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Review article

Additively manufactured Bi-functionalized bioceramics for reconstruction of bone tumor defects☆

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ABSTRACT

Bone tissue exhibits critical factors for metastatic cancer cells and represents an extremely pleasant spot for further growth of tumors. The number of metastatic bone lesions and primary tumors that arise directly from cells comprised in the bone milieu is constantly increasing. Bioceramics have recently received significant attention in bone tissue engineering and local drug delivery applications. Additionally, additive manufacturing of bioceramics offers unprecedented advantages including the possibilities to fill irregular voids after the resection and fabricate patient-specific implants. Herein, we investigated the recent advances in additively manufactured bioceramics and ceramic-based composites that were used in the local bone tumor treatment and reconstruction of bone tumor defects. Furthermore, it has been extensively explained how to bi-functionalize ceramics-based biomaterials and what current limitations impede their clinical application. We have also discussed the importance of further development into ceramic-based biomaterials and molecular biology of bone tumors to: (1) discover new potential therapeutic targets to enhance conventional therapies, (2) local delivering of bio-molecular agents in a customized and "smart" way, and (3) accomplish a complete elimination of tumor cells in order to prevent tumor recurrence formation. We emphasized that by developing the research focus on the introduction of novel 3D-printed bioceramics with unique properties such as stimuli responsiveness, it will be possible to fabricate smart bioceramics that promote bone regeneration while minimizing the side-effects and effectively eradicate bone tumors while promoting bone regeneration. In fact, by combining all these therapeutic strategies and additive manufacturing, it is likely to provide personalized tumor-targeting therapies for cancer patients in the foreseeable future.

Statement of significance

To increase the survival rates of cancer patients, different strategies such as surgery, reconstruction, chemotherapy, radiotherapy, etc have proven to be essential. Nonetheless, these therapeutic protocols have reached a plateau in their effectiveness due to limitations including drug resistance, tumor recurrence after surgery, toxic side-effects, and impaired bone regeneration following tumor resection. Hence, novel approaches to specifically and locally attack cancer cells, while also regenerating the damaged bony tissue, have being developed in the past years. This review sheds light to the novel approaches that enhance local bone tumor therapy and reconstruction procedures by combining additive manufacturing of ceramic biomaterials and other polymers, bioactive molecules, nanoparticles to affect bone tumor functions, metabolism, and microenvironment.

1. Introduction

In 2008, the International Agency for Research on Cancer reported that the number of new cancer patients per year is expected to double (~21 million new cases) by 2030 [1]. Beside elevated incidence of cancer, its high mortality rate further contributes to the severity of this disease. Despite many efforts in im-

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proving current therapies (*i.e.,* local and systemic chemotherapy, radiotherapy, hormonal therapy, and surgery), the effectiveness of the therapies remains suboptimal. Hence, the worldwide economic burden of cancer is still significant (US$ 470 billion annually) and increasing rapidly [2].

Among the 45 types of bone tumors identified, osteosarcoma (OS) and Giant Cell Tumor (GCT) are known as the most prevalent ones [3]. Treatments for OS and GCT include surgical resection of the tumor and eventual bony metastasis, additional adjuvant therapy, systemic chemotherapy, or a combination of them [4,5]. However, significant drawbacks have been reported, such as both short- and long-term toxic side-effects as well as chemotherapy drug (e.g. doxorubicin, methotrexate, and cisplatin) resistance, and tumor recurrence following resection [6–9]. Moreover, surgeons usually remove surrounding bone tissue during the resection. Consequently, non-union fractures might develop in the patients, thereby causing impaired bone regeneration; a condition that demands multifunctional bone implants [10–12].

The employment of customizable 3D-printed bone implants therefore offers several advantages including the possibility to fill irregular voids after surgery, incorporate a wide variety of drugs and therapeutics, and customize its mechanical as well as biological properties [4,13–17]. An ideal bone implant mimics the features of true bone in terms of architecture, chemical composition, and mechanical properties. Therefore, bioceramics are among the most common scaffolds for bone tissue engineering due to their similarities with bone properties and composition, [4]. In short, bioceramics not only share similar properties as native bone, but they also display biocompatibility, hydrophilicity, bioactivity, osteoconductivity, and osteoinductivity [4,14]. Moreover, their macro- and microstructures (i.e., porosity, pore size, topography, and roughness) can be modified to obtain an implant with desired transport of nutrients and oxygen, cell attachment, cell differentiation, and other relevant characteristics to facilitate new bone formation [4,14,15,18].

Interestingly, further research into bioceramics has enabled the realization of 3D-printed composite bioceramics (or hybrids) by combining 3D-printed bioceramics with nanoparticles and/or polymers which provides the biocermaics unprecedented opportunities [19–22]. These hybrid biomaterials can incorporate a wide variety of drugs and therapeutics to serve multiple functions simultaneously (i.e., photothermal therapy, magnetothermal therapy, local chemotherapy, and tissue regeneration). Since bioceramics composite have displayed relevant bone-forming and local antitumor targeting properties, they represent an effective solution for the current limitations of bone cancer treatments including chemotherapy toxicity and drug resistance, tumor recurrence, and non-union fractures following the surgery. Thanks to the recent advances in nanomedicine, material design, and additive manufacturing techniques, bioceramics can now be fabricated in a combination with various adjuvants, or drugs and, soon, adapt to its host to render their multifunctionality efficiently [23,24].

In this review, we have described the materials and processes that allow the development of the third-generation of bioceramics for bone cancer treatment and regeneration. We have also taken a glimpse at the future of bone cancer treatment through a fourth generation and most futuristic class of bioceramics. Finally, we have discussed how new “spontaneous” biomaterials for bone tissue engineering, will provide optimal treatment for its local host, a necessary feature to treat a heterologous disease like cancer.

2. Bone tumor defect

Cancer is a dynamic and multi-faceted disease characterized by continuous development and evolution during the disease progression. In the first stage, cancer cells arise from a series of mutations that dysregulate basic cellular processes (i.e., cell division-cycle) without leading to apoptosis [25]. The primary tumor continues to grow in the origin site depending on several factors, such as stress conditions, nutrition rate, pH, hypoxia, osmotic, and hormonal conditions [26]. Later, the equilibrium between many growth factors, cytokines as well as pro- and anti-angiogenesis factors (*i.e.,* VEGF, TGF-ß, IL-6, etc.) is altered, thereby triggering new blood vessel to grow towards the primary tumor mass to provide a constant nutrient supplement [27]. At this stage, cancer cells acquire a “malignant” phenotype as they can invade the circulatory or even lymphatic system; during the intravasation process, the intercellular junctions of the endothelium of the vessels are widened so that cancer cells can pass through the basal membrane. The cancer cells thus start a metastasis process. In fact, the metastasis process includes a sequence of steps that lead to the spreading of cancer cells over the body in search of a new site to further proliferate. This sequence of processes has been elegantly explained with the “seed and soil” theory in which the tumor would be the “seed” that finds a proper “soil” with the best-growing conditions [28]. Concerning this theory, the bone tissue exhibits critical factors for metastatic cancer cells and represents an extremely pleasant “soil” for the further growth of tumors. Obviously, cancer and metastasis in bone are associated with not only cancer cells but also cancer-supporting cells like tumor-associated macrophages (TAMs), cancer-associated fibroblasts, cancer-associated adipocytes and other immune cells as well as their microenvironments which should be seriously considered. Therefore, we invite the interested reader to study the relevant works such as [29,30].

Bone tissue is a combination of two different tissues. First, the cortical bone that represents the 80% of the skeletal mass and composes the outer layer of the bones, mainly present in the diaphysis. Second, the trabecular bone that constitutes 20% of the skeletal mass by occupying the inner space of the bones, mainly found in the metaphysis and epiphysis (Fig. 1).

The extracellular matrix (ECM) of the bone is composed of both organic (proteoglycans, glycosaminoglycans, glycoproteins, osteonectin) and mineralized (calcium-phosphates) composition [31]. Bone homeostasis is strictly regulated by two principal processes: bone resorption and deposition. The three cell types that play a major role in this dynamic regulation are (1) osteoclasts, multinucleated cells derived from pre-osteoclasts of the monocyte-macrophage lineage known to dissolve bone ECM by the release of degrading protease, (2) osteoblasts, specialized and well-differentiated mono-nucleated cells derived from mesenchymal stem cells (MSCs) and responsible for the deposition of a new mineralized matrix, and (3) osteocytes, the most abundant cell lineage in the bone with mechanosensitive properties. Moreover, the inner space of the bone is filled by bone marrow (BM) where both the players involved in bone homeostasis are co-located, the immune cells from the hematopoietic lineage and BM adipocytes that have been defined as important players in the maintenance of the health condition and the progression of cancer disease [32].

