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Integrating nanomedicine into clinical radiotherapy regimens

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ABSTRACT

While the advancement of clinical radiotherapy was driven by technological innovations throughout the 20th century, continued improvement relies on rational combination therapies derived from biological insights. In this review, we highlight the importance of combination radiotherapy in the era of precision medicine. Specifically, we survey and summarize the areas of research where improved understanding in cancer biology will propel the field of radiotherapy forward by allowing integration of novel nanotechnology-based treatments.

Contents

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1. Introduction

Despite significant progress in the diagnosis and treatment of cancer, this collection of malignances remains one of the leading causes of death worldwide. Epidemiologic predictions by Siegel et al. estimated that in 2019 there would be approximately 1.8 million new cancer diagnoses and over 600,000 cancer-related deaths in the US alone [1]. These high rates of incidence and mortality highlight the need for continued advances in novel and more effective treatments.

Currently, radiotherapy (RT) is a mainstay of oncology, serving both as a first line treatment and used in combination with surgery and chemotherapy in many forms of cancer [2,3]. Although it is highly effective, its use is often viewed as a double-edged sword which does not discriminate between healthy and diseased tissue [4,5]. As such, one of the biggest challenges associated with RT is determining the effective dose for killing malignant cells without incurring collateral damage to healthy tissues. As this technology driven discipline has evolved from archaic lead shielding to multileaf collimators (MLCs) and artificial intelligence-guided treatment plans, engineering advancements have vastly improved the safety, accuracy, and efficacy of RT. However, as the great progress in medical physics and technology-based innovation begins to plateau, new multidisciplinary areas must be explored to further widen the therapeutic window of RT. Importantly, radiation oncologists are well-equipped to adopt innovative new technologies, such as nanomedicine, based on the ever-evolving space in which they practice.

While the success of RT can be attributed to the technological advancements made over the past decades, recent successes lie with the combination of chemotherapy, targeted therapy, and immunotherapy with radiation therapy (*i.e.,* multimodal radiotherapy or MMRT) [6]. In its essence, MMRT capitalizes on the quick succession of decisive blows that add to the primary damage which left a target vulnerable. Thus, the sequence and time in which systemic agents and ionizing radiation (IR) are administered during MMRT are as important in treatment efficacy as the therapeutic doses. For example, concurrent chemoradiotherapy (CRT) has proven superior to sequential treatment and demonstrated improved survival in many cancers. However, concomitant therapy oftentimes further increases the toxic burden on the patient [6].

The implementation of innovative drug delivery methods, such as nanoparticle-based carriers, in CRT has proven to be an advantageous approach for mitigating the increased toxicity of combination therapy in healthy tissue [7]. Accordingly, this new paradigm has attracted significant interest with exciting preclinical work presenting intricate answers to complicated problems. However, the complexity of the human body renders clinical translation a highly convoluted process resulting in a scarce amount of clinically approved nanomedicines. In part, researchers may better bridge this translation gap, through inclusion of clinical approaches in their experimental designs. Investigation into the influence of treatment parameters on the efficacy of nanoparticle-based MMRT may prove beneficial for the development of complementary approaches, which better predict clinical success. Looking to the future of oncology, the most promising advances in survival and quality of life outcomes will likely emerge from further biologic insight and subsequent engineering resulting in rational combinations of radiation with other therapeutic strategies.

The continued advancement of nanotechnology in MMRT will depend on both fundamental and translational research. However, the latter may not be as widely understood in the academic research community. As such, the purpose of this review is to provide a brief overview of CRT with a strong focus on the current clinical practice and its corresponding influence on nanoparticle drug delivery.

2. Advent, growth, and limitations of radiotherapy

Soon after discovery by Röntgen in 1895, X-rays were quickly adapted for use in oncology as its therapeutic efficacy became clear in the first patients treated [8,9]. However, the early biomedical applications of IR frequently resulted in undesirable side-effects garnering a public fear of radiation [10]. Later scientific innovation including significant advancements in radiation dose planning and instrumentation improved overall delivery accuracy and presented control over various aspects of IR. Currently, oncologic standard of care comprises three main treatment options; surgical resection, RT, and systemic therapy, utilized individually or in various combinations [2]. Overall, 50% of patients are estimated to receive RT at some point during their treatment [11]. Ultimately, while RT is an effective therapeutic strategy, it still has a narrow therapeutic index, is primarily limited to localized disease, and may induce secondary malignancies [6–8].

2.1. History and adaptation to oncology

After the initial observation that X-rays could effectively treat otherwise inoperable malignancies, the field of radiation oncology grew rapidly. Illustrated in Fig. 1, the 1900s saw continual technologic advancements related to treatment planning and control over dose delivery resulting in an exquisite reduction in adverse side-effects from treatment. However, since its inception, determining the optimal dose and dosing schedule to achieve the greatest therapeutic ratio—the balance between effective treatment of diseased tissue and sparing of healthy tissue—has remained a challenge (Fig. 2) [12–16]. Initially, the limited depth penetration of low-energy devices restricted treatment to superficial lesions. Upon the introduction of high-energy devices, treatment limitations transitioned to side-effects associated with non-conformal single high-dose delivery. Implementation of fractionated dosing alleviated some of these side-effects, but the overall lack of dose-mapping and planning continued to adversely affect healthy tissues. The advent of linear accelerators, improvements to imaging and treatment planning, image-guidance, and updated fractionation schedules enabled physicians to further improve the therapeutic ratio of RT [9,17,18].

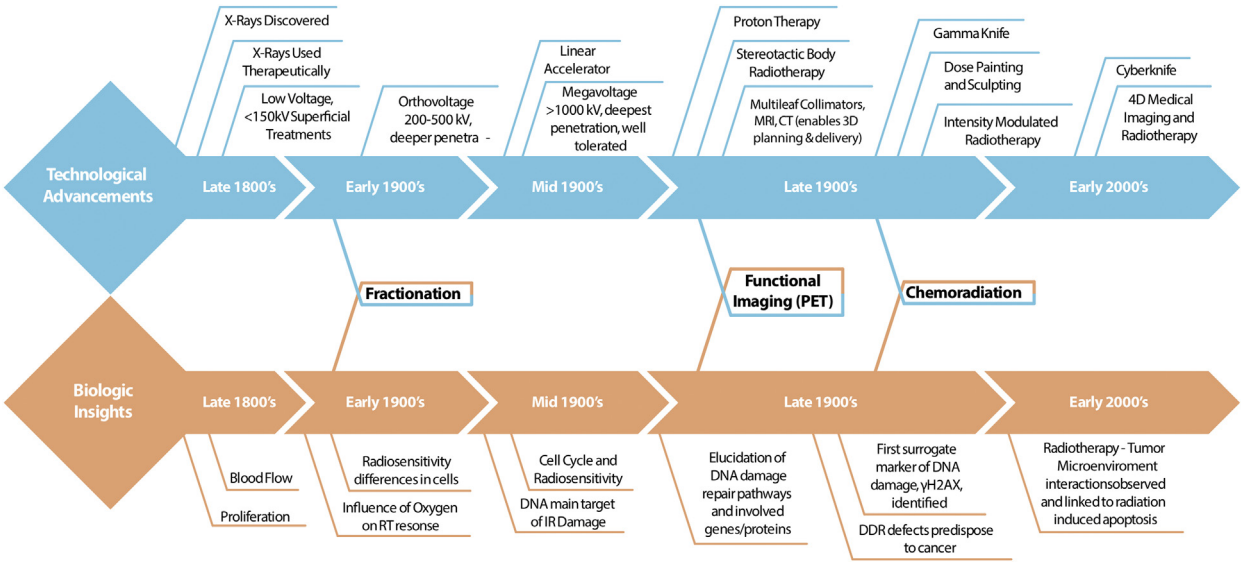


Fig. 1. Timeline mapping seminal biological findings and technological advancements that have propelled radiation therapy to its current standard. Here we visualize the interplay between several insights and advancements, such as that of PET imaging, where an innovation has allowed physicians and scientists to elucidate biologic function thus improving combination therapy strategies.

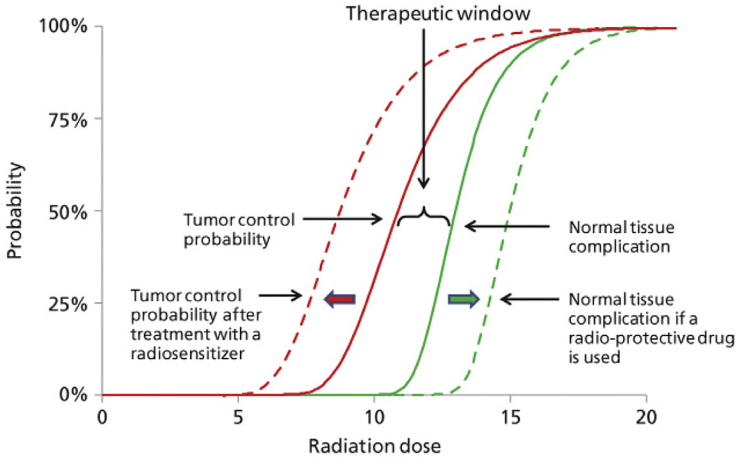


Fig. 2. The therapeutic window of radiation therapy is a balance between tumor control and normal tissue complications. Addition of radiosensitizers reduce the dose of radiation required for the same tumor control probability. Addition of radio-protective drugs increase the dose of radiation required for the same probability of normal tissue complications. Together, radiosensitizers and radio-protective drugs can enhance the therapeutic window of RT. Reprinted with permission from [19].

2.2. Equipment, technology, and clinical dosing regimens

Currently, the most common form of RT is delivered *via* external beam radiation therapy (EBRT). Modern EBRT treatment variables, summarized in Table 1, demonstrate the versatility that arose from the multitude of technologic advancements. While an extensive description of each variable is beyond the scope of this review, detailed descriptions can be found in other reports [11,20]. Even with many advances, treatment standards are established based on a narrow therapeutic index, which frequently leads to suboptimal dosing across patient populations [21]. Despite the plethora of treatment options, the majority of patients are prescribed conventionally fractionated RT, consisting of daily doses approximately 2 Gray (Gy) × 5 days per week over a period of 1–2 months [22]. Several important factors emphasize the rationale for clinical implementation of fractionation and are known as the four R's of radiobiology (repair, repopulation, redistribution, and reoxygenation). In terms of repair, the timing between fractionated doses, as well as the dose itself, is extremely important as the repair process for malignant tissue is much slower than it is for normal tissue. Additionally, the time between fractions allows cells to transition into phases with enhanced sensitivity (redistribution) and provides an opportunity for oxygen exposure in hypoxic cells (reoxygenation), decreasing their radioresistance [23]. When evaluating conventionally fractionated RT, it has been suggested that repopulation is one of the main mechanisms of treatment failure [24]. When too much time is given between sublethal fractions, accellerated repopulation may occur allowing for faster growth of the treated tumor than an untreated tumor.

One way to combat this issue, is by delivering lethal doses of radiation, however this may not always be possible. If tumors are a safe distance away from at-risk organs, stereotactic radiosurgery (SRS) may be used to deliver a few 15–20 Gy fractions [14]. Although advances, such as SRS, have improved the safety and efficacy of RT, further expansion of RT's therapeutic index is still necessary [14,16,25–27]. However, selecting a treatment regimen which maximizes the therapeutic ratio, or the difference between eliciting tumor control and inducing normal tissue toxicity, remains a formidable obstacle [28].

Table 1. This table summarizes the key variables encompassed in designing an external beam radiation therapy treatment plan. Physicians must decide on the optimal machine, mode of therapy, fractionation

Table 1
Prominent external beam radiotherapy treatment plan options.

