in radiotherapy. Despite these advances, their exists inherent printing defects from the standard printing process of FDM and are yet to be characterized in terms of radiotherapy clinical use. This highlight further investigation of currently printed clinical radiotherapy tools, in particular patient-specific bolus devices.

Also, further development is geared toward the process of MMAM and will be increasingly utilized in the future as they provide low-cost and rapid fabrication, simultaneous fabrication of multiple materials during printing, and achievable patient-specific heterogeneity. However, it is important to consider the associated AM material(s), specifically photopolymer resins as they degrade more compared to standard printing filaments.[96]

The 3D printing Special Interest Group within The Radiological Society of North America has released their recommendations and guidelines to design and manufacture anatomical models, not only for diagnostics but also for clinical use. With the rapid growth of AM for radiotherapy application, an increase in the development of novel printing materials is expected, particularly in accurately simulating dose distributions in clinical scenarios. Guidelines/workflows as such will need to be flexible to accommodate this change especially for up and coming AM processes and materials.

Lastly, it is important to remind ourselves that the ideal or optimal patient treatment should not depend mainly from these "patient-specific" phantoms but to combine them with treatment planning systems, along with clinicians to provide better radiotherapy outcomes.

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Supplemental Material

Supplemental material for this article is available online.

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