Importantly, the trabecular bone is particularly targeted by metastatic cancers because of its specific features. First, it is characterized by a heterogeneous architecture loosely organized with a widely porous matrix, crammed with vascularized networks, and loaded with growth factors [33]. Moreover, the bone is strictly interconnected with the bloodstream. In particular, the slow blood flow of the venous circulation from the breast and prostate toward the vena cava may increase the probability of cancer cells to enter the bone. Metastatic bone lesions are classified as osteolytic when the tumor induces abnormal resorption of the bone by stimulating osteoclasts activity while inhibiting osteoblasts activity. The lesions can also be osteoblastic when growth factors generated from the tumor, such as BMPs and endothelin-1 (ET-1), stimulate the recruitment of osteoblast progenitors leading to the production of new pathological bone [34,35].

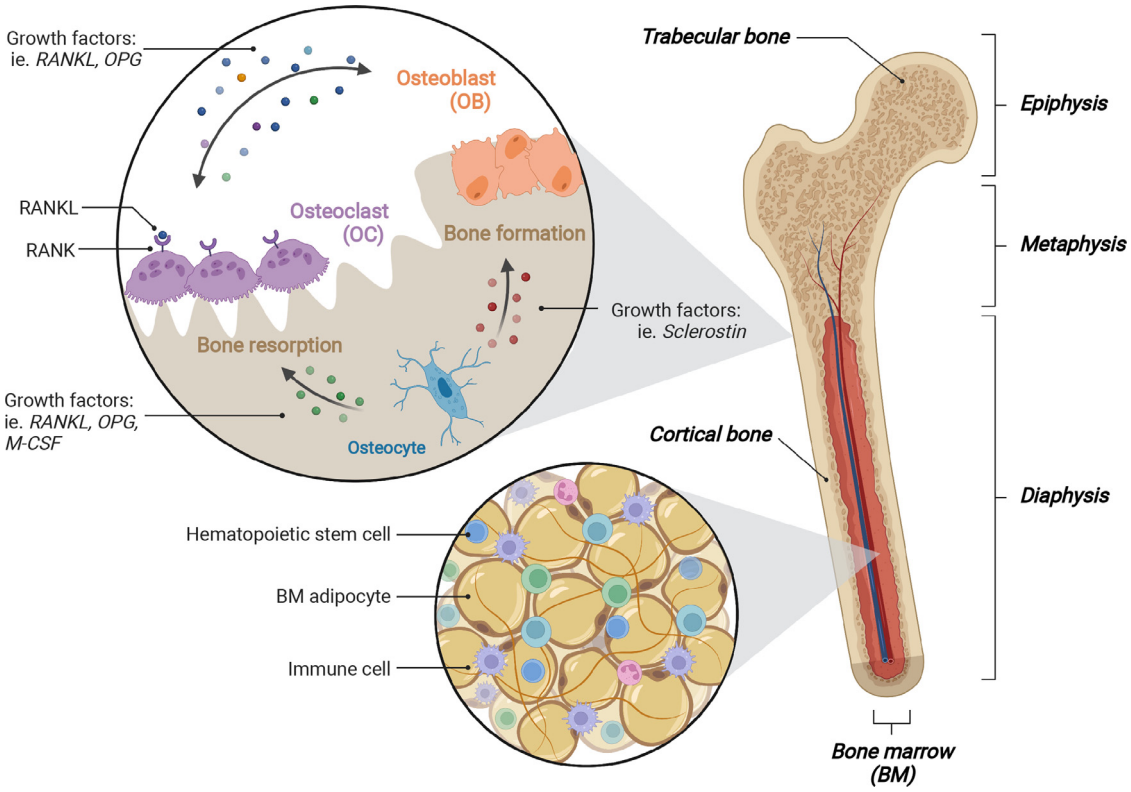

Fig. 1. An integrative perspective of bone anatomy, histology and cellular/molecular components (Created with BioRender.com).

Beyond the involvement of bone as the target for metastatic osteo-tropic tumors, bone tissue is also subjected to the growth of primary tumors that arise directly from cells comprised in the bone milieu. Primary bone cancers have a relatively low incidence in the population and less than 0.2% of all cancers [36]. But in the last decade, their incidence is constantly rising by about 0.3%. Among all, osteosarcoma (35%), chondrosarcoma (30%), and Ewing sarcoma (16%) are the most common forms of potentially malignant primary bone tumors while, the remaining percentage is split between benign bone tumors as osteochondroma, giant cell tumor, osteoblastoma, and others more rare types [37]. They all display a wide heterogeneity in the histologic origin, symptomatology, care treatments, and disease prognosis.

Osteosarcoma is a predominantly malignant bone tumor that mostly affects adolescents. For patients younger than 25 years, the metaphysis of long bones, specifically the distal femur and proximal tibia, is the most common origin site. In this bone portion, characterized by a high cell division rate, the incorporation of mutations leads to the growth of pleomorphic osteoblasts that overproduce osteoid tissue. The progression into metastasis is the major cause of osteosarcoma-related death, both bony and lung metastasis are associated with a drastic reduction in the patient's life expectancy [38].

Benign bone tumors are neoplasia that arises in the bone without the development of a malignant profile. The most frequent one is osteochondroma, representing 30% of all benign tumors. It is a cartilaginous bone tumor that mostly occurs in the distal femur and proximal tibia of men younger than 25 years old. It arises from mutations in the genes coding for exostosis 1 and 2, proteins that have an important role in the synthesis of heparin sulfate, a regulator of the growth plate. This dysregulation in the growing process subsequently leads to the formation of lateral bony projections called exostosis [39]. Another benign tumor is the Giant cell tumor (GCT) marked by a high-risk factor in case of bony trauma or radiation exposure. This tumor represents 20% of all benign tumors and has a higher incidence in people between the ages of 20 to 40. GCT typically originates in the epiphysis area of long bones next to the knee joint where it arises from osteoclast cells developing into multi-nuclei cells (<50), eventually leading to the formation of a lytic cystic lesion [40].

3. Biomaterials for bone tumor defects

Clinical treatments of cancerous bone tumors currently include chemotherapy, radiotherapy, hyperthermia and surgery, which is extended to immunotherapy [41–43]. The natural physiological, enzymatic and physical barriers in the body and wide side effects of conventional chemotherapy drugs on healthy organs have encouraged the researchers to concentrate on developing local drug delivery systems [44]. Different strategies for local cancer therapy based on materials structure and colloidal systems are presented in Fig. 2.

These drug delivery systems are mostly based on micro/nanoparticles loaded with therapeutic agents and drugs which are targeted to the tumor site through chemical (active targeting) or physical (passive targeting) clues [45,46]. The common systemic drugs that are applied as chemotherapeutic agents in osteosarcoma include adriamycin (ADM), doxorubicin (DOX), cisplatin (DDP), methotrexate (MTX), cyclophosphamide (CTX) and epirubicin (EPI) [47]. Adjuvant and co-delivery of different agents have also been studied in addition to these conventional drugs [48,49]. Different nanoparticulate systems based on polymers, metals and ceramics have been designed to deliver these drugs locally to minimize side effects [50–52]. Stimuli-responsive systems offer the on-demand release of the drug which is mostly following a physical cell ablation method [53]. Feedback regulated and rate programmed release systems are other kinds of stimuli-responsive systems which are controlled by biological triggers inside the tumor or the cells [54]. In addition to drug delivery platforms, engi-

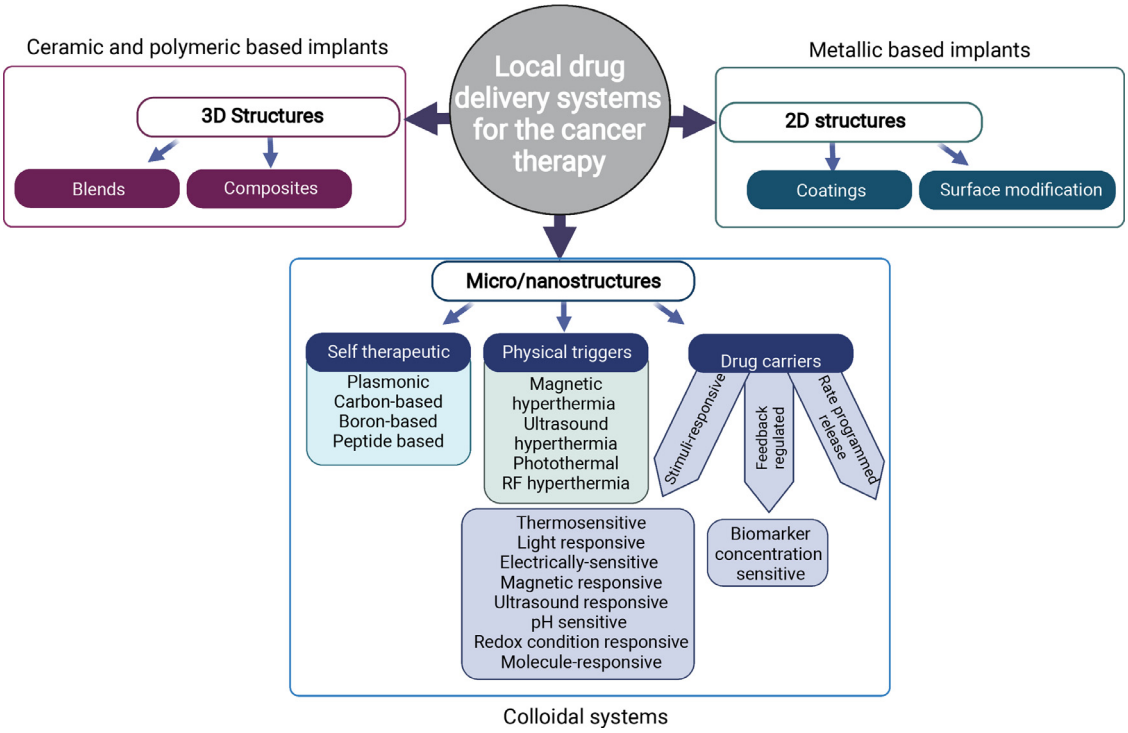

Fig. 2. Local cancer therapy methods are categorized based on materials structure and effective compounds (Created with BioRender.com).

neered micro/nanoparticles were studied as physical mediators for cell ablation.