Machine	Linear accelerator, cobalt machine
Mode	Stereotactic radiosurgery (SRS), Image-guided (IGRT), 3D Conformal (3D-CRT), Intensity-modulated (IMRT), Tomotherapy
Fractionation/Regimen	Conventional, Accelerated, Hyperfractionated, Continuous Hyperfractionated Accelerated, Hypofractionated
Aim	Curative, Palliative, Prophylactic, Total Body
Timing	Adjuvant, Neoadjuvant, Concurrent

schedule, aim of the plan, and the timing in accordance with other modalities.

2.3. Current limitations of radiotherapy and opportunities

There are few cancers where RT is completely curative, thus justifying the need for combined modality treatment regimens. In addition, a subset of cancer patients present with tumors resistant to RT. Moving forward, approaches that exploit and enhance the fundamental processes occurring on the physiological level in response to RT will prove beneficial for advancement of the field. However, the rational design of these approaches will require a further understanding of the effect of radiation on both cancerous and healthy tissue. In part, the significant progress made in recent years regarding the understanding of cancer biology has created new opportunities for improving therapeutic options.

2.3.1. Limitations

Biologically, RT utilizes IR to damage DNA both indirectly through the formation of free radicals and directly *via* electron ionization [25]. However, the characeristics of the local tumor microment can render RT highly insufficient. For example, as the main mechanism of DNA damage is derived through interactions with oxygen and subsequent free radical formation ($^1O_2$, $\cdot OH$), overall DNA damage yields are highly dependent on local oxygen concentrations. However, hypoxia, or insufficient oxygen supply, is a commonly encountered phenomena in oncology and is highly heterogenous and unpredictable. Oftentimes this hypoxia, confers radiation and chemotherapeutic resistance, resulting in suboptimal responses [29,30]. Therapeutic resistance can also result from genetic mutations or alterations in molecular pathways [31]. Regardless of the exact mechanism in which resistance is accrued, there are currently no clinically approved methods for enhancing radiosensitivity [32].

2.3.2. Opportunities

The lack of clinically approved radiosensitizing protocols presents a unique opportunity for the application of nanomedicines to enhance therapeutic efficacy. As the best evidence to date indicates that free radical generation is a large component of cell killing after radiation, nanomaterials designed to increase radical production are an exciting way to enhance DNA damage and subsequent cell death. In terms of nanotechnology, inorganic-based particles containing high *Z*-elements have proved promising for augmentation of RT through enhanced dose deposition and subsequent increased generation of free radicals. Additionally, these types of nanomaterials can preferentially absorb X-rays over human tissue, which may prove beneficial for decreasing the debilitating side-effects associated with RT toxicity. A more extensive discussion of this particular application of nanomedicine in RT is provided by alternative sources [33–35]. Here, the focus will lie with nanomaterials made of organic materials which have no physical interaction with radiation aside from their ability to deliver therapeutic agents to exploit the biologic response to IR.

3. Landscape of multimodal radiotherapy

Over recent decades, the potential of MMRT to improve treatment outcomes was realized as evidence continued to show improved survival rates, as well as local and metastatic tumor control [6,36,37]. According to Seiwert et al., there are three main reasons concurrent chemoradiation is clinically indicated: organ-preservation, radiosensitization/local control, and metastatic control [37]. These reasons can also be broadly applied to the combination of IR with any therapeutic agent including immunotherapy, targeted therapy, or chemotherapy. Importantly, the understanding of tumor biology has evolved on the same timeline as the critical technical advancements in RT, refining the way we utilize these multimodality therapeutics.

3.1. Chemotherapy

Although the first therapeutic application of IR took place in 1895, and chemotherapy use in patients was established in 1943, the clinical combination of these cytotoxic entities was not introduced until 1979 by Gordon Steel and Michael Peckham. Chemoradiation can be implemented temporally in the neoadjuvant or adjuvant setting in either a concurrent or sequential fashion. The Steel Paradigm was an early description of concurrent chemoradiation that introduced the concept of spatial cooperation. Spatial cooperation attributes locoregional disease control to radiation and micrometastatic disease control to chemotherapy. Beyond spatial cooperation, chemotherapy serves to sensitize within the RT treatment field in an additive or supra-additive fashion by a variety of mechanisms [37]. Implementation of CRT is predicated upon rational design of a radiation treatment plan and interdisciplinary coordination with medical oncology for drug dosing and scheduling [38]. To determine the frequency of radiation and chemotherapy administration, both radiation and medical oncologists work together on direct clinical evaluation to ensure safe treatment delivery and mitigate treatment toxicity. Chemoradiation is a resource intensive endeavor justified by its clinical efficacy and evidenced by the National Comprehensive Cancer Network's (NCCN's) guidelines promoting it as a first line therapy in a number of cancers.

Given its biological basis and temporal nature, robust clinical data has ascribed superiority to concurrent chemoradiation over sequential chemoradiation or radiation alone. Although concurrent therapy confers increased adverse effects over either alone, this is effectively managed by close follow-up in the immediate and long-term post-treatment setting. This is exemplified in the report by Pignon et al. where meta-analysis of 93 randomized head and neck trials compared various CRT schedules (with chemotherapy delivered as induction therapy, concurrently, or neoadjuvantly) to chemotherapy alone. Upon analysis CRT, regardless of timing, was found to result in an overall survival (OS) benefit of 4.5%. When comparing concurrent CRT to chemotherapy, this sequence resulted in the greatest absolute benefit with OS reaching 6.5%. Similarly, in locally advanced lung cancer, concurrent CRT significantly increases the absolute 5-year OS and 3-year progression free survival by 4.5% and 2.9%, respectively [39]. The benefit of sequential CRT was limited to a non-significant 2.2% increase in 5-year OS. In cervical cancer, a meta-analysis of 13 CRT trials demonstrated 6% absolute benefit in OS compared to radiation alone [40]. Furthermore, a number of studies have established the critical advantage of concurrent timing in several cancer sites including, but not limited to, esophageal, pancreatic, rectal, anal, and glioblastoma multiforme [41–45]. Mounting evidence among all the aforementioned modalities of oncology implicates the sequence and timing as crucial factors contributing to successful patient outcomes.

3.2. Targeted therapy

Advances in cancer biology have yielded numerous molecularly targeted therapy to exploit the malfunctioning mechanisms of cancer [46]. This further understanding of the biological changes associated

with cancer progression has allowed for the rational design of therapeutics that target these molecular pathways. Targeted therapies are utilized for their specific ability to disrupt important cellular processes associated with a tumor's development, such as metabolism, proliferation, and survival [47]. Again, however, as a consequence of cancer heterogeneity targeted therapy is not always beneficial for patients whose molecular signatures indicated it would be, particularly in advanced stages of the disease [47,48]. Furthermore, tolerance and resistance to the single-agent administration can develop leading to unresponsive tumors [49]. In general, targeted therapies are categorized as antihormonal (*e.g.,* tamoxifen), tyrosine kinase inhibitors (*e.g.,* Gleevac), phosphoinositide 3-kinases (PI3Ks) (*e.g.,* idelalisib), folate receptors (*e.g.,* methotrexate), monoclonal antibodies (*e.g.,* trastuzumab), or serine/threonine kinase inhibitors (*e.g.,* everolimus), to name a few [46,50]. Characteristically, targeted therapeutics are only toxic in cells which are over-expressing a particular (target) protein (*i.e.,* cancer cells). According to the NCCN, endocrine and HER2 targeted therapies may be utilized in combination with RT with certain types of breast cancer, however, there is conflicting thoughts regarding this strategy [51]. In glioblastoma, EGFR therapy in combination with RT has demonstrated superior outcomes [52]. In general, the combination of targeted therapies with additional agents, such as RT, allows for optimal spatiotemporal control and presents an excellent opportunity to combat therapeutic resistance.

3.3. Immunotherapy

Like RT, cancer immunotherapy traces its origins to the 1890s, with William Coly's early exploration into the association between cancer and the immune system [53]. However, the first antibody approvals were only granted in the late 1990s [54]. Immunotherapy is a field where a fundamental understanding of biology has opened new doors for rational design. While the immune system is normally extremely efficient at clearing invaders, cancer has become highly proficient at immune evasion in order to thrive. Therefore, the potential of immunotherapy in oncology to stimulate the native immune system to attack the invading cancer is very promising. Comparatively, in targeted therapy the main goal is to inhibit the cellular processes associated with oncogenesis and disease progression. Current immunotherapy strategies employ checkpoint inhibitors, monoclonal antibodies, oncolytic viruses, engineered T-cells, cytokines, and agonistic costimulatory antibodies [55,56]. Recent years have seen significant growth of clinically approved immunotherapies, with 12 approvals occurring between 2010 and 2014 and 50 approvals between 2015 and April 2019 [54].

The combination of immunotherapy and RT may overcome some of the limitations associated with each individual therapy. For example, many immunotherapies are single agents for a specific antigen. Due to the high heterogeneity of cancer, this can lead to less than ideal responses, relapse, or resistance [57]. Furthermore, if a patient does not express the specific antigen or expression is being masked, they will likely be unresponsive to immunotherapy. However, RT is highly effective at stimulating the release of tumor antigens in the tumor environment. This release of tumor antigens *via* RT, may enhance the efficacy of immunotherapy agents. Furthermore, immunotherapy could prove highly effective for the treatment of metastatic disease, an area where RT fails as a monotherapy [58]. Micrometastases are often not detectable and total radiation dose limitations prevent effective treatment of disseminated disease. Accordingly, radio-immunotherapy has seen a resurgence as a clinically viable option for the elimination of undetectable micrometastases with several important FDA approvals recently. With the increasing number of FDA approved immunotherapies, there is significant interest in these new combinations. A survey of clinicaltrials.gov using the search terms “radiation” and “immunotherapy” resulted in 533 studies (active, recruiting, enrolling, and completed) in this area.

3.4. Limitations and opportunities in multimodal radiotherapy

Due to the intrinsic toxicity of cancer therapies, the major drawback of combining various agents is the resulting increase in toxicity despite improved response rates. This makes investigation of new combination therapies difficult and failures abundant. For instance, the widely used chemotherapeutic, cisplatin, proves highly effective but can often leave the patient with lifelong, debilitating side-effects. In addition to nephrotoxicity and neurotoxicity, ototoxicity, which can lead to permanent hearing loss, is a common side-effect that presents a substantial, lifelong burden. As such, chemotherapeutic treatments typically require a risk-benefit analysis that may result in choosing to harm the patient for the end goal of survival.

Previously, the increased success of RT and reduction of toxic side-effects came from altering the radiation source, planning, delivery, and fractionation schedule [9]. Moving forward, the combination of radiation with multiple other therapies, including chemotherapy, targeted therapy, and immunotherapy, may provide the opportunity to greatly improve survival and quality of life outcomes for cancer patients. While the translation of targeted therapeutics aims to reduce toxicity, this will likely remain a barrier to their clinical adoption [59]. Improving biomarker screening, in addition to thorough characterization and understanding of biological influences will prove imperative, particularly when integrating into RT. Adapted from the NCCN, Table 2 is a comprehensive overview of cancer types for which a MMRT is currently a therapeutic option. Additionally, Table 2 lists drug classes that are utilized for MMRT. With at least 55 different cancers indicating MMRT as potential treatment, the significance of this multidisciplinary treatment regimen has become apparent.

The importance of increasing the therapeutic index of RT is evident after surveying the literature [60–64]. Ultimately, despite the growing interest in combination therapy as a mode to boost the therapeutic index of RT, there is a lack of funding for combination RT clinical trials in the pharmaceutical industry [65]. By intelligently designing combination therapies that increase the efficacy of RT while reducing toxic side-effects, academia serves a critical role by stimulating interest in early pharmaceutical-RT clinical trials.