Alternative magnetic field, ultrasound, radiofrequency and UV-Vis spectra can affect nanoparticles (NPs) with defined physical and morphological properties to induce hyperthermia, photodynamic therapy, and controlled release [55]. Photothermal, magnetic, ultrasound, electro and RF hyperthermia are the methods that take advantage of living cell sensitivity to elevated temperatures. At temperatures higher than 41°C (mild hyperthermia), caspase enzymes get activated and change cellular compartments through proteolysis that eventually ends in cell apoptosis and necrosis [53,56]. For magnetic hyperthermia, the initiators are mostly ferromagnetic and superparamagnetic NPs. Inside an alternative magnetic field, the NPs and also their magnetic spins rotate which provides thermal energy loss [57,58]. For absorbing ultrasound locally and turning it into thermal energy, microbubbles, silica, manganese dioxide, gold, titanium dioxide, carbon nanotubes, Prussian blue, and magnetic NPs were reported as the sonosensitizer [59]. In the case of photothermal therapy, the key is the depth of penetration of UV-Vis wavelength through the human body. In particular, the near-infra-red (NIR) spectrum and specifically 808nm laser showed the highest penetration depth based on the computational and experimental studies [60–62]. Currently, most of the optically responsive platforms are triggered with UV wavelength. This has encouraged the application of upconversion NPs in biomaterial-cell interfaces. These NPs are able to convert NIR light to UV or visible light to address the limitations of low penetrating ability and efficiency [61,63]. All these NPs can also be used as imaging contrast agents and to deliver drug cargo as a multifunctional platform [64]. Of note, the immunogenic cell death induced by photothermal therapy using nanoparticles overcome limitations of radiotherapy and chemotherapy including tumor recurrence [65]. A representative work by Xiaogang Qu et al. showed that nanoscale GO carrier functionalized with PEG-PEI co-polymer (GO- PEG-PEI) to deliver adjuvant CpG ODNs increased the production of pro-inflammatory cytokines and enhanced the immunostimulatory effect of CpG under near-infrared (NIR) laser irradiation [66]. In fact, by exploiting the physiological processes underlying the natural anti-tumoral activity of the immune system, it is possible to create long-term immunity from tumor recurrence.

Besides, some nanoparticles based on gold, carbon, boron, and engineered peptides have shown selective toxicity for cancer cells through specific accumulation in subcellular compartments [67]. Chen et al. studied the effect of gold nanorods on some cell lines and compared it with healthy epithelial cells. They explained the cancer-selective targeting and toxicity of these NPs based on the fate of the NPs after endocytosis. The NPs have escaped the lysosomes in cancer cell lines and accumulated in the mitochondria, while in the healthy cells, the lysosomal membrane was intact and the cell could eradicate the NPs [68]. Carbon-based materials were conventionally explored as imaging and drug delivery agent [69]. In the last decade, several studies showed the anti-cancer properties of these materials with a focus on their intracellular activity and mechanism of action. It was shown that carbon-based structures are able to accumulate in the nucleus of the cell and inhibit the proliferation and migration of the cells [70]. Boron-based materials also were reported as hydrolytic enzymes and intracellular calcium signal inhibitors which can suppress the normal function of cancer cells [71]. In case of the engineered peptides, the main studied feature was binding ability into cell membrane that provides active targeting of the drug carriers. However, peptides showed to be cytotoxic through different mechanisms such as membrane disruption, angiogenesis inhibition, immune regulation, and disruption of cell signaling pathways that end to apoptosis [72].

Despite broad research on colloidal systems, there are some disadvantages in using them that need to be addressed. The main challenges are first low targeting efficiency of solid tumors and second the physiological barriers which prevent the performance of the designed colloid [73]. For being efficient, NPs need to be penetrated into the tumors and also be taken up by cells. However, it is impossible to promote these two phenomena simultaneously.

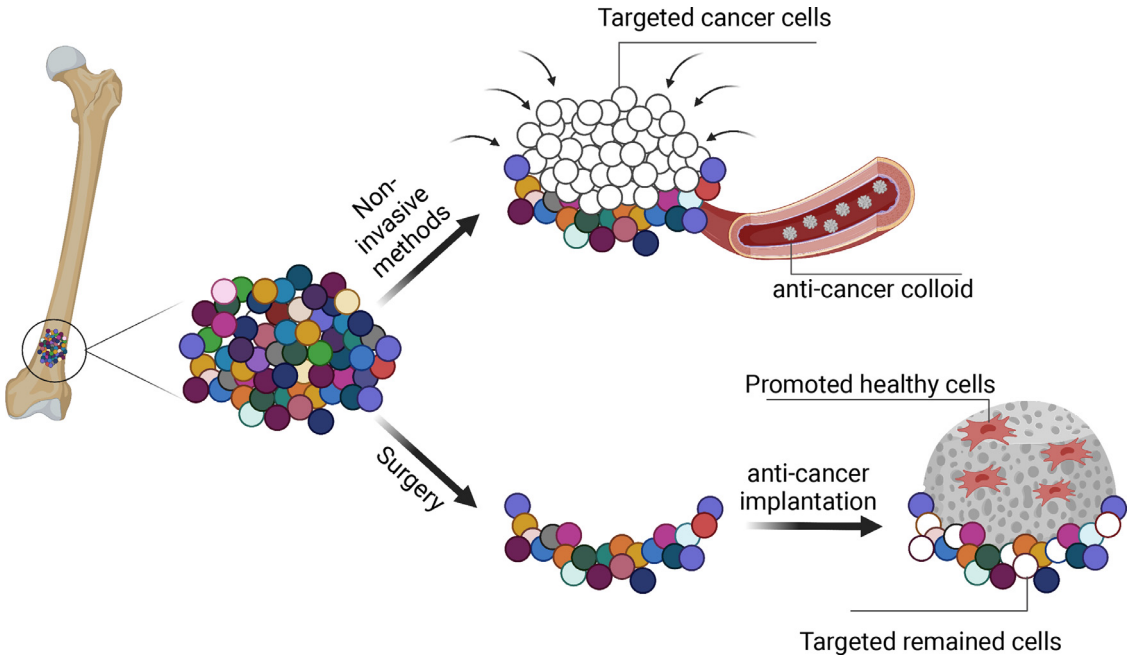

Fig. 3. Schematic explaining two categories of invasive (surgery) and non-invasive methods for local cancer therapy (Created with BioRender.com).

Tumor accumulation and cellular uptake of NPs depend on various parameters such as size, morphology and surface charge of NPs, as well as tumor permeability and lymphatic drainage in the targeted tissue [73,74]. Reducing particle size leads to higher Clathrin-Mediated Endocytosis (CME), and Caveolin-Mediated Endocytosis (CvME) as the main pinocytosis pathways [75]. Moreover, spherical positively charged NPs showed the highest increase in tumor penetration and cellular uptake when it comes to the surface charge and morphology of NPs [74,76]. However, this advantage comes with the> low accumulation efficacy of the NPs in the tumor site [73]. Low permeability and protein corona are also the main physiological barriers that eliminate the performance of colloidal systems, specifically at nanoscale [77,78]. For example, protein corona changes the surface microstructure, diffusion coefficient and hydrodynamic diameter of NPs which dictate the properties of the colloidal system [79]. To overcome these complexities, researchers started embedding organic and inorganic anti-cancer reagents in 3D-printed implants, which can also be used to regenerate the lost tissue [80]. It is noteworthy that in the case of non-cancerous tumors, the anti-cancer drugs can be replaced with suitable alternatives. These implantable 3D structures can also reduce surgery invasiveness. In fact, when targeted colloids are used, a part of cancerous cells remained, while anticancer implants lead to a higher efficiency of local cell removal (Fig. 3).

Currently, the resection of the tumor includes the whole surrounding limb and tissue, which is known as limb-sparing surgery [81]. In complex cases, this surgery might be replaced with amputation, which is even more invasive [82]. Filling the sectioned area with an anti-cancer implant would provide many advantages. First, it can target the remaining cancer cells; as there is a hypothesis that the remained cancerous cells are more prone to metastasis after surgery, targeting remained cells locally right after surgery would eliminate metastasis chance [83]. Second, removing the surrounding healthy tissue is not needed anymore. Third, it will minimize the impact of surgeons' skills on the final results. Fourth, it will provide suitable mechanical properties to support the normal function of the tissue; in fact, mechanical support is a substantial concern after tumor resection in the load-bearing bones [84]. Last but not least, assisting in the regeneration of the tissue by implanting porous degradable implants which refer to combining cancer therapy and tissue engineering concept [85].

As we mentioned before, there are three general groups of anti-cancer implants with metallic, ceramic and polymeric backbones. Metallic bone implants are currently used as permanent and temporary fixator biomaterials to provide mechanical stability and attachment to the surrounding tissue [86]. Among various metallic elements and alloys, titanium (Ti), titanium-based alloys and stainless steel are commonly applied as orthopedic implants [87]. Since they are bioinert, different surface modification and coating strategies have been used to load therapeutic agents and depot them in the vicinity of implants [88]. Mg-based alloys as biodegradable implants have been receiving significant attention during past years. Once they are degraded, Mg ions and hydroxide ions will be released and led to an alkaline environment [89]. In fact, the high concentrations of these elements cause the cancer cells apoptosis, however it is also essential to adjust the degradation rate of these implants with respect to the bone regeneration for reconstruction of bone tumor defects [90]. Anti-cancer agents and drugs can be loaded on the surface through physical or chemical interactions. The anti-cancer coatings on the metallic implants mostly tried to encapsulate drugs (curcumin, DOX, etc) and inorganic agents to release cytotoxic ions (Selenium, Samarium, etc) [91]. Tran et al. decorated Ti surface with selenium nanoclusters through *in situ* reduction and nucleation. This study found a critical dose range of selenium coatings that inhibits cancerous osteoblast function, while still promoting healthy osteoblast function [92]. Murugan et al. also showed that rose flower-like Se-Mn hydroxyapatite coating on AZ91 Mg alloy could selectively target cancer cells [93]. Guo et al. used electrostatically self-assembled polyelectrolytes of hyaluronic acid, methylated collagen, and terpolymer (HEMA-MMA-MAA) coating on the surface of porous tantalum as a drug delivery system for sustained release of DOX [94]. Jing et al. also loaded cisplatin into 3D-printed titanium alloy implants using a thermosensitive hydrogel to control the drug release [95]. The released drug selectively targeted osteosarcoma cell lines without any effect on the healthy cells.

Kannan et al. tried an alternative approach by surface modification of implant through anodizing followed by loading Samarium

oxide into the nanotubular structure. In addition to corrosion resistance, it was estimated that Sm^{3+} ions could eradicate cancer cells by 95% efficiency while supporting the apatite formation [96]. Overall, the same strategy with drugs has been used to control the diffusion and release profile [97–99]. By studying the selective effect of chemicals on cancerous cells, Sarkar et al. showed a synergistic effect of curcumin and vitamin K2 that led to enhanced osseointegration on Ti implants, while the same combination reduced MG-63 cancer cells [100].

With the tissue engineering approach, a biodegradable porous structure is needed to support the attachment and proliferation of the cells in 3D [101]. In addition to the biodegradable alloys, polymers and ceramics could fulfill this requirement. In comparison, polymers are more flexible than ceramics. Polymer-ceramic composites take advantage of both phases by tuned mechanical properties and osteoconductivity [22]. Polymeric and polymer-based composite scaffolds were used to deliver anti-cancer drugs, ions, biomolecules, self-therapeutic and gene therapeutic nanoparticles and sensitizers [102–105]. For example, cyclodextrin siRNA NPs were embedded in collagen scaffolds as a composite for controlled release and targeting prostate cancer bone metastases by knocking down the cancer cells genetically [105]. Natural and synthetic polymeric scaffolds were developed in the form of hydrogels, fibers and 3D printed porous structures. Although synthetic polymers provide appropriate mechanical properties, they are mostly hydrophobic and not promoting cell attachment. In contrast, natural polymers are mechanically weak but promote cell attachment and provide higher biodegradation rate [106]. Therefore, the combination of natural and synthetic polymers has received much attention in biomedical applications [107]. The regular fabrication methods include gel injection, electrospinning, lyophilization, salt-leaching, supercritical foaming, and phase transformation [108–118]. To mention some recent smart scaffolds, Shi et al. demonstrated 3D-printed poly(lactic-co-glycolic acid), gelatin, and chitosan scaffold as pH-sensitive scaffolds made by an electrohydrodynamic jet 3D printer. Released 5-fluorouracil and DOX showed hemostatic function to prevent breast cancer recurrence *in vitro* and *in vivo* [119]. Liu et al. in another study showed the use of 3D printed NIR-responsive (photothermal) hydrogel/PCL core/shell fiber scaffolds to combine cancer therapy and wound healing applications. They loaded DOX and coated the scaffolds with a layer of polydopamine that could provide photothermal properties *in vitro* and *in vivo* [120]. He et al. loaded an immune adjuvant (R837) and niobium carbide (Nb_2C) MXene in a 3D-printed biodegradable scaffold to effectively treat bone metastasis of breast cancer. They basically showed that the designed scaffold could target primary tumors, activate the immune response, prevent long-term immunological memory and eventually suppress in *in vivo* murine models [121]. Importantly, more than 120 studies have confirmed the importance of targeting the tumor microenvironment to overcome the poor outcomes observed when employing immune checkpoint inhibitors. Interestingly, the infiltration of many immune cells is detected in the tumor microenvironment, and a high count of TAMs has been reported to facilitate cancer progression, angiogenesis and metastasis. To this end, drug-loaded nanoparticles can be used to modulate TAM phenotype and functions (i.e., M1-like vs M2-like) to prevent TAM-mediated tumor growth and immune-escape [122,123]. Thus, modulating TAM functions can greatly impact tumor development by impeding tumor-mediated angiogenesis and enhancing cytotoxic T lymphocytes and natural killer anti-tumoral activity [123]. In particular, TAMs consume key metabolites (arginine, cysteine, and tryptophan) needed to induce effector T cell proliferation, thus inhibitors of tryptophan metabolism, together with inhibitors of the immune checkpoints, have been loaded into nanoparticles and their release was triggered by both the acidic pH of the tumor surroundings and the presence of matrix metalloproteinase (MMPs), which are common features of the tumor microenvironment [124]. Of note, M2 macrophages are also key players in the bone biomaterial response, and they were noted to release cytokine and soluble factors resulting in the recruitment and osteogenic differentiation of hMSCs leading to augmented bone deposition *in vitro* and *in vivo* [125]. In fact, osteoimmunomodulatory calcium phosphates with sub-micron surface topography that promote macrophage polarization towards the M2 phenotype have shown better performances in inducing bone deposition. Hence, macrophages presented in the tumor microenvironment represent a valid target to accomplish both tumor elimination and bone regeneration.

Ceramic implants such as hydroxyapatite were also loaded with anti-cancer drugs such as methotrexate, 5-fluorouracil and cisplatin in some cases to overcome cancerous cells in hard tissue [126]. In other cases, the cytotoxic effect of doped ions was determined in cancer therapy [127]. The number of reports using ceramic-based implants is limited because of brittle fractures during compression [96]. In contrast, ceramic-polymer implants could provide suitable mechanical stability, biological properties and manufacturability. Li et al. fabricated a wireless piezoelectric ceramic through a polarization process [127]. Selenium doped potassium–sodium niobate (KNNSe) scaffolds were used to combine electrotherapy and chemotherapy methods. *In vitro* studies showed that the scaffolds could induce mitochondrial damage and apoptosis in osteosarcoma cells [127]. Although various fabrication methods of anti-cancer implants have been reported, filling the irregular voids needs injectable or personalized fillers. As the injectable fillers can't provide the required mechanical properties in load-bearing applications, it is crucial to focus on additively manufactured patient-specific implants. In Section 4, the additively manufactured ceramic scaffolds with a dual application of anti-cancer and bone regeneration will be reviewed and discussed. Table 1 summarizes some reported research on anti-cancer implants and scaffolds. Besides preventing cancer metastasis and tumor recurrence, bone regeneration is a crucial application of bifunctional scaffolds that are designed to fill the voids formed after tumor resection. Ceramic biomaterials are characterized by similar chemical properties to the mineral phase of bone and a high Young's Modulus, conferring high mechanical stiffness and low elasticity [128]. A vast range of ceramics is present on the market and has found applications in the field of orthopedics. Calcium sulfate, calcium phosphate (CaP) ceramics, CaP cements, bioactive glass (BG) or combinations are commonly used as synthetic bone substitutes [128]. Bioactive ceramic/glass has received the highest attention in this case due to higher osteointegration which prevents fibrous encapsulation of the implant [129]. Ceramic and glasses can be fabricated as a biodegradable implant which facilitates a controlled release of therapeutic metal ions to promote bone regeneration/integration and induce cancer cell apoptosis [130].