4. Advancing multimodal radiotherapy through nanotechnology

With origins in liposomal drug carriers dating back five decades, nanotechnology has attracted significant attention for its potential to improve patient outcomes in oncology, particularly for delivering therapeutics [66]. There are numerous advantages of nanoparticles as drug delivery vehicles, including increased circulation time, protection from degradation, spatially controlled delivery of multiple drugs, tumor accumulation *via* the enhanced permeability and retention (EPR) effect, among others [67]. Unfortunately, despite creative concepts and promising preclinical data, clinical translation of nanomedicines has been challenging, sparse, and time-consuming (Table 3) [68]. This significant gap in translation may stem from preclinical studies that fail to accurately recapitulate the disease and clinical setting in which the technology is being applied [69].

Recently, the advantages of nanoparticle-based drug delivery have been investigated in a growing body of work to improve CRT. Through enhanced delivery methods, many studies have attempted to capitalize on the additional DNA damage induced in the direct tumor vicinity while minimizing off-target drug delivery and required radiation doses. In this review, we limit our discussion to nanoscale materials that are specifically engineered to alter the properties of an anticancer agent.

4.1. Rationale/benefits of nanomedicine

Although 50 years of innovation has led to many unique nanoparticle formulations, which possess a myriad of functionalities, the classical features of nanocarriers remain some of the most important. The ability

Table 2
Multimodal radiotherapy in the clinic.

Cancers
Anal Carcinoma* | **B-Cell Lymphomas:** Diffuse Large B-Cell Lymphoma†, Follicular Lymphoma*, Mantle Cell Lymphoma*, Nodal Marginal Zone Lymphoma* | **Bladder:** Bladder*, Primary Carcinoma of the Urethra* | **Breast:** Inflammatory*†, Invasive* | **Bone:** Ewing Sarcoma*† | **Central Nervous System:** Adult Medulloblastoma*‡, Anaplastic Gliomas/Glioblastoma*††, Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (WHO Grade II) *‡, Primary CNS Lymphoma† | **Cervical*** | **Colon*** | **Esophageal and Esophagogastric Junction*** | **Gastric*††** | **Gestational Trophoblastic*** | **Head and Neck:** Ethmoid Sinus*, Glottic Larynx*, Hypopharynx*, Supraglottic Larynx*, Lip (Mucosa)*, Maxillary Sinus*, Nasopharynx*††, Mucosal Melanoma*, Oral Cavity*, Oropharynx*, Salivary Gland*, Very Advanced Head and Neck*‡ | **Hepatobiliary:** Extrahepatic Cholangiocarcinoma*, Gallbladder*††, Intrahepatic Cholangiocarcinoma* | **Hodgkin Lymphoma*†** | **Malignant Pleural Mesothelioma††** | **Merkel Cell*** | **Neuroendocrine and Adrenal Tumors:** Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)*, Poorly Differentiated (High Grade)/Large or Small Cell*†‡ | **Non-Small Cell Lung*††** | **Occult Primary*** | **Pancreatic Adenocarcinoma*††** | **Penile*** | **Primary Cutaneous Lymphomas:** Mycosis Fungoides/Sezary Syndrome* | **Prostate*** | **Rectal*‡** | **Squamous Cell*** | **Small Cell Lung*** | **Soft Tissue Sarcoma:** Extremity/Superficial Trunk or Head and Neck*‡, Retroperitoneal/Intra-Abdominal* | **T-Cell Lymphomas:** Extranodal NK/T-Cell Lymphoma (Nasal Type)*††, Peripheral T-Cell Lymphoma* | **Testicular:** Metastasized Testicular non-Seminoma* | **Thymomas and Thymic Carcinomas†** | **Thyroid:** Anaplastic Carcinoma‡ | **Uterine Neoplasms:** Endometrial Carcinoma*†, Uterine Neoplasm*†, Uterine Sarcoma* | **Vulvar***

Therapeutics
Chemotherapy - Alkylating Agents: Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Procarbazine, Temozolomide, Trabectedin | **Antimetabolites:** 5-Fluorouracil (5-FU), Capcitabine, Gemcitabine, Hydroxyurea, Methotrexate, Mitomycin-C, Premtrexed, Lecovorin | **Antitumor Antibiotic:** Bleomycin | **Anthracyclines:** Doxorubicin, Liposomal Doxorubicin♦, Epirubicin | **Plant Alkaloids:** *Brentuximab Vedotin (MMAE),* Docetaxel, Etoposide, Paclitaxel, Albumin-bound Paclitaxel♦, Vinblastine, Vincristine, Irinotecan, Liposomal Irinotecan♦, Vinorelbine | **Platinum-Based:** Carboplatin, Cisplatin, Oxaliplatin | **Other:** Eribulin
Targeted Therapy – Hormonal: Tamoxifen, aromatase inhibitors, LNRH agonists or antagonists, 1st generation anti-androgens | **Enzyme:** PEGylated L-asparaginase♦ | **Other:** Dexamethasone, Pazopanib
Immunotherapy - Antibodies: Nivolumab, Rituximab, Cetuximab, Durvalumab | **Antibody-Drug Conjugate:** *Brentuximab Vedotin (MMAE)*

Table 2. Data in this table was compiled from the National Comprehensive Cancer Network's guidelines for treatment of cancer by site listing any cancer where chemotherapy, targeted therapy, immunotherapy or a combination thereof + radiation was mentioned for at least 1 stage of disease. Cancers grouped together can be found in the same guidelines. Specific drugs listed in the guidelines were organized into their classes. Italicized drugs are combinations of multiple classes and listed under both classes. Drugs listed in this table are not inclusive and only include those drugs that were specifically mentioned in the various guidelines. As many other drugs are likely used, and the guidelines are constantly updated, this is meant to provide a broad overview of the type of therapeutics utilized. Symbols represent the type of chemoradiation schedules that are possible for at least one stage of the cancer listed. (* concurrent, † neoadjuvant, or ‡ adjuvant) Nanoparticle therapeutics utilized are denoted by the ♦ symbol.

Table 3
Clinically approved nanomedicines for oncology.

Name	Description	Approval date	RT clinical trials
Liposomes			
Doxil®	Doxorubicin hydrochloride covered in Stealth® liposomal technology	1995	Completed phase 3: 1 active phase 3: 0
Marqibo®	Liposome-encapsulated vincristine	2012	Completed phase 3: 2 active phase 3: 0
Onivyde®	Liposome-encapsulated irinotecan	2015	None
Vyxeos®	Liposome-encapsulated daunorubicin and cytarabine	2017	None
Polymer-based Nanoparticles			
Eligard®	Polymeric matrix formulation of leuprolide acetate	2002	1
Oncaspar®	L-asparaginase covalently conjugated to PEG	1994/2006	Recruiting: 1
Biomacromolecules and conjugates			
Imlygic™	Genetically engineered enveloped herpes simplex virus type-1	2015/2005	Completed phase 3: 1 active phase 3: 1
Abraxane®	Albumin-bound paclitaxel	2005/2012	Completed phase 3: 3 active phase 3: 1

Table 3. A summary of nanomedicines with FDA approval for oncologic applications; their descriptions, approval dates, and phase 3 clinical trials investigating their combination with RT.

of nanomedicine to not only improve safety but also efficacy compared to systemic administration of toxic agents remains a cornerstone of the rationale behind their use. Additionally, nanoformulations can be applied to revive products that had been abandoned due to poor solubility and/or pharmacokinetic and release profiles (Fig. 3). In addition, nanoparticles provide protection to their cargo, which becomes especially important for the delivery of nucleic acids. The future of nanomedicine promises many of these advantages along with enhanced targeting functionality, better stealth properties, and externally stimulated release to name just a few. Unfortunately, medicine has not yet fully capitalized on the clinical potential of nanotechnology, and significant efforts are still necessary to show safety and efficacy *in vivo* for translation to the clinic [70].

4.2. Applications of nanotechnology in radiotherapy

Nanoparticles have been investigated in therapeutic, diagnostic, and theranostic applications over the past several decades. Specifically, nanoparticles have been utilized as MRI, PET, and CT contrast agents for enhanced imaging, as radiation dose enhancers (inorganic nanoparticles), and as radiation sensitizers [70]. Early efforts were focused on altering nanoparticle design to achieve increased tumoral accumulation, however recent efforts have also investigated modulating the tumor microenvironment to prepare the area for effective treatment [71]. Nanoparticles are desirable due to their ability to carry both hydrophilic and hydrophobic cargo, increased circulation time, and ability to target specific tissues [72]. Here, we will focus specifically on organic-nanoparticle delivery of radiation sensitizers and timing as an important treatment parameter.

Nanoparticles have been applied to radiation oncology in several ways. Some studies have reported the combination of chemotherapeutics with radiation dose enhancing nanoparticles for superior tumor control [73]. Other studies report nanoparticles which release their payload upon exposure to a reducing agent, such as RT [74]. There are also investigations of nanoparticles which deliver both chemotherapeutics and radiopharmaceuticals [75]. Various chemotherapeutics have been investigated for nanoparticle enhanced CRT including camptothecin, docetaxel, paclitaxel, doxorubicin, cisplatin, and ATM-kinase inhibitors with promising results demonstrating increased efficacy over chemotherapy or radiation alone [14,15,73,76–78]. These compounds are only a fraction of the drugs that may enhance the efficacy of CRT. Throughout the late 1990s and early 2000s, several phase I and phase I/II clinical trials investigated the tolerance and efficacy of stealth nanoparticle-radiotherapy combinations [79–86]. These clinical trials showed efficacy in previously radioresistant sarcomas and demonstrated minimal toxicity in other cancers including head and neck, non-small cell lung, and breast cancer. Preclinical research conducted simultaneously investigated a wider array of nanoparticles designed to enhance the efficacy of CRT. These studies presented evidence radiation may also increase the amount of tumoral accumulation of nanoparticles [14,50,87–95].

4.3. Clinically approved nanomedicine

Logically, the effective integration of nanomedicine into multimodal radiotherapy regimens, begins by exploring those therapeutics currently

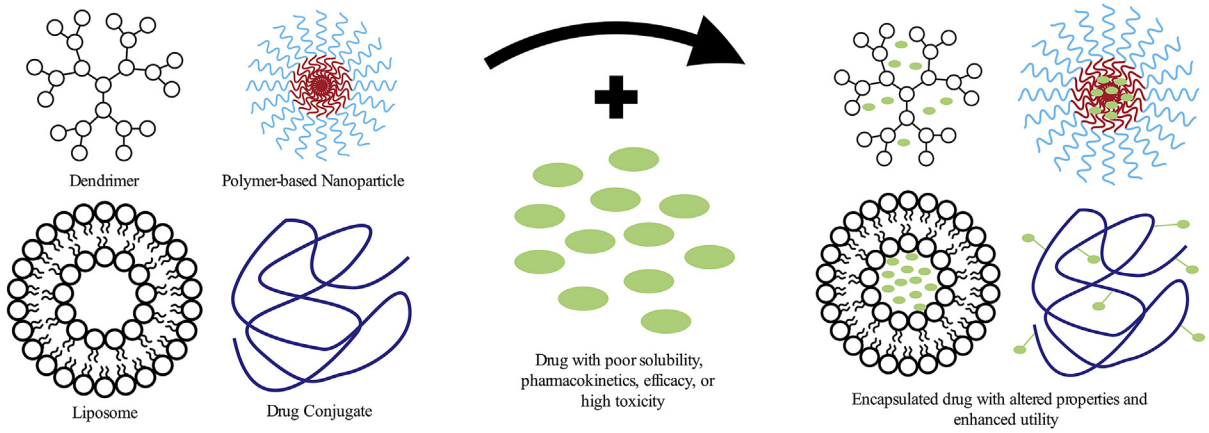


Fig. 3. Schematic illustration of the types of nanoparticles discussed in this review and the benefits of utilizing these carriers to delivery poorly soluble or toxic therapeutic agents.

approved. In nanomedicine, there are not many approved agents but those that are approved should be investigated for their combination with RT as the bar for clinical approval and translation may be lower. As individual therapeutics, one particular class of nanocarrier, liposomes, has obtained significantly more clinical approvals (5) in comparison to other drug delivery nanomaterials. The successful translation of Doxil (1995) and subsequent approvals of DaunoXome (1996), Marqibo (2012), Onivyde (2015), and most recently Vyxeos (2017) has demonstrated the utility of these nanoformulations. These liposomal formulations carry anthracyclines (doxorubicin and daunorubicin), topioisomerases (irinotecan), antimetabolites (cytarabine), and vinka alkaloids (vincristine sulfate) underscoring the diversity of products that have been approved. However, of these liposomal formulations only Vyxeos demonstrated a significant increase in survival when compared to the free compounds increasing survival from 5.9 to 9.6 months [66]. Interestingly, in 2016 and 2017, DaunoXome and DepoCyt (a microparticle sized liposomal formulation) were both discontinued in the US by manufacturers citing "commercialization" manufacturing challenges [96,97].