4. Additively manufactured Bi-functionalized ceramics

4.1. Bioactive ceramics

Bioactive ceramics has received great attention in the field of bone regeneration as they promote hydroxyapatite deposition, cell attachment and differentiation. To apply 3D-printed ceramic structures for simultaneous anti-cancer and bone-forming application, two approaches have been followed so far; First using engineered ceramic structures and second ceramic composites. The later will be discussed in 4.2 but the former was mostly modified with three approaches: (1) ion doping, (2) surface treatment with photo-magnetothermal agents, and 3) drug loading to induce tumor ablation.

Table 1
Implantable biomaterials with anti-cancer properties to refill the void caused by tumor removal.

Category	Type	Basic implant	Anti-cancer agent	Mechanism of action	Fabrication method	Ref.
Metal	Coating	Ti alloys Mg alloys Ta alloys Stainless steel	Toxic ions (Selenium, etc) Anticancer drugs (DOX, Curcumin, etc)	Self-therapeutic Drug/ion delivery	Precipitation Solution casting	[91–94,96,100] [95]
	Surface modification	Anodized Ti and Mg alloys	TNF-related apoptosis-inducing ligand (TRAIL) Toxic ions (Samarium, etc) DOX	Self-therapeutic Drug/ion delivery	3D printing and Anodization of Ti Electrophoretic Deposition	[97–99]
Polymer	Gel	Collagen PLGA RADA-KLA peptide	Tannic acid 2-methoxyestradiol (2-ME) RADA-KLA peptide	Self-therapeutic Drug delivery	Casting Solvent extrusion	[102,131,132]
	Fiber	PMMA- PVP poly (l-lactic acid-co-ε-caprolactone) (PLACL) Polycaprolactone (PCL) Poly(N-isopropylacrylamide-co-acrylamide-co-vinylpyrrolidone) P(NIPAAM-AAm-VP)	Released oxygen Magnesium oxide (MgO) nanoparticles Curcumin Trametinib Graphene oxide (GO) Doxorubicin (DOX)	Self-therapeutic Drug/ion/nanoparticle Photothermal	Electrospinning	[67,103,133–135]
	Foam	PLGA Gelatin Poly-L-lysine Silk fibroin Chitosan PCL	Fe powder DOX Doxorubicin-Black phosphorus Iron oxide (Fe_3O_4) Polydopamine nanoparticles Polyphenols 5-fluorouracil Emodin Gene therapeutic nanaoparticles Gold nanoparticles Gambogic acid (GA) MOS_2	Self-therapeutic Drug/ion delivery Magnetic hyperthermia Photothermal	Colloid to be injected Lyophilization Salt-leaching Supercritical CO_2 foaming Phase transformation in oleosol	[108–118] [105]
	3D printed	PLGA Polyetheretherketone (PEEK) Glginate-gelatin@ PCL Dopamine-modified alginate and polydopamine (PDA)	5-fluorouracil DOX Cisplatin Polydopamine Immune adjuvant (R837)-niobium carbide (Nb2C) MXene Cu, Fe, Mn, Co dopant elements	Self-therapeutic Drug/ion delivery photothermal Immunotherapy	E-jet 3D printing Melt electrowriting Solution-based extrusion	[104,119–121,136–139]
Ceramic	Foam	Calcium phosphate Potassium-sodium niobate (KNN) Hydroxyapatite	Methotrexate 5-Fluorouracil Cisplatin Selenium	Self-therapeutic Drug/ion delivery	Powder sintering and drug absorption	[126,127,140]
	3D printed	Will be discussed in Section 4.				

Liu et al. doped 5% of Cu, Fe, Mn and Co as transition metals in bioactive glass ceramics (BGC) to add the photothermal property to the 3D printed ceramic implants [139]. Their results showed the trend of 5Cu-BGC > 5Fe-BGC > 5Mn-BGC > 5Co-BGC regarding the photothermal performance by exposing NIR (808 nm). Using power density of 0.3 W/cm^2, the maximum temperature in wet state was 52 (5Cu-BGC), 47 (5Fe-BGC), 45 (5Mn-BGC) and 44 °C (5Co-BGC) [139]. Besides, scaffolds containing Fe and Mn showed promoted bone formation [139]. Wu et al. developed 3D printed β-tricalcium phosphate (β-TCP) scaffolds using PVA as the binder and then modified them with graphene oxide (GO) [141]. In this regard, the scaffolds were soaked in GO suspension after sintering. The provided platform showed excellent photothermal effect with exposure of 808 nm laser which suppressed cancer cell proliferation and promoted tumor ablation. Besides, GO could promote osteogenesis due to its active groups and high protein absorption [141]. In another study, Wang et al. used molybdenum disulfide (MoS_2) nanosheets as the photothermal agent [142]. They 3D printed the ceramic scaffold with a similar method and then precipitated MoS_2 by hydrothermal method. Although these scaffolds showed high photothermal yield, they acted bioinert regarding bone regeneration issue [142]. Zhuang et al. added ferric element to akermanite (AKT) bioceramics to add NIR photo/magnetothermal property. Fe-doped scaffolds not only reduced cancer cell viability but also could increase osteogenesis *in vitro* [143]. This group in another study post treated 3D printed AKT scaffolds with ferromagnetic Fe_3S_4 layers to provide magnetic hyperthermia performance [144].

Wang et al. used black akermanite which was made by a magnesiothermic reduction process on akermanite [145]. They showed this agent could enhance the photothermal effect compared to akermanite itself. As a novel alternative photothermal agent, Dang et al. synthesized Cu-TCPP metal-organic framework on tricalcium phosphate (TCP) through solvothermal method [146]. Tumor ablation and increased osteogenesis were established *in vitro* and *in vivo*. Ma et al. used Cu-doped mesoporous silica to add photothermal therapy function to 3D printed TCP and could show

bifunctionality of the prepared scaffolds *in vitro* [147]. Following the same purpose, Fu et al. also synthesized photothermal 3D printed carbon/ larnite scaffolds with high temperature treatment of printed silicone resin /$CaCO_3$ [148]. Yin et al. loaded Nb_2C MXene into 3D printed bioactive glass scaffolds and showed these nanosheets provide NIR photothermal property. Released Nb also could promote neogenesis and blood vessel penetration in the defect site [149]. Xiang et al. in another work developed a new photothermal agent known as NIR-absorbing cocrystal (DTC) by using two small molecules of dibenzotetrathiafulvalene (DBTTF) and tetracyanobenzene (TCB) as the electron donor and acceptor, respectively [150]. They post-loaded 3D printed bioactive glass scaffolds with the mentioned agent and consequently showed the bifunctionality of the designed platform. He et al. also decorated 3D printed CaPCu with ancient pigment Egyptian blue and showed it increased NIR photothermal performance [151]. Ma et al. synthesized Nagel bioceramic powders ($Ca_7Si_2P_2O_{16}$) by a sol-gel method. To print the ceramic scaffolds, the ink was prepared by mixing bioceramic powder with sodium alginate powder and pluronic F-127 aqueous solution [85]. After extrusion printing, the samples were sintered to obtain pure bioceramic scaffolds. They applied a coating of polydopamine on the surface of ceramic scaffolds to provide photothermal properties and successfully inhibited tumor growth in mice while promoting attachment and proliferation of healthy cells [85]. Dang et al. also 3D printed bioactive glass scaffolds with a similar method [152]. They decorated the scaffold with $CuFeSe_2$ nanocrystals using the solvothermal method. Triggering $CuFeSe_2$ with 808 nm laser, showed photothermal properties that ablated cancer cells after short-term use, while the bioactive glass promoted bone regeneration [152]. They later loaded DOX and hemin particles on 3D printed SiO_2-$CaSiO_3$-$Ca_3(PO_4)_3$ bioactive glass scaffolds [153]. With a very similar method, they synthesized BGC through the sol-gel method and then printed the ink including pluronic F-127. During the sintering procedure, the binder polymer was burned and single particles fused to each other. To load the therapeutic reagents, they dissolved and distributed DOX and hemin particles in Poly (DL-lactide) (PDLLA) solution, respectively. This composite was applied on the surface of 3D printed scaffolds using the deep coating method. The optimum concentrations of DOX and hemin provided an effective combination of NIR (808 nm) photothermal therapy and chemotherapy to suppress tumor growth *in vivo* [153]. However, the effect of scaffolds on bone regeneration was not studied. They also loaded TiN microparticles mixed with DOX through the same method and showed that TiN can also provide excellent photothermal properties [154]. With a similar method, Wu et al. loaded 5-FU using Soluplus (SOL) and polyethylene glycol (PEG) as the carrier [137]. They showed the entire loaded drug was released *in vitro* and eradicated the cancer cells.

In addition to the conventional chemotherapeutic agents, other reactive chemical such as estrogens were delivered using 3D printed ceramic scaffolds. Estrogens including isoflavones have shown anti-carcinogenesis properties, as well as osteogenesis in both men and women. One of the suggested mechanisms of its action is targeting the receptor activator of NF-κB ligand (RANKL) expression in bone lining cells [155]. Sarkar et al. loaded genistein, daidzein, and glycitein onto a TCP scaffold fabricated with a binder jetting technique [156]. A sustained release was achieved due to the controlled pore size and led to *in vitro* cancer cell apoptosis, bone cell proliferation and immune-modulatory activity. To sum up, the developed ceramic scaffolds with anti-cancer and bone regeneration applications are taking advantage of NIR photothermal therapy. The main advantage of photothermal/magnetotherapy over chemo/radiotherapy is the selectivity to target tumor cells without damaging healthy tissue in the surrounding area [4]. Table 2 summarized some of the published researches in this area.

To sum up, among all the discussed bioactive ceramics, TCP-based bioceramics were the most common 3D printed ones for dual application of cancer therapy and bone regeneration. Furthermore, surface treatment of bioceramics namely with photo-magnetothermal agents provided anti-cancer properties. Interestingly, doping inorganic elements with bioceramics rendered photothermal properties due to high penetration of NIR through the body. Not surprisingly, the combination of chemotherapy with physical methods such as photothermal and magnetic hyperthermia is the major current trend aiming to increase the efficacy of cancer therapy.

4.2. Novel ceramic-based composites

Abundant research on bioceramics has led to a shift from the use of bioinert ceramics to the third generation of printable bioceramics capable of promoting bone regeneration [22]. Bioceramics can be used either alone, or as composites in combination with other polymers or NPs to improve their properties or to gain additional functionalities [22]. Composite bioceramics, or hybrids, showed increased mechanical and bone-forming properties than bioceramics alone, hence the focus is now on the discovery of the most suitable combinations to obtain a bone implant with desired properties and bioactivity [157–160]. Many strategies for bi-functionalization of 3D-printed bioceramics have been explored during past years.

Among them, hybrids of hydroxyapatite (HA) including chitosan/HA, collagen/HA, and nano-HA/Coll/Alg have been shown to promote increased bone precursor cell adhesion, proliferation, and differentiation than either material alone [161–163]. Developing platforms to allow the easy and rapid printing of these systems, along with discovering new bioprintable and bioactive materials, is highly needed to successfully employ these materials as patient-specific bone implants [164]. Interestingly, bioceramics coated with soy isoflavones displayed increased bone-forming, anti-inflammatory, and anti-tumoral properties, and promoted the attachment, proliferation, and differentiation of bone cells [156]. This study remarks on how multifunction bioceramics represent an ideal therapeutic protocol for bone tumor therapy and reconstruction following resection.

Composite materials harvesting regenerative properties can be used as drug delivery systems to dispense anti-tumor drugs locally, which aims to accomplish tumor ablation and bone regeneration simultaneously [4,158,165–167]. Collagen/HA composites are acquiring increased attention since collagen can efficiently incorporate and release a wide variety of drugs, analgesics, cytostatics, vitamins, bisphosphonates, antibiotics, and complex systems [105,168]. A porous nano-HA/collagen composite loaded with adriamycin (ADM)-encapsulated poly(lactic-co-glycolic acid) (PLGA) microspheres has been investigated for the treatment of osteosarcoma. Upon implantation in rats, the release of ADM-PLGA microspheres (17,6% of the load in 24h) showed effective local tumor killing (3-to-5-fold reduction in tumor size), while the nano-HA/collagen composite promoted augmented regeneration by end of 12 weeks post-implantation with no adverse immune reactions noted [21]. This composite was able to release ADM continuously for 28 days. Furthermore, a $CaCo_3$/Collagen-I composite loaded with CeO_2 NPs and DOX was able to induce 100% of osteosarcoma cell death [167]. However, a study investigating 3D-printed PLA/nHA composites revealed that the incorporation of growth factors and proteins directly on the materials is lacking due to the high temperatures of FDM printing, hence the fabrication of these hybrids at low temperatures is recommended [159]

Besides being loaded with anti-tumoral drugs, pro-osteogenic bioceramics can also be functionalized with photocatalysts to carry out photothermal/magnetothermal therapy [139,141,169]. An in-

Table 2
3D printed scaffolds with anti-cancer properties to fill the void caused by tumor removal.

Type	Basic implant	Anti-cancer agent	Mechanism of action	Fabrication method	Regeneration function	Ref.
Doped	Bioactive glass ceramics (BGC)	Cu, Fe, Mn and Co	Photothermal therapy	Extrusion 3D printing+ post sintering	Osteogenesis by Fe and Mn	[139]
	Akermanite (AKT)	Fe	Photothermal therapy	Extrusion 3D printing+ post sintering	Osteogenesis	[143]
Post-treated	β-tricalcium phosphate (β-TCP)	GO	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Osteogenesis	[141]
	AKT	Molybdenum disulfide (MoS_2) nanosheets	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Bioinert	[142]
	AKT	Ferromagnetic Fe_3S_4	Magnetic hyperthermia therapy	Extrusion 3D printing+ post sintering +hydrothermal	Osteogenesis	[85]
	Black AKT	Color centers formed due to oxygen vacancies	Photothermal therapy	Extrusion 3D printing+ post sintering +calcination in magnesium powder	Osteogenesis	[145]
	Tricalcium phosphate (β-TCP)	Cu-TCPP metal-organic	Photothermal therapy	Extrusion 3D printing+ post sintering +solvothermal	Osteogenesis	[146]
	Tricalcium phosphate (β-TCP)	Cu doped mesoporous silica	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Osteogenesis	[88]
	Carbon/ larnite	Carbon	Photothermal therapy	Extrusion 3D printing+ post heat treatment	Osteogenesis	[148]
	Bioactive glass	Nb_2C MXene	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Neogenesis and blood vessels penetration	[149]
	Bioactive glass	NIR-absorbing cocrystal (DTC)	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Osteogenesis	[150]
	CaPCu	Ancient pigment Egyptian blue	Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Osteogenesis	[151]
	Nagel bioceramic powders ($Ca_7Si_2P_2O_{16}$)	polydopamine	Photothermal therapy	Extrusion 3D printing+ post sintering +*in-situ* reaction	Osteogenesis	[85]
	Bioactive glass	$CuFeSe_2$	Photothermal therapy	Extrusion 3D printing+ post sintering +solvothermal	Osteogenesis	[152]
Drug loaded	Bioactive glass	DOX and hemin particles	Chemo and Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Possible osteogenesis (not investigated)	[153]
	Bioactive glass	DOX and TiN particles	Chemo and Photothermal therapy	Extrusion 3D printing+ post sintering +deep coating	Osteogenesis	[154]
	Calcium phosphate cement (CPC)	5-FU	Chemotherapy	Extrusion 3D printing+ post sintering +deep coating	Possible osteogenesis (not investigated)	[137]
	Tricalcium phosphate (β-TCP)	Genistein, daidzein, and glycitein	Chemotherapy	binder jetting technique	Modulated neutrophil	[156]

novative composite scaffold of PLGA/Mg obtained through 3D-printing at low temperature was developed for photothermal treatment of post-surgical osteosarcoma patients [170]. Moreover, a 3D-printed multifunctional hybrid consisting of Graphene Oxidized (GO) and β-TCP (GO/β-TCP) could prevent osteosarcoma cell growth both *in vivo* (80% of tumor cell necrosis) and *in vitro* (90% reduction in osteosarcoma cell viability) upon laser irradiation while stimulating increased bone formation compared to β-TCP scaffolds after 8 weeks (15 vs 30% new bone area respectively) [141]. Another temperature-controlled 3D system based on nano-hydroxyapatite/graphene oxide/chitosan (nHA/GO/CS) was able to eliminate osteosarcoma cells and promote osteogenesis in MSCs upon NIR irradiation [171]. Finally, a new Ti_6Al_4V-based hybrid was fabricated for the first time by combining multiple 3D-printing techniques and incorporating drug-laden Gel/HA nanocomposites. It displayed several advantages including tailed mechanical properties to the bone, ideal microstructure for drug release, and localized phototherapy [169].

Aside from photothermal therapy, magnetothermal treatment can also be used to eliminate tumor cells and promote bone regeneration. Zhang et al. developed a magnetic bone graft consisting of β-TCP–Fe–GO which displayed superior magnetothermal properties compared to Fe_3O_4 NPs coated on the surface of the scaffold [172]. However, Shuai et al. developed a polyglycolic acid (PGA)/Fe_3O_4 composite scaffold which rearranges upon irradiation with an external static magnetic field to promote cell adhesion, proliferation, and bone formation while eliminating tumor cells [173]. Moreover, Fe_3S_4 layers were constructed on the surface of AKT scaffolds obtained through 3D printing and induced tumor killing by releasing H_2O_2, magnetothermal therapy (MTT), and chemodynamic therapy (CDT) thus eliciting both magneto-thermic and chemotherapeutic functions [174].