Although liposomal formulations have seen the most success of any nanomedicine class, several other nanoscale carriers have been approved. Abraxane which is an albumin-bound formulation of paclitaxel, was approved in 2012, PEGylated L-asparaginase was approved in 2006, and the polymeric conjugation of paclitaxel, Opaxio, was given orphan drug designation in 2012. Polymeric nanoparticle, Eligard, was approved in 2002 and Imlygic, a modified oncolytic virus, was approved in 2005 [98].

As shown in Table 2, four of these clinically approved nanomedicines are specifically mentioned as options for chemoradiation by the NCCN. While FDA approved nanomedicines are dominated by liposomal formulations, there is an even split between liposomes and other types of nanoformulations when evaluating therapeutics utilized for chemoradiation. The four approved nanomedicines which may be utilized in chemoradiation include liposomal doxorubicin (Doxil), liposomal irinotecan (Onivyde), albumin-bound paclitaxel (Abraxane), and PEGylated L-asparaginase (Oncaspar). Specifically, Doxil is indicated most frequently with mentions on the guidelines for diffuse large B-cell lymphoma, Hodgkin lymphoma, multiple myeloma, endometrial carcinoma, uterine sarcoma, peripheral T-cell lymphoma, extremity/superficial trunk, head/neck soft tissue sarcoma, retroperitoneal/intra-abdominal soft tissue sarcoma, and mycosis fungoides/Sezary syndrome. Abraxane is the second most frequent nanomedicine utilized in CRT with mentions in the guidelines of pancreatic adenocarcinoma, endometrial carcinoma, non-small cell, cervical, and invasive breast cancer. The two final nanomedicines are each only indicated for CRT in one cancer type with Oncaspar being mentioned for Extranodal NK/T-Cell Lymphoma and Onivyde being mentioned for pancreatic adenocarcinoma.

4.4. Types of nanocarriers

In MMRT, the original promise of nanoparticle inclusive therapy was derived from their potential to improve delivery of chemotherapeutics and dampening their side-effects. In this area, research has taken two different approaches: drug delivery vehicles that employ organic molecules and those that use inorganic elements as the building material. Organic-based nanosystems can typically fall in several generalized categories: liposomes, polymers, and dendrimers. Utilization of these "soft" materials proves advantageous in terms of improving drug loading, pharmacokinetics, efficacy, and biodegradation.

4.4.1. Liposomes

Liposomes consist of small, spherically shaped particles of one or more lipid bilayer and an aqueous core. As such, these formulations are often utilized as carriers for hydrophilic drugs, although hydrophobic drugs can be transported through encapsulation within the lipid bilayer [99]. Individually these lipid molecules are generally amphiphilic in nature, consisting of a hydrophilic head and a hydrophobic tail. As a delivery system, one of the major drawbacks of liposomes is their rapid clearance from the blood. Accordingly, research has aimed at decreasing the rate of elimination through the incorporation of immunoglobulins, and coating with biocompatible polymers, such as polyethylene glycol (PEG) [100]. In particular, these PEGylated liposomes display increased circulation times and higher accumulation in tumors compared to the parent material [101].

Preclinical evaluation of Promitil, a liposomal formulation of the prodrug mitomycin C (MMC), was assessed as a radiation responsive material for use in MMRT. *In vivo* studies evaluated the toxicity of both free MMC and Promitil in combination with three daily fractions of 5 Gy (15 Gy total). Toxicity was monitored through blood counts and cosmetic (skin and hair) monitoring. All mice that were treated with MMC + RT died from treatment related toxicity, whereas, Promitil + RT resulted in no deaths, suggesting the enhanced safety of this regimen. To assess efficacy, Promitil was combined with fluorouracil-based CRT against SW480 and HT29 models resulting in improved efficacy compared to MMC, suggesting its potential as a well-tolerated treatment regimen [102].

To date, multiple liposome-based nanosystems are currently utilized in clinical settings or are undergoing clinical trials [103]. The first clinically used nanoparticle-based therapeutic was a PEGylated liposomal doxorubicin (Caelyx®, Doxil®, Lipo-Dox®), which is approved for multiple cancers [104]. A 2002 clinical study reported by Koukourakis et al. evaluated whether RT and the two drugs Stealth® liposomal doxorubicin and docetaxel (Taxotere®) could be safely combined [79]. In this study, 25 patients with stage IIb non-small cell lung

cancer, patients received a daily dose of 2 Gy for approximately 7 weeks (total of 64 Gy), with cryoprotective agent amifostine administered prior to each RT fraction. The addition of the amifostine was rationalized based on a prior Phase I/II study where the individual drugs in combination with RT resulted in high mucosa toxicity forcing a dose reduction in the treatment regimen and potentially decreasing treatment efficacy [105]. Taxotere and Doxil were administered weekly and every two weeks, respectively, with newly enrolled patients receiving escalated doses after adverse side-effects were not observed. Complete response was observed in 40% of patients with partial responses accounting for 87% of the patient population. Only a small reduction in lymphocyte counts and mild esophagitis was observed, suggesting that administration of a cytoprotective agents allows patients to tolerate an aggressive treatment regimen.

Another study by Tsoutsou et al. evaluated the efficacy hypofractionated, accelerated RT in combination with vinorelbine, Doxil, and amifostine in 14 patients with locally advanced non-small cell lung cancer [106]. Patients received 15 fractions of 3.5 Gy over 4 weeks, Doxil every two weeks, and vinorelbine every one or two weeks depending on treatment group. As vinorelbine was administered at three increasing doses, patients that received the higher doses required delayed chemotherapy due to grade 3 neutropenia in 2/5 and 2/4 of the patients. Partial responses were observed in 64% of patients, minimal response in 21% and stable disease in 14% with overall median survival being approximately 8 months.

Furthermore, several clinical studies have evaluated liposomal cisplatin formulations, but while promising, nothing has been approved for use in MMRT [81,107].

4.4.2. Polymeric carriers

Polymer-based nanoparticles are derived from either synthetic or natural polymers. Examples of commonly used synthetic polymers include poly(ε-caprolactone), poly(styrene-maleic anhydride) copolymer, poly (lactic acid), PEG, polyester, poloxamers, among many others [99,108]. Examples of natural polymers include chitosan, alginate, collagen, and dextran [108]. Synthetically derived polymers can prove advantageous over natural polymers due to properties such as extended drug release times. Furthermore, there is evidence suggesting that certain natural polymers, such as alginate, may act as radioprotective agents. As such, these types of polymeric nanoparticles may not be suitable for MMRT [109]. Depending on the physiochemical properties of the polymer, various nanoparticle architectures will form. For instance, nanoparticles known as polymersomes exhibit the same architecture as liposomes and can form particles that range in size from nanometers up to micrometers [110]. Typically, these copolymers are biomimetic analogs of phospholipids. In solution, the hydrophobic portions will interact with each other while the hydrophilic portion interacts with the surrounding solution.

Polymeric micelles are nanosized colloids of amphiphilic block copolymers which will spontaneously form in water (*e.g.*, poloxamers). The inner hydrophobic portions can be used for the transport of hydrophobic drugs, whereas the outer hydrophilic region serves to stabilize the core. These types of particles exhibit a critical micelle concentration (CMC), meaning that below the CMC, colloidal micelles will not form. Nanoparticles polymer formulations consist of colloidal systems in which the drug can be dissolved, dispersed, or covalently attached to the polymer.

Several preclinical studies have investigated the use of polymeric-based nanoparticles in MMRT. For example, Werner et al. assessed the use of Genexol-PM, a nanoparticle formulation of paclitaxel for treatment of non-small cell lung cancer pre-clinically [94]. Mice were treated with either Genexol-PM or paclitaxel, six hours prior to irradiation with five daily fractions of 3 Gy. Treatment with Genexol-PM led to significantly longer delays in tumor growth compared to paclitaxel, suggesting its utility for enhancing the therapeutic window of RT. In another study, Au and colleagues demonstrated the ability of PEG-PLGA nanoparticles loaded with wortmannin (PI3K inhibitor) and docetaxel to enhance RT [111]. Mice were first treated with wortmannin/docetaxel nanoparticles then 4 Gy radiation 3 and 15 h after chemotherapy. *In vivo* tumor growth delay studies revealed that the dual-loaded nanoparticles significantly delayed tumor growth, increased survival rates, and demonstrated significantly increased DNA damage and apoptosis (Fig. 4 **a**). Furthermore, encapsulation of the drugs in the PEG-PLGA nanoparticles significantly reduced toxicity compared to the free drug counterparts. Overall, these findings proved promising for enhancing the therapeutic window of MMRT.

More recently, Zhang and colleagues evaluated the influence of co-delivered PLGA-PEG encapsulated wortmannin and cisplatin in ovarian cancer models [113]. Mice received clinically relevant doses of dual-loaded nanoparticles (cisplatin and wortmannin) immediately before receiving 5 Gy for three subsequent day (15 Gy total). Treatment with dual-loaded nanoparticles showed enhanced therapeutic efficacy across all treatment groups when combined with RT when compared to free drugs + RT. Additionally, these particles were found to outperform the single-loaded particles of cisplatin or wortmannin, implying a synergistic response.

In our previous work, we utilized a poloxamer based micellar formulation to deliver two DNA damage repair inhibitors, talazoparib and buparlisib (PARP and PI3K inhibitors respectively). This formulation was administered during a course of RT in a mouse model representative of late stage breast cancer. Mice received three consecutive daily doses of 5 Gy with the initial dose of RT delivered just after nanoparticle administration. While this therapeutic strategy demonstrated promise, there was no enhanced efficacy or survival of the dual-drug micelles with radiation over radiation alone, likely because study endpoints had been reached due to metastatic burden. However, tumor growth curves were beginning to separate, and tumor histology revealed more extensive apoptosis (Fig. 4 **b**) and an increase in DNA damage in the mice treated MMRT, mirroring the aforementioned study by Au et al. Future iterations of the work will likely explore the sequence of agent administration, fractionation/dose parameters, and drug dose increases to further optimize the treatment. In general, this study aimed to more realistically mimic the clinical paradigm in terms of the tumor model, treatment schedule, and inclusion criteria. Clinically, new therapeutics are often tested in groups that have advanced stage disease and have failed other therapies, therefore employing highly metastatic models and randomizing at larger tumor volumes in preclinical studies may more accurately predict the likelihood of translational success [112].

Currently there is one clinically approved polymer-based nanoparticle for oncologic applications in the US (Eligard) with three others worldwide: Genexol-PM (South Korea), Zinostatin (Japan), Zinostatin stimalamer Paclical (Russia) [114]. As of 2018, 15 polymeric nanoparticles were undergoing clinical trials, however, none of these have been evaluated clinically for MMRT.

4.4.3. Dendrimers

Another class of synthetic polymers are dendrimers, which are highly branched macromolecular structures that emanate from a central core and grow outward in concentric layers. Some of the most commonly evaluated dendrimers for use in nanomedicine include poly (amidoamines) PAMAM, polyester, glycodendrimers, carbosilanes, poly (L-lysine) and polypropyleneimines [115]. Dendrimer-based nanoparticles can serve as drug carriers either through conjugation of the drug or entrapment within the dendritic branches. Various compounds, including doxorubicin, campthothecin, cisplatin, and paclitaxel have been carried by dendrimers for enhanced drug delivery [115]. A study by Wu et al. designed a radiosensitive dendrimer loaded with doxorubicin. Here, L-cysteine was conjugated to the G 4.5 PAMAM dendrimer, disulfide bonds were forged between individual L-cysteine molecules, and doxorubicin was loaded [116]. The efficacy of CRT was tested *in vivo* in a zebrafish model inoculated with HeLa cells. Zebrafish were first treated with the doxorubicin-loaded dendrimer derivative and irradiated 2 h later (5 Gy). Results suggested that compared to free doxorubicin, the doxorubicin-loaded dendrimers decreased the proportion of HeLa cells remaining following treatment, implying a synergistic response.

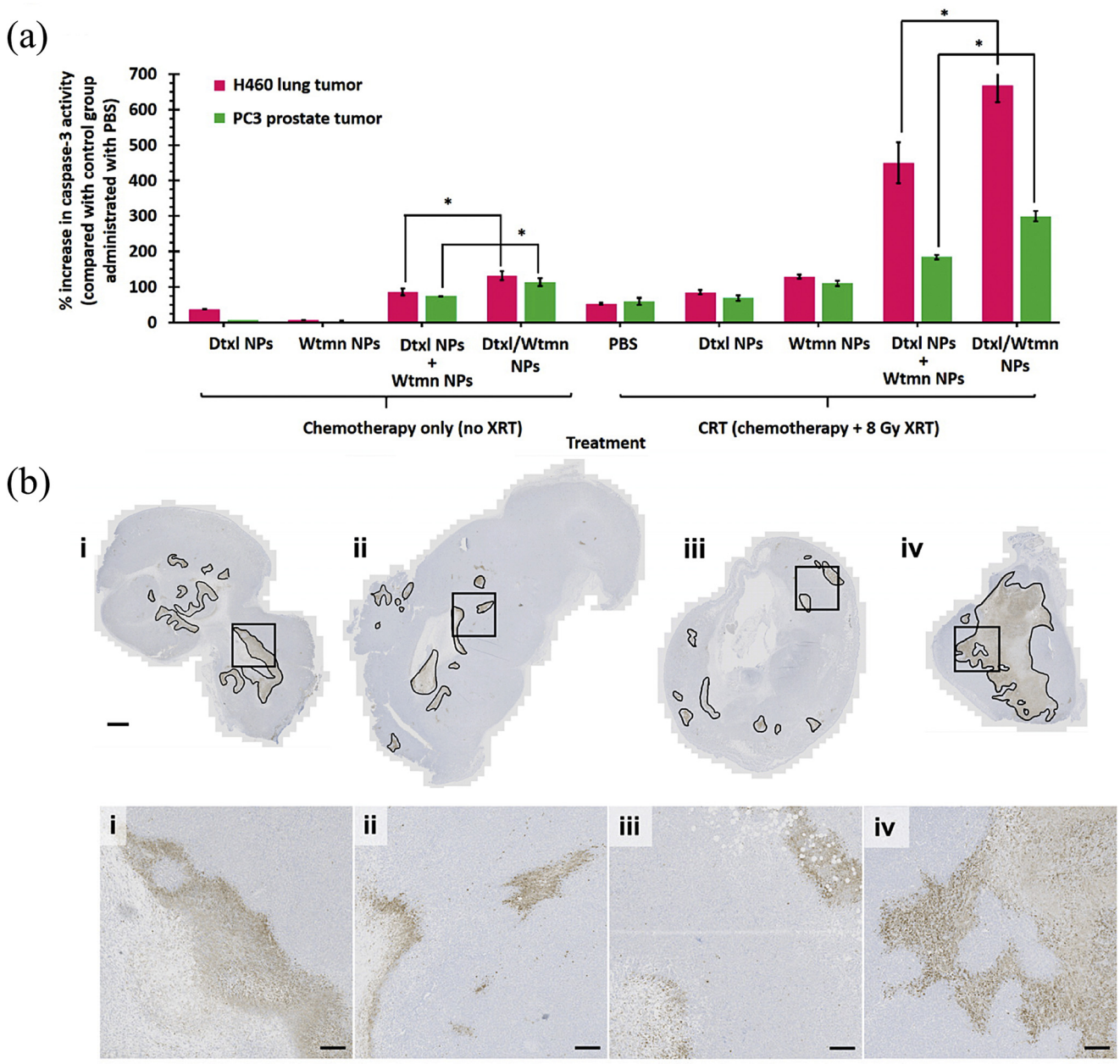


Fig. 4. (a) Quantification of cleaved-caspase 3 (CC3) staining in tumor sections of mice treated with various nanoparticles with or without IR compared to no treatment control. Adapted with permission from **[111]**. (b) Tumor sections stained with CC3 for (i) empty micelle, (ii) dual-loaded micelle, (iii) empty micelle + IR, and (iv) dual-loaded micelle + IR. Inset sections represent the corresponding boxed region in whole-tumor image. Outlined sections are designed to illustrate the extent of CC3 staining and thus apoptosis. Adapted with permission from **[112]**.

Overall, while there have been preclinical reports of dendrimers utilized in CRT, they have not moved forward to clinical trials and there are currently no clinically approved dendrimers. Based on a search of clinicaltrials.gov, to date, there is currently one recruiting trial to evaluate the efficacy and safety of Imdendrim for the treatment of inoperable liver cancer.

4.4.4. Biomacromolecules and conjugates

Various combinations of biomacromolecules and chemically coupled therapeutic agents fall within the classification of nanomedicine. An important distinction to make between nanoparticles and nano-conjugates is the difference in drug release as conjugates rely on active cellular-processes for cleavage and subsequent drug release, while nanoparticles are freely and continually releasing drug during circulation. However, polymer-, protein-, and antibody-drug conjugates change the size of chemotherapeutic agents effectively altering their solubility and pharmacokinetics, a key criterion for nanoparticles [117].

Polymer-drug conjugates have long been investigated for drug delivery and have had several products approved for clinical use. The main benefits of polymer-drug conjugations include enhanced drug solubility, increased drug circulation, immune-evasion, and altered release profiles leading to enhanced safety and efficacy [118]. The field of polymer chemistry has grown in parallel with drug delivery providing conjugates with unique properties which can be superior to traditional polymers. As of 2018, 16 polymer-drug conjugates were in various stages of clinical testing for oncology applications. Additionally, according to clinicaltrials.gov, there are numerous ongoing studies into the efficacy of MMRT utilizing both clinically approved and experimental polymer-drug conjugates. These studies include combinations of CRLX101 with radiation or Eligard with Docetaxel and radiation.

Protein-drug conjugates are an interesting class of nanomaterials that also offer similar properties to nanomaterials and polymer-drug

conjugates, but have additional benefits such as low endogenous toxicity, enhanced cellular uptake, and their inexpensive renewable sources to name a few [119,120]. Many studies have and continue to investigate the potential of enhanced therapeutic efficacy of combining Abraxane and RT in various cancers, with various sequences and combinations with additional drugs [121–123]. These studies demonstrate the benefit of administering a nanoparticle-based paclitaxel, which is a known radiosensitizer, in conjunction with RT to mitigate common toxicities associated with free paclitaxel regimens [124].

For antibody-drug conjugates (ADC), there is some investigation into chemoradiotherapy although most ADCs utilized for RT are delivering a radioactive substance rather than a chemotherapeutic [125–127]. One limitation of the utility of ADCs is the lack of a diverse array of targets, as currently there are four approved ADCs targeting only four proteins. Three of these ADCs are approved in blood cancers with the other approved for breast cancer. Therefore, combinations of ADCs with RT are limited at present date. However, there are approximately 175 ADCs in the various stages of development with around 16 currently in clinical trials. The approvals of new ADCs targeting solid tumors will open the field for a wide array of investigation into ADC-MMRT.

Furthermore, there are other nanoparticle platforms that do not fall into any of the prior categories such as Imlygic, an approved oncolytic virus. The nanoparticle itself is made up of a genetically modified herpes simplex virus which targets cancer cells and lyses them to stimulate an immune invasion [128,129]. Importantly, several ongoing clinical trials are investigating the combination of Imlygic with RT. Additionally, hybrid nanomaterials made out of casein, collagen, and ferritin are being investigated for their potential as drug delivery carriers.

4.5. Current strategies and considerations for nanoparticle multimodal radiotherapy

When aiming to develop nanoparticle-based MMRT the incorporation of clinically utilized parameters will prove advantageous toward successful clinical translation. In particular, a deeper understanding of the local tumor environment and the influence of RT will aid in the optimization of nanoparticle-based therapy. The following sections aim to describe preclinical studies which evaluate various effects that RT has on its local environment, all of which may guide future rational design of nanoparticles for MMRT. Additionally, important considerations that influence rational combinations and timing are noted, specifically in regard to their application with nanomaterials as these carriers have many effects. Furthermore, areas of research opportunities are noted to stimulate interest in elucidating parameters that may prove critical in the development and translation of these technologies.

4.5.1. Nanoparticle accumulation and the influence of ionizing radiation on the tumor microenvironment

For years, the enhanced permeability and retention (EPR) effect has been promoted as a mechanism for tumoral drug delivery by nanoparticles. Conceptually, this phenomenon is based on the notion that increased vascular leakiness exists due to the rapid proliferation of cancer cells and the surrounding blood vessels [130]. This leakiness creates an environment of high vascular permeability allowing nanoparticles and other high molecular weight macromolecules to permeate into the local tumor environment to a greater extent than healthy tissue. In healthy tissues, this size species is cleared by the lymphatic system, but in cancer the lymphatic function is typically impaired leading to increased retention. Collectively, the leaky vasculature and impaired drainage allows for enhanced permeability and decreased clearance resulting in higher tumoral particle accumulation amounting to the EPR effect.

Regardless of the EPR effect, there are additional factors that can influence overall tumor physiologically and subsequent drug accumulation. One example of this is the increased interstitial fluid pressure (IFP) that is characteristic of solid tumors [131]. Increased tumoral IFP is a direct result of the enhanced blood vessel permeability, reduced perfusion and lymphatic drainage, and cellular density in tumors [132]. The increased permeability allows a multitude of blood plasma constituents to travel into the tumor interstitium [133]. Consequently, osmotic pressure differences between the blood vessels and interstitial space is no longer maintained and the IFP approaches vasculature pressure [133]. Thus, the gradient pressure loss results in decreased transportation efficiency of the nanoparticles as escape from the blood vessels is largely a diffusion driven process [134]. Accordingly, nanoparticles accumulate near tumor blood vessels rather than distributing evenly throughout the tumor microenvironment, a direct contradiction to EPR. Previous research encapsulating a liposomal-CT contrast agent evaluated the overall distribution of the nanoparticles in tumors, observing more uniform uptake in tumors with lower IFP [135,136]. Researchers proposed a direct correlation between increased uniformity and more consistent perfusion. Largely, for these reasons and a lack reproducibility in human tumors, the EPR effect remains highly debated. In general, while the EPR effect may contribute to nanoparticle accumulation, this phenomenon is significantly more complex and less broadly applicable than initially postulated.