Bioactive glasses (BGs) have also been used to deliver anti-tumoral agents locally and promote the regeneration of the missing bone. BG scaffolds fabricated through 3D printing and soaked in 2D black phosphorus (BP) to obtain BG-BP showed relevant photothermal properties both *in vivo* and *in vitro*, and the elimination of residual tumor cells upon implantation and NIR laser irradiation was observed [175]. A 3.7-fold increase in osteogenesis at week 6 was also observed in BP-BG groups. Another BG ceramic element-doped and 3D-printed (5Cu-BGC, 5Fe-BGC, and 5Mn-BGC) demonstrated osteogenic differentiation accompanied by photothermal tumor elimination *in vivo* [139]. Moreover, copper-based photothermal agents show several advantages including low costs, tunable size, high absorption of NIR, photostability, and easy fabrication [176]. Aside from silicate bioglasses, borosilicates have also been

used as regenerative biomaterials. Borosilicates consist of silica with at least 13% of Boron trioxide. They are resistant to thermal expansion and degradation making them suitable candidates for 3D printing. The regenerative Cu- and Mn-doped borosilicate nanoparticles and a combination of MoS_2 nanosheets with 3D printed bioactive borosilicate glass scaffolds were used to accomplish the elimination of tumors while enhancing bone formation [177,178]. The advantage of using these nanoparticles resides in their tunable degradation by adjusting the ratio of $[SiO_4]/[BO_3]$ while incorporating ions to promote tumor elimination and bone regeneration. Moreover, borosilicate BGs exhibited optimal photothermal properties under 808 nm excitation, and by fixing the MoS_2-PLGA film on its surface it was possible to reduce possible side effects due to released Mo.

Other than responding to external cues such as laser irradiation, bioceramics composites have also been designed to promote bone cancer elimination and regeneration in response to internal stimuli including pH levels, antigens, proteins, ions, and bacteria [179]. Lectin-conjugated pH-responsive mesoporous silica NPs (MSNs) for targeted bone cancer treatment have been developed to treat breast cancer bone metastases. MSNs have shown accelerated bone regeneration and augmented drug bioavailability at the local site. In fact DOX-loaded MSNs showed an 8-fold increase in drug accumulation at the tumor site [180,181]. Moreover, MSNs can be functionalized with a wide variety of 1) polymers including poly (l-lactic acid)/poly (ε-caprolactone), polylysine-modified polyethylenimine, poly (lactic-co-glycolic acid), and poly (citrate-siloxane); or 2) biological polymers like alginate, chitosan, and gelatine; or 3) drugs/osteogenic factors including antibiotics, BMP-2, and DEX to promote bone regeneration [182]. Functionalized MSNs have been designed to respond to a plethora of stimuli (temperature, pH, light, redox potential, and enzymes), making them among the most suitable candidates for a controlled release of drugs in bone cancer therapy and reconstruction [180,182,183].

Although additive manufacturing technologies have been proven as an essential tool to create patient-specific implants, minimally invasive injectable bone grafts are also a promising solution to fill bone defects and carry out bone tumor therapy. In fact, a recently developed injectable composite hydrogel based on carbon particles for photothermal therapy of bone cancer and regeneration induced the ablation of tumor cells and the formation of new bone *in vivo* [184]. Another injectable hydrogel incorporating graphene was fabricated in one step and used to fill bone voids and elicit photothermal therapy. Through this fabrication method, it was possible to develop *in situ* polymerizing GO-hydrogel composites to form a 3D network in the defect [185]. However, the biocompatibility and toxicity of graphene are still controversial [186,187]. Of note, these hydrogels can also be used as thermal-triggered drug delivery systems [186]. A chitosan-modified chemically reduced GO (CrGO) incorporated into a thermo-sensitive nanogel (CGN) showed high loading capacity and was able to release DOX upon NIR irradiation [188]. Moreover, a methacrylate-modified gelatin (GelMA)/HA-DA hydrogel consisting of β-cyclodextrin (βCD)-functionalized GO and BNN6 was used to prevent bacterial growth, and promote collagen deposition, angiogenesis, and wound healing [189]. Finally, GO-loaded CS hydrogel (CS/rGO) was fabricated through electrodeposition and loaded with a photocatalyst. Upon NIR irradiation, photothermal conversion was achieved and bone regeneration was observed ($19.68 \pm 3.38\%$ increase in bone formation) [190].

In conclusion, organic nanocarriers represent valid drug delivery systems for local therapy, but they lack mechanical properties and show a high degree of degradation following injection [46,191,192]. Innovative composite ceramics functionalized with organic nanocarriers have been shown to increase the local bioavailability of the drug and possess adequate biomechanical properties for bone implantation and loco-regional administration. Further modifications of composite materials with elements that catalyze photothermal/magnetothermal therapy allowed the development of ceramic-based composites. Such composites that elicit multiple functions make them among the most suitable candidates to treat bone cancer and promote bone regeneration. However, more investigations are needed to tune their physicochemical mechanical properties to consent to their application as injectable systems. Pioneering works in injectable composite hydrogels have demonstrated relevant mechanical properties to support bone formation and an augmented accumulation of drugs locally via *in situ* polymerization. Hence, further research into these systems could enable the development of composite hydrogels capable of eliminating tumor cells and promoting bone regeneration through a minimally invasive approach. Fig. 4 illustrated to reflect different strategies to provide ceramic-based composite that has been discussed here.

From a manufacturing point of view, 3D printing technology has an important role in the development of 3D-printed drug delivery systems for personalized drug-loaded medical devices, providing various strategies for personalized drug therapy [4]. However, a great effort should still be taken to design and develop drug delivery systems. Systems that can overcome some remaining issues such as permeability, bioavailability, and retention effects of drugs in tumor site and can allow the printing of multiple materials simultaneously.

5. Next generation of bioceramics for bone tumor defects

Due to the advances made in the field of biomaterials over the past decades, the definition of 'smart' biomaterials has been revisited. Up to date, smart biomaterials can be divided into four generations depending on the level of smartness biomaterials possess: (1) the first generation corresponds to inert biomaterials (such as metals and alloys including titanium and stainless steel); (2) the second generation refers to active biomaterials (such as bioercamics and biopolymers including HA, BG, and Collagen); (3) the third generation includes responsive biomaterials (such as (Nano)Composites/Hybrids including HA/PLA, BG/PLA, Collagen/HA); (4) and the fourth generation comprises spontaneous biomaterials (such as multifunctional and dynamic materials including the combination of Nano HA/Collagen/cellular and biological factors) [193,194]. To achieve both effective bone regeneration following tumor resection and elimination of remaining tumor cells, third- and fourth-generation smart biomaterials are the most promising therapeutic solutions. In fact, the third generation of smart biomaterials reacts to external or internal cues to initiate a bioactive function (i.e., the killing of tumor cells) [23,193]. For instance, biomaterials can be doped with ions to deliver photothermal/magnetothermal therapy upon external cues (i.e., laser irradiation) or coated with pH-sensitive NPs to trigger the release of bioactive molecules like Doxorubicin or cytokines only in the presence of acidic environments (i.e., the TME) [23]. Thus, these biomaterials elicit their function when and where it is most needed, reducing the risk of systemic side-effects and locally increasing the bioavailability of the anti-tumor or regenerative drugs. Notably, further research into the third generation of biomaterials can result in the development of highly selective materials that navigate the bloodstream to eliminate circulating cancer cells and recruit stem cells. To illustrate, smart nanoparticles can be produced to trigger the release of their content to specific sites and cells through active targeting by binding ligands expressed by target cells [195]. For instance, a thioaptamer with a high affinity for E-selectin (up-regulated in bone-marrow capillaries) improved the nanoparticle accumulation in the bone tissue of up to 8-folds and their consequent release of paclitaxel [196]. Interestingly, bone cancer