In a 2016 clinical trial, Clark et al. evaluated tumor accumulation of nanoparticles following systemic administration. Here, tumor and adjacent healthy tissue biopsies were obtained before and after administration of CRLX101. After treatment, biopsies revealed that drug was present in tumor tissue of all patients but not in the surrounding healthy tissues. Supporting the concept of EPR effect clinically, the intact nanoparticle was also observed in 5 of the 9 patients. Importantly, in a mouse model, the same experiment displayed significantly enhanced accumulation in tumor tissue compared to human patients, further supporting the heterogeneity of the EPR effect across species and even individuals [137].

Doxil was initially approved for the treatment of Kaposi's sarcoma (KS) and later multiple myeloma (MM) as a result of increased efficacy and decreased toxicity [138]. The success of Doxil in these cancers may be derived from the extremely leaky blood vessels characteristic of KS and the unique properties of blood cancers, such as MM, where EPR, IFP, or other problems associated with solid tumors are not factors [139,140]. Comparatively, in other solid tumors that lack EPR, Doxil does not significantly improve the efficacy of treatment upon comparison to the free drug. However, it does alter the overall biodistribution and decrease cytotoxicity, particularly treatment-limiting cardiotoxicity, and is highly beneficial for these reasons [141]. Ultimately, the clinical influence of the EPR effect is largely ambiguous and unlikely to be present equally in all tumors. Importantly, there is evidence that RT may prove beneficial for enhancing tumor accumulation, thus increasing the therapeutic efficacy of nanoparticles by increasing accumulation, stimulating the immune system, and modulating the tumor microenvironment [142]. Capitalizing on these aspects of a combined nanoparticle-RT therapeutic regimen, in addition to the benefits of multimodal therapy, may prove to be a niche where nanoparticles can fulfill their early promises. A thought-provoking review by Stapleton et al. details the influence of RT on the tumor microenvironment and how this effect would likely lead to increased uptake of nanoparticle formulations over small molecule therapeutics (Fig. 5 **a**) [135]. If these effects are translatable from animal models to patients, this would essentially make the EPR effect a clinically viable phenomenon.

As the longest FDA approved nanomedicine, much of the investigation into RT enhanced accumulation has been done with Doxil. In a human osteosarcoma xenograft model, Davies et al. found that doxorubicin uptake was increased 2–4 times (single fraction, 8 Gy) or 1–3 times (fractionated, 3.6 Gy × 3 days) when Doxil was administered 24 h prior to RT. Furthermore, both RT + Doxil regimens significantly delayed tumor growth compared to the untreated controls [87]. Clinically, after radiotherapy, Doxil has been demonstrated to preferentially accumulate in tumor tissue over healthy brain tissue in patients with metastatic brain lesions and primary glioblastoma [144]. From this study, the authors concluded that liposomes are able to overcome the blood-brain barrier, but only to reach tumor tissue. However, in this study patients were treated with Doxil on days 1 and 21 in addition to

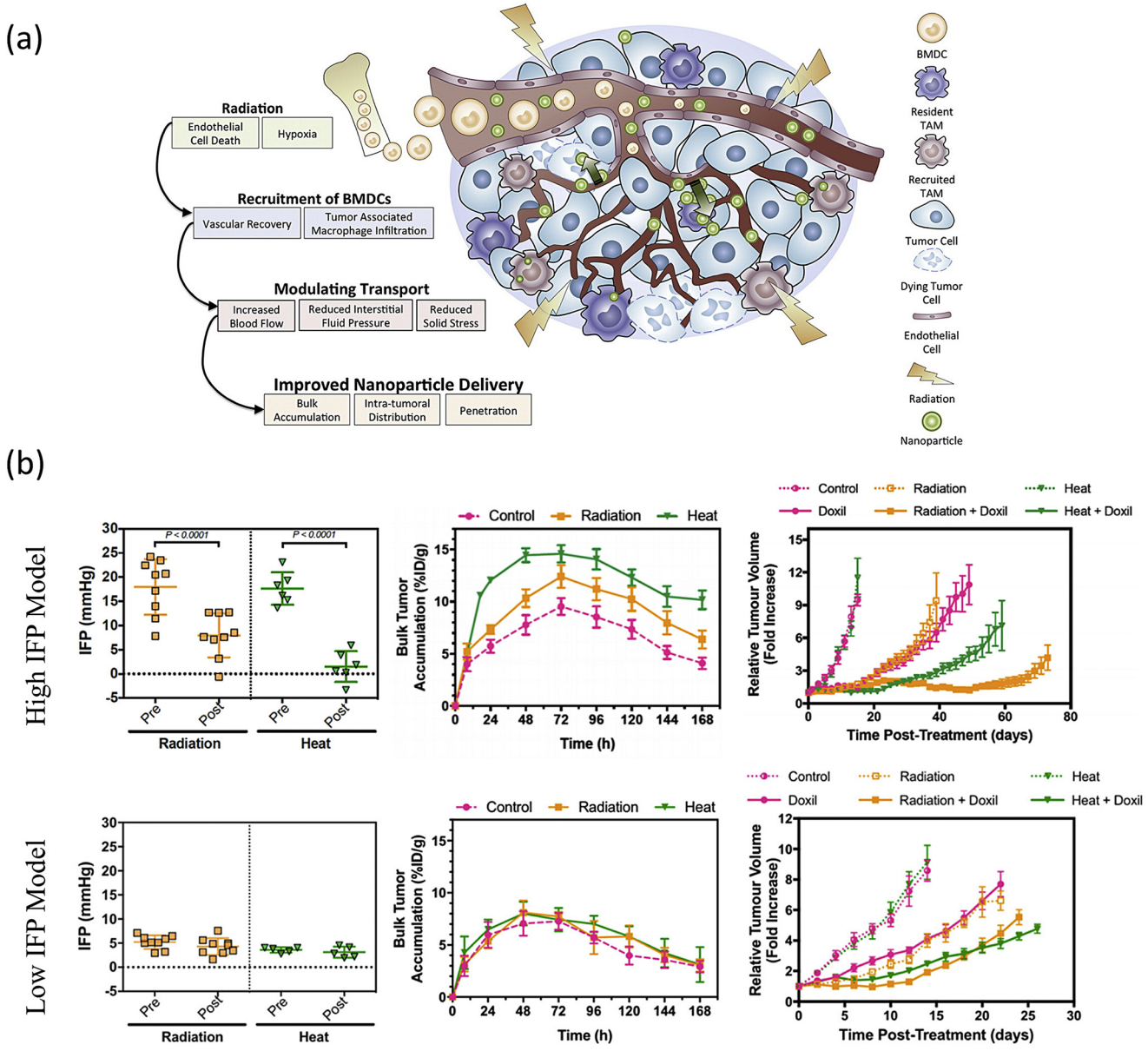


Fig. 5. Radiation influences the tumor microenvironment in many ways and recently research has begun to further understand these effects and the complex way they may be exploited to enhanced tumoral accumulation of nanoparticles. (a) Graphical abstract highlights some of these influences. Adapted with permission from **[135]**. (b) (top) Pretreatment with radiation decreased IFP 24 h post-treatment and the intratumoral bulk accumulation in MDA-MB-231 tumors. (bottom) Tumor IFP was low (4.5 ± 1.5 mmHg) but not negligible in the 4T1 tumors. A significant change in IFP following radiation was not observed and radiation does not improve the bulk accumulation, intratumoral distribution. In *in vivo* studies radiation or followed by Doxil resulted in a modest increase in tumor growth delay compared to all other treatments in the 4 T1 tumor model. Adapted with permission from **[143]**.

fractionated RT and a booster dose over the course of 23 days. Unfortunately, patients without RT were not included and therefore a causal relationship of enhanced accumulation from irradiation could not be determined.

Although IR affects much of the tumor microenvironment, the influence of IR on tumor vasculature is one of the most well-studied. To that end, radiation induced vascular changes have been linked to both the total dose and the fractionation of RT. Vascular volume often decreases in a dose- dependent fashion after single radiation doses of 5 Gy or more, correlating with an increasing extent of vascular damage [145]. In addition, in single moderate- to high-dose regimens, as vascular damage increases, vascular permeability also increases. However, investigation of these effects during a clinically relevant conventionally fractionated radiotherapy (CFRT) schedule revealed enhanced accumulation of macromolecules despite a lack of observed vascular disruption [36]. In contrast to high-dose radiation, despite increasing accumulation, CFRT appears to induce vascular maturation thus implicating alternative mechanisms of enhanced accumulation rather than increased extravasation. This underscores the importance of investigating multiple fractionation schedules and highlights the complex interplay between radiation and the tumor microenvironment for enhancing accumulation.

Closely related to the tumor vasculature, the influence of IFP on the tumor microenvironment has been examined on several occasions. Lammers et al. investigated the effect of RT on tumoral accumulation of HPMA copolymers. Here, mice were exposed to a dose of 2 or 20 Gy, at 1 or 24 h before copolymer administration. Unsurprisingly, tumoral copolymer accumulation was found to increase for all treatment groups compared to unirradiated animals. Importantly, however, the highest increases were observed with a 24-h gap between IR (20 Gy) and copolymer administration. While the authors hypothesized that this course of RT was resulting in lower IFP, this was not directly measured. Toward this end, a recent report by Stapleton et al. demonstrated that a single dose of RT could significantly enhanced accumulation and

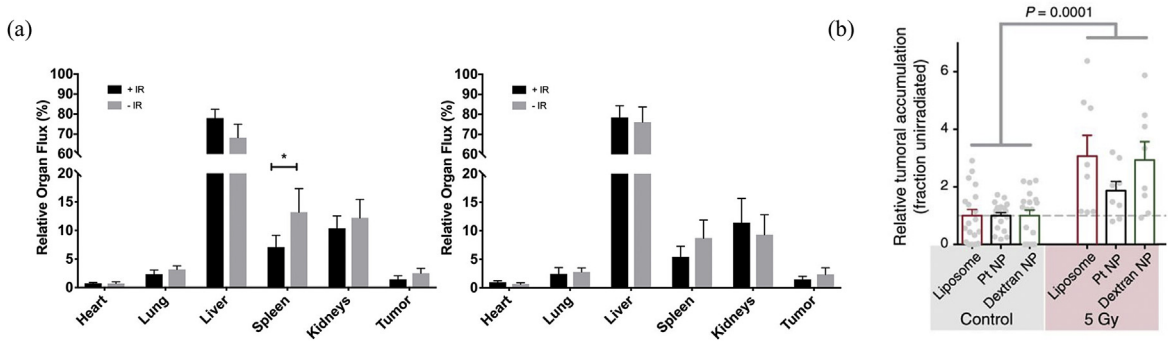


Fig. 6. Radiation influences on tumoral nanoparticle accumulation. (a) Tumor accumulation of NIR-fluorescent polymeric micelles administered either 24 h or 72 h after the last dose of RT (3 consecutive daily doses of 5 Gy) in a 4 T1 model. Adapted with permission from **[112]**. (b) Tumor accumulation of 3 different fluorescent nanoparticles administered 72 h after a single dose of 5 Gy in 4 T1 bearing mice. Adapted with permission from **[146]**.

distribution of nanoparticles in tumors [143]. Specifically, they investigated how an altered IFP after RT affected particle uptake (Fig. 5 **b left, middle**). In a high IFP human breast cancer model, a single fraction of 15 Gy significantly enhanced nanoparticle accumulation and distribution when administered 24 h prior. Additionally, RT both decreased IFP by 50% and enhanced treatment efficacy in this model. Comparatively, in a low IFP murine breast cancer model, RT did not increase nanoparticle accumulation or alter the IFP. However, in both models, treatment with RT followed by Doxil resulted in delayed tumor growth albeit to a greater extent in the high IFP model (Fig. 5 **b, right**). In the same low IFP model, we recently investigated the influence of RT on organ accumulation of a different nanocarrier type, mixed poloxamer micelles (MPMs). Here, mice implanted with 4 T1 tumors were injected with Cy 7.5-loaded MPMs either 24 or 72 h after 3 consecutive daily doses of 5 Gy. *Ex vivo* analysis of organs 24 h after MPM administration, demonstrated no significant change in tumor accumulation at either timepoint (Fig. 6 **a**). Despite no increase in tumor accumulation enhanced efficacy was evident. Both of these findings coincides with a report by Harrington et al. where a single fraction of RT delivered anywhere between 30 min to 72 h prior to radiolabeled liposome administration did not increase nanoparticle uptake but did enhance therapeutic efficacy in a human KB head-and-neck xenograft model. [95] However, these studies directly contradict a previous report where administration of 5 Gy 3 days prior was found to increase tumor accumulation 3 different particle types (liposome, polymeric micelle, dextran nanoparticle) in the low IFP 4 T1 model (Fig. 6 **b**).

Due to the impact of the cancer-immune response on the tumor microenvironment, understanding RT's effect on the immune system is fundamental as these effects may also alter accumulation [135]. In addition to implicating IFP and the microvasculature in enhanced accumulation, some studies have linked the increase in tumor-associated macrophages (TAM) to an increased delivery of nanomedicines after radiation [146]. Studies have shown that radiation activates and upregulates the expression and excretion of a number of pro-inflammatory chemokines, genes, proteins, and pathways [147]. In response to inflammation, which is induced by IR, pericytes upregulate the intracellular adhesion molecule 1 (ICAM-1) and excrete a chemoattractant known as macrophage migration inhibitory factor (MIF), two stimulatory signals capable of recruiting macrophages to sites of inflammation [148]. Thus, theoretically, macrophage phagocytosis of nanomedicines and subsequent transportation to tumor tissue may be a factor influencing the enhanced accumulation observed after RT.

In general, IR induces changes in the tumor microenvironment resulting in increased accumulation of macromolecules and nanoparticles alike. Despite evidence of enhanced accumulation, there has been no systematic investigation into elucidating this phenomenon. Establishing a framework for RT enhanced nanoparticle accumulation may greatly improve the potential for clinical approval and translation. Determining the boundaries of this effect is very important as clinical radiation schedules vary widely based on tumor location, type, stage, and other parameters. Furthermore, by screening ineffective nanoparticle types and radiation schedules before large clinical investment occurs, valuable investigational resources can be directed to the most promising therapeutic regimens.

4.5.2. Enhanced targeting through radiotherapy induced expression

In contrast to relying on passive tumoral accumulation through phenomena such as the EPR effect, active approaches have evolved as a more specific and complementary strategy. In a meta-analysis report surveying the past ten years of literature, it was found that less than 1% of administered nanoparticles reach the tumor volume [149]. These findings highlight the rationale behind current efforts to actively target various tumor pathophysiologies for increased nanoparticle accumulation. As previously noted, there are two primary approaches for enhancing tumor accumulation: targeting through either passive or active mechanisms. Approaches to improve passive targeting by enhancing biological interactions include physical modification of nanoparticle size, shape, or general composition. Comparatively, active targeting utilizes nanoparticle surface-bound targeting moieties to target cancer, vasculature, or immune-specific receptors for enhanced accumulation, internalization, and efficacy. Ligands are selected based on their ability to bind receptors that are overexpressed in the target tissues. Targeting moieties such as proteins, antibodies, peptides, aptamers, and small molecules have all been investigated for nanoparticle-based targeting [150,151]. Receptors commonly over-expressed in cancer and exploited for targeting include; folate receptor, CD44, HER2, and EGFR [152]. The proliferative and metastatic nature of cancer induces upregulations in these receptors which are implicated in processes that help facilitate growth and spread.

For example, CD44, is a cell surface glycoprotein known to participate in a variety of cellular processes including; proliferation, growth, and angiogenesis. A study by Arabi *et al,* modified Doxil with a monoclonal antibody against CD44 (CD44-Doxil) and evaluated cellular uptake and efficacy [150]. Here, mice treated with CD44-Doxil exhibited significantly higher doxorubicin concentrations inside the tumors than the unmodified Doxil. Additionally, the CD44-Doxil nanoparticles displayed decreased tumor volumes and increased median survival rates. Overall, these results are promising for increasing internalization, efficacy, and survival. Alternatively, several reports have suggested that while cellular internalization of nanoparticles is improved by incorporating targeting ligands, tumor localization is not [153,154]. In addition, it remained unclear the influence of internalization on therapeutic efficacy. In direct contrast, Jin et al. investigated EGFR-targeting peptides conjugated to curcumin-loaded, PLGA-PEG nanoparticles [151]. Despite promising internalization data *in vitro*, there was no significant difference in therapeutic efficacy *in vivo* between the targeted and untargeted nanoparticles. However, like many other aspects of nanoparticle therapeutics, it is important to consider the influence that nanoparticle and/or animal model characteristics may have when comparing results.

Although inducing an EPR effect may be one of the most beneficial consequences of RT, reports have noted that certain cellular adhesion molecules, such as P- and *E*-selectin, GRP78, ICAM-1 and more, may be upregulated after RT. Thus, due to the targeted nature in which IR can be delivered, enhanced targeting may be possible by exploiting these receptor changes [88,89,155,156] rather than universally receptors which can be cancer-overexpressed, such as EGFR. Combining RT enhanced accumulation and RT upregulated targets could impart significant effects on both nanoparticle accumulation and internalization. For instance, P-selectin, an inflammatory adhesion molecule that can recruit leukocytes (inflammatory response) or facilitate metastasis (cancer induced), was discovered to be expressed in many human tumor cancer cells [155]. Additionally, P-selectin can be activated and upregulated after administration of endogenous cytokines or IR, making it a potential target for RT-guided targeting. A report by Shamay et al. utilized an algae derived polysaccharide, fucoidan, to formulate nanoparticles, due to its affinity for P-selectin. Selective targeting of fucoidan nanoparticles was assessed *in vitro* under stimulated inflammatory conditions through activation with tumor necrosis factor-alpha (TNF-α) or IR (6 Gy). Following activation by both TNF-α and IR, fluorescence imaging demonstrated that the fucoidan nanoparticles selectively bound to the cancer cells (Fig. 7 **a-d**). The effect of IR on P-selectin targeting was then assessed *in vivo*, in a mouse model where P-selection expression is not normally observed. As early as four hours after IR (6 Gy) and immediately following nanoparticle administration, the expression of P-selectin and its utility as a targeting agent became apparent. At 24-h post IR, irradiated tumors displayed 3.8-fold higher fluorescence intensity values compared to unirradiated tumors. In mice that received both IR and nanoparticles complete tumor regression was observed, thus demonstrating the promise as P-selectin targeting for RT-guided drug delivery. P-selectin represents one option for RT-guided drug delivery, though it may not be the optimal choice. Further study is warranted regarding the opportunities and challenges for RT-guided drug delivery.

4.5.3. Radiotherapy and the immune system: Applications of nanotechnology to radioimmunology

Cancer immunotherapy has seen a surge in utility due to remarkable outcomes in several forms of cancer, which has led to many key approvals. An effective anticancer immune response results when the steps of the cancer-immunity cycle (Fig. 8 **a**) are initiated and proceed in an iterative manner [157]. In cancer patients, the cycle is deficient and must be either initiated or re-implemented. By identifying the missed or malfunctioning step, the processes can be stimulated through various means. As such, researchers are exploring potential strategies to utilize RT, nanotechnology, and the combination to induce this response. By releasing tumor associated antigens (TAA), RT has the ability to overcome the immunosuppressive environment stimulated by cancer. Additionally, IR activates pathways responsible for recruiting immune cells and modifies the tumor microenvironment which may allow for better penetration of administered immunotherapeutics. In traditional oncology, nanoparticles are designed to primarily target cancer cells, whereas in immune-oncology nanoparticles can be designed to target immune-specific cells such as antigen presenting cells (APCs). The ability of nanoparticles to target these cells may facilitate the delivery of antigens, adjuvants, antibodies, and help modulate the tumor microenvironment [158]. Taking advantage of aspects from both RT and nanotechnology proves a promising approach to enhance the applicability and efficacy of immunotherapy.

One clinical approach involves combining checkpoint inhibitors and RT to elicit the abscopal effect, where local tumor treatment leads to regression of systemic metastatic spread [160]. An innovative study by Min et al. employed antigen-capturing (AC) nanoparticles formulated from PLGA [159]. After formulation, various surface chemistries were employed in order to evaluate the influence of nanoparticle surface on capture of TAA released after RT. The authors hypothesized that the proper surface chemistry would enhance TAA capture and subsequent delivery to APCs thus improving the local immune response and stimulating the abscopal effect (Fig. 8 **b**). Following successful demonstration that various surface modifications influenced TAA capture, the AC-nanoparticles were then evaluated for their ability to induce the abscopal effect. To investigate this, mice were inoculated with dual-flank tumors one of which was treated with IR after checkpoint inhibitor therapy. Following RT, AC-nanoparticles were administered, and responses evaluated for all formulations. Excitingly, results showed that two formulations achieved significantly delayed tumor growth and abscopal effect induction. This observed enhancement also translated to an increased survival rate with a complete response observed in 20% of the animals. This study is an example of the important role nanotechnology may play at the radiation-immunotherapy interface and make clear the importance of evaluating nanoparticle characteristics in these types of studies.

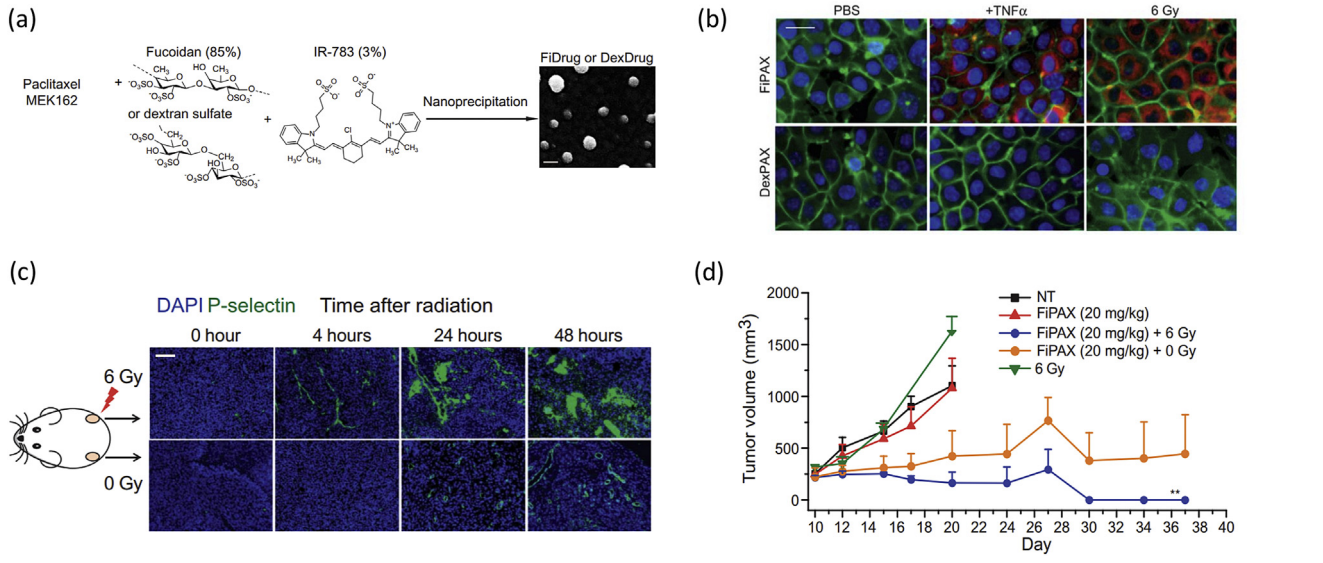


Fig. 7. P-selectin targeting for enhancing RT **(a)** synthetic scheme of the preparation of fucoidan-encapsulated paclitaxel nanoparticles (FiPAX). **(b)** Fluorescence images of human endothelial monolayer treated with TNF-alpha and IR (6 Gy) to induce P-selectin. Red, NIR dye in FiPAX or control DexPAX nanoparticles; green, CellMask membrane stain; blue, DAPI nuclear stain. Scale bar, 5 μm. **(c)** Immunofluorescence measurements of 3LL tumors extracted from mice after radiation treatment. Green, P-selectin; blue, DAPI nuclear stain. Scale bar, 50 μm. **(d)** Tumor growth inhibition after irradiation and single-dose administration of drug treatments. All treatments were given on day 10 after tumor inoculation. Adapted with permission from **[155]**.

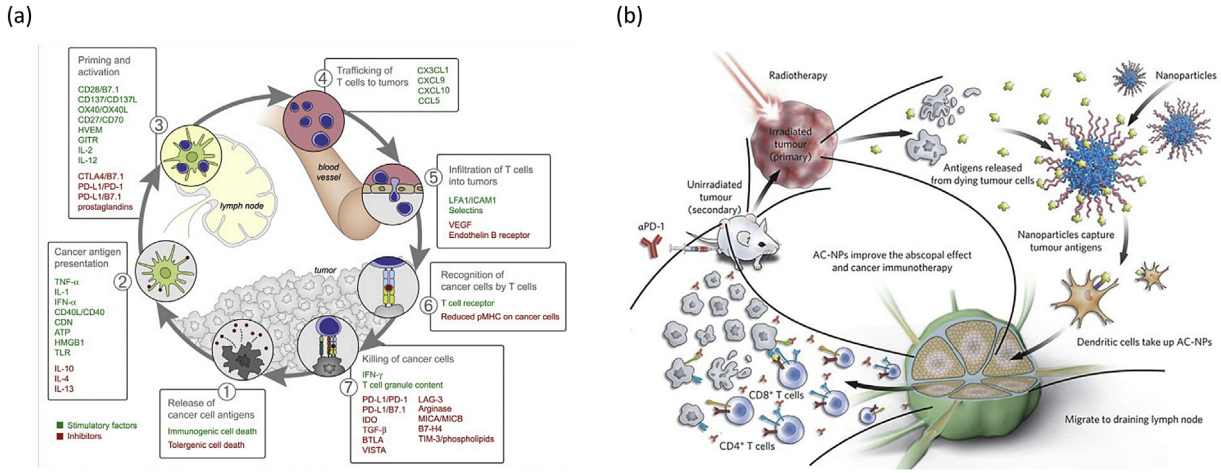


Fig. 8. Immunotherapy and RT **(a)** cancer-immunity cycle with stimulatory and inhibitory factors. Stimulatory factors shown in green promote immunity, whereas inhibitors shown in red help keep the process in check and reduce immune activity and/or prevent autoimmunity. Immune checkpoint proteins, such as CTLA4, can inhibit the development of an active immune response by acting primarily at the level of T cell development and proliferation (step 3). We distinguish these from immune rheostat ("immunostat") factors, such as PD-L1, can have an inhibitory function that primarily acts to modulate active immune responses in the tumor bed (step 7). Examples of such factors and the primary steps at which they can act are shown. Although not illustrated, it is important to note that intratumoral T regulatory cells, macrophages, and myeloid-derived suppressor cells are key sources of many of these inhibitory factors. Reproduced with permission from **[157]**. **(b)** Schematic illustration depicting the utilization of antigen-capturing nanoparticles (AC-NPs) to improve cancer immunotherapy. After RT, AC-NPs will bind to tumor antigens and improve their presentation to dendritic cells. Reproduced with permission from **[159]**.

Along with its effects on the immune system, radiation can influence the entire tumor microenvironment [161]. Properly capitalizing on the various aspects of RT's local influence for enhanced accumulation and efficacy may markedly improve the fields of MMRT and nanomedicine through their optimal integration.

4.5.4. Pharmacokinetics/release

One of the major advantages of nanoformulations over their free drug counterparts are the clinically observed improved pharmacokinetics (PK) and drug release rates [162]. In addition to other parameters, overall treatment efficacy will likely be influenced by the drug release kinetics. For example, a preclinical report by Sethi et al. assessed the effect of drug release on the therapeutic efficacy of wortmannin and docetaxel. Following formulation, nanoparticles were evaluated *in vitro* to determine their release kinetics [163]. Drug release studies demonstrated a decreased rate of drug release through variation of polymer ratios. *In vivo*, the relationship between therapeutic efficacy and drug release was clear as nanoparticles exhibiting slower drug release profiles were more effective (Fig. 9b). This observation is supported by the notion that slower release can increase intra-tumoral drug availability. These results correspond with the observation that sustained release of chemotherapeutics lead to increased cytotoxic effects. Furthermore, nanoparticle formulation with slower drug release kinetics displayed reduced hepatotoxicity. Taken together, these findings provided evidence that enhanced therapeutic efficacy and reduced toxicity are achievable through manipulation of drug release kinetics.

In addition to enhanced PK, nanoparticles can be utilized for delivery of multiple chemotherapeutics to further induce synergistic effects [166]. A study by Tian and colleagues, analyzed the efficacy of co-encapsulation of docetaxel and cisplatin (prodrug) in a lung cancer model. Evaluating the *in vivo* efficacy revealed that dual-encapsulation significantly blunted tumor growth compared to all treatment arms, including the individually loaded nanoparticles administered together. Furthermore, Wan et al. observed similar results when utilizing a poly(2-oxazoline) polymeric micelle for the co-delivery of paclitaxel and cisplatin [167]. Researchers hypothesize that the enhanced efficacy is a result of better spatiotemporal delivery of drugs at specific ratios and doses, both of which are critical components in optimizing combination therapies [164].

Some of the most innovative approaches are aimed at the development of tumor microenvironment-responsive nanoparticles, which exploit common tumor characteristics. These types of stimuli-responsive nanoparticles undergo drastic changes which alter their physiochemical properties in response to stimuli such as pH, temperature, hypoxia, and reduction/oxidation resulting in a triggered release [168]. The difference in acidity between the tumor microenvironment (pH 6.5–6.8) and the surrounding tissues (pH 7.4) due to the increased production in lactic acid (Warburg effect) forms the rationale for the development of pH sensitive nanoparticles [169,170]. This variation in pH, can prove promising for the development of carriers which are stable under normal physiological conditions (pH 7.4) but degrade in acidic conditions, subsequently releasing the drug payload into the surrounding environment [171]. pH-sensitive nanoparticles have also been developed through the incorporation of an acid-labile linker that will undergo hydrolysis releasing the drug. Chytil and colleagues conjugated doxorubicin to a micelle-forming amphiphilic N-(2-hydroxypropyl) methacrylamide (HPMA) through a hydrazone-based linker (Fig. 9c) [165]. Additionally, various cholesterol-based moieties were conjugated to HPMA-based polymers creating variation in micelle disintegration, allowing investigation on the influence of hydrolysis rate on *in vivo* efficacy. The resulting HPMA doxorubicin conjugates demonstrated stability at physiological pH, however degraded under acidic conditions. *In vivo* studies suggested that efficacy was directly correlated to stability of the micellular structure, where HPMA doxorubicin conjugates with faster hydrolysis rates displayed faster blood clearance and lower tumor uptake ultimately decreasing their anticancer activity (Fig. 9d).

Many have also investigated the development of nanoparticles which are responsive to external stimuli, such as light and ultrasound [172]. Several reports have also utilized X-rays to trigger the release of a therapeutic payload. A large majority this work, however, have focused on the utilization of inorganic based materials due to the poor X-ray absorption of organic molecules [172]. Extremely high radiation doses are often required to break the covalent attachments in the polymeric nanoformulations, thus limiting their clinical utility. To circumvent these limitations, several reports have focused on redox-sensitive nanoparticles that respond to the increased concentration of ROS following irradiation [173]. Several reports have utilized DNA to conjugate a therapeutic agent to an inorganic nanoparticle. During irradiation, X-rays act as the triggering event generating ROS induced DNA break strands, capitalizing on a well-known ability of IR [173,174]. Additionally, the incorporation of an inorganic core can aid in augmenting the concentration of ROS generated, thus improving nanoparticle and increasing overall drug release and therapeutic efficacy. Deng et al.

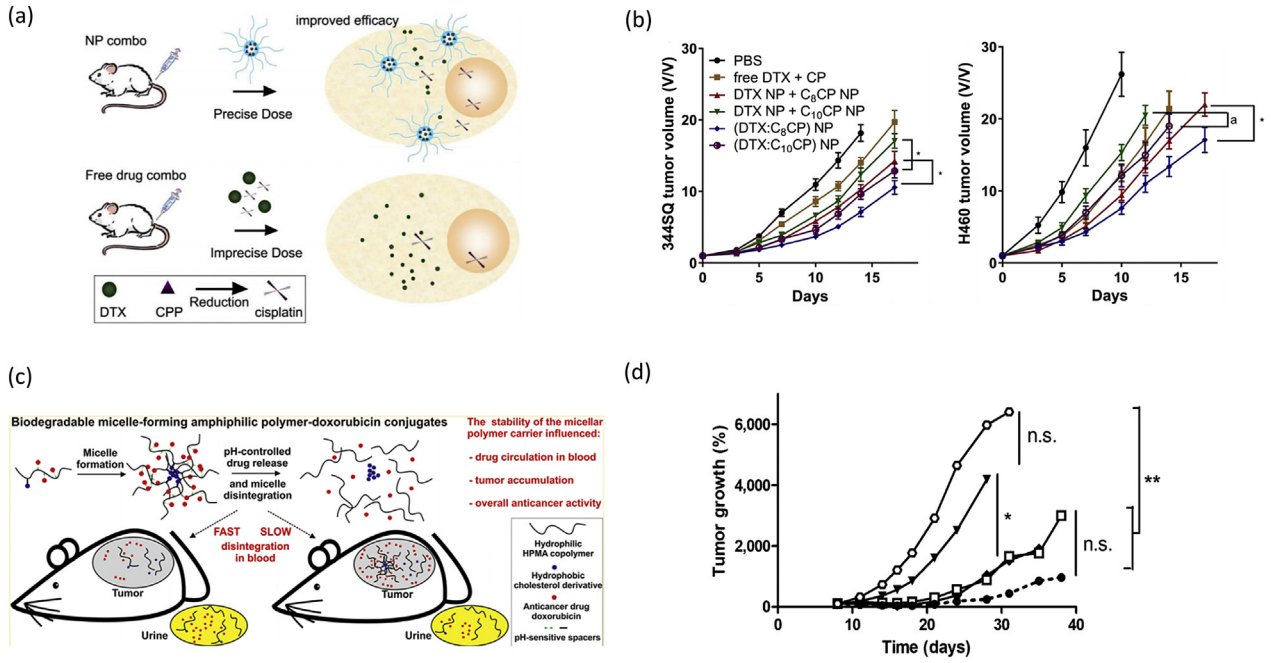


Fig. 9. Influence of drug combinations on *in vivo* efficacy **(a)** nanoparticle co