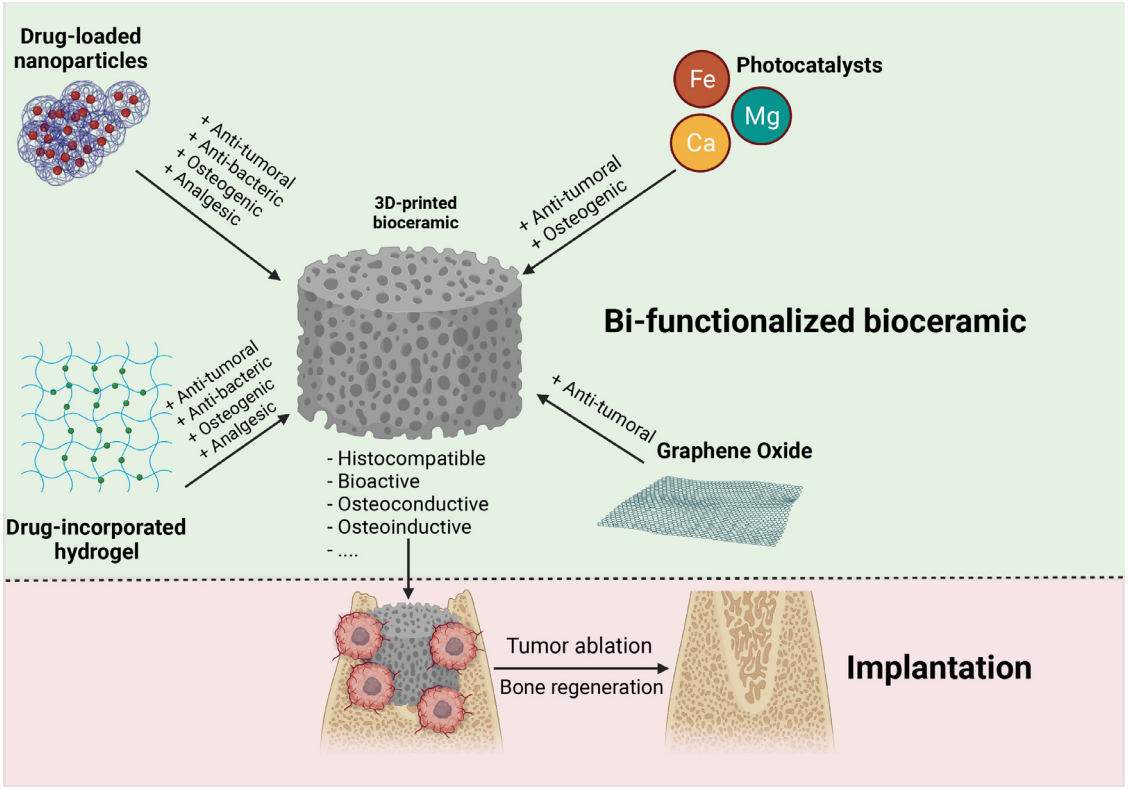

Fig. 4. Strategies conferring bi-functionalization of 3D-printed bioceramics composites (Created with BioRender.com).

cells highly express $\alpha v\beta 3$ integrin and functionalizing nanoparticles containing docetaxel with ligands for $\alpha v\beta 3$ integrin conferred them with higher specificity for cancer cells [197]. Hence, developing nanoparticles with high specificity for the bone tissue and cancer cells through active targeting strategies represents a promising strategy to specifically target the release of therapeutics into cancer cells. By developing nanoparticles capable of targeting also stem cells, it will be also possible to create a circulating drug delivery system that enhances the elimination of circulating cancer cells as well as the recruitment and differentiation of bone precursor cells [198] into the bone tissue. However, third-generation biomaterials are still far from being able to mimic the microenvironment where they are implanted and induce ideal responses because they cannot adapt to the dynamic and complexity of environments. Hence a fourth and most futuristic class of biomaterials is under development.

Fourth-generation biomaterials are considered self-sufficient since they act like living tissue by interacting detection, responding, and adjusting to complex environments. In contrast to the third generation of biomaterials which usually respond to one specific trigger, fourth-generation ones closely mimic natural tissues molecularly and biochemically, and they can also respond to multiple cues. Pioneering works into this last generation of biomaterials led to the development of peptide hydrogels capable of operating like a computer system. These hydrogels exploit logic-based responsive cross-linkers to output several biological signals in response to multiple environmental triggers including enzymes, light, and pH. These biomaterials have already been used to promote stem cell attachment, survival, and differentiation depending on the cell state [199]. However, further research is still needed to create bone biomaterials with enough complexity to mimic the bone microenvironment and trigger the release of highly selective and specific proteins and therapeutics. Ideally, in the field of bone cancer, the fourth-generation biomaterials can sense what are the most suitable bioactive molecules to release into the tumor microenvironment to accomplish a successful tumor elimination and tissue regeneration. Importantly, many factors can contribute to the maturation and spread of cancer cells (i.e., vascular niche, immune niche, bone niche, and so on). Hence, targeting the most prominent ones is crucial to increase the efficacy of the therapy to prevent tumor recurrence following resection. Importantly, the development of bone biomaterials with tuned chemistry and surface topography to closely mimic the bone microenvironment and trigger specific biological processes underlying bone homeostasis and regeneration (i.e., macrophage polarization towards M2 phenotype) is critical for the translation of these biomaterials into the clinics [125]. In fact, bone biomaterials with tuned chemistry and surface topography were capable of inducing M2 macrophage polarization resulting in sustained bone deposition both *in vivo* and *in vitro*. However, research is still needed to translate these properties to the fourth-generation biomaterials.

In addition to the challenges arising from the discovery and design of biomaterials with spontaneous function, fabricating a patient-specific fourth-generation biomaterial is still challenging in many aspects. Although third-generation biomaterials can already be fabricated using current 3D printing technology and have shown relevant anti-tumor and regenerative functions, 4D printing technology appears more suitable to create smart stimuli-responsive biomaterials [200]. 4D printing consists of using 3D printing technology with biomaterials that change their shape and properties dynamically. To accomplish this, several challenges remain to be tackled for a successful design and fabrication of an orthopedic fourth-generation biomaterial. Among them are found: (1) lack of mechanical properties; (2) slow and inaccurate actuation; (3) insufficient control over the various phases of deformation; 4) lack of biocompatibility, non-cytotoxicity, and a calibrated response that does not harm the host; and (5) dynamic biological microenvironments are complex and different for each patient.

Once more controlled smart biomaterials have been designed, 4D-printed biomaterials could interact with both tumoral and normal cells to trigger specific local and/or systemic processes including tumor killing and tissue regeneration simultaneously and precisely. In fact, it is important to note that cancer can have transitions from a local disease to a systemic one. Thus, developing therapies capable of eliminating remaining tumor cells locally and eventual metastatic cells systemically are highly recommended. To this end, self-assembling nanorobots fabricated with 4D-printing technology using pH-sensitive hydrogels are under development. They are capable of navigating blood vessels to reach cancer cells and release antitumoral drugs on-site through changes in morphology at acidic pH. Further research into these nanorobots could equip them with both tumor-killing and regenerative properties so that they could be coated on bone-like scaffolds to carry out both local and systemic functions.

In conclusion, the current third generation of biomaterials together with new 3D printing technologies are achieving unprecedented results in conferring multifunctionality, targeted release, and patient-specific properties to biomaterials for bone tissue engineering and therapies; however, they still lack dynamicity to effectively reduce the risk of tumor recurrence before symptoms arise. To this end, 4D printing and dynamic biomaterials offer new opportunities to design materials with a higher degree of multifunctionality and to trigger local and systemic responses spontaneously. Further research into this class of biomaterials will allow the fabrication of biomaterials that can identify the most effective therapy to prevent bacterial infection, carry out local and/or systemic tumor cell killing functions, and trigger tissue regeneration at a due time within the host.

Finally, creating *in vitro* models to safely test the biomaterials is also essential to bring these therapeutic solutions safely and effectively into the clinics. Until now, most studies rely on either *in vitro* or *in vivo* studies to assess the anti-cancer or regenerative properties of the materials. The generation of humanized mice has allowed the development of more relevant *in vivo* models; however, they fail to even remotely recapitulate human physiology. Thanks to the recent developments of multi-material printing systems to allow the simultaneous deposition of different cell types it is now possible to better recreate the tumor microenvironment at different stages *in vitro*. Moreover, the possibility to include a vascular compartment in 3D-printed bone models significantly augments their physiological relevance to study bone cancer treatments. However, challenges remain to be addressed: (1) increase cell model complexity; (2) better mimicking of ECM complexity; (3) increased use of ceramic to merge nanoscale morphological cues and biomimetic composition; and (4) investigation of pore size or topography to select the best parameters.

6. Conclusion

Due to high similarity with the bone tissue, bioceramics have been the most commonly employed bone implants to accomplish local bone tumor therapy and reconstruction. However, bioceramics alone fail to regenerate the bone and are not sufficiently equipped to carry out complete tumor elimination. Hence, bioceramics including bioactive glasses, AKTs, b-TCPs, CPCs, and HA scaffolds have been functionalized with a variety of polymers, NPs, or ions to obtain a bone implant that accomplishes both sustained bone regeneration as well as tumor therapy (i.e., chemotherapy, and photothermal/magnetothermal therapy). Different strategies to obtain a bi-functional bioceramic were found: (1) ion doping (i.e., Mg, Fe, Mn, Cu); (2) post-treatment (i.e., GO, MoS_2, Fe_3S_4), or (3) drug-loaded NP coating (i.e., DOX, Cisplastin). These hybrid materials have shown sustained local drug release, efficient tumor killing properties, and augmented bone regeneration both *in vivo* and *in vitro*. Moreover, a reduced risk for systemic toxicity and tumor recurrence has been observed when these bone grafts were used. Hence, functionalized bioceramics are promising bone implants surpassing the limitations of traditional bone tumor therapy. Furthermore, 3D printed Bi-functionalized systems with osteoinductive and tumoricidal properties (bioceramics composites, injectable hydrogels, etc.) reflected powerful treatments for bone tumors therapy and reconstruction. Of note, it is essential to create reliable pre-clinical models to test the efficacy of the biomaterials and verify the cytotoxic effects. Additionally, the fabrication of new bio-compatible materials containing therapeutic agents with improved mechanical performance is critical in bringing them into the clinics. Finally, developing “smart” biomaterials which are capable of releasing drugs under stimuli responses is highly recommended to avoid side-effects and specifically target tumor cells.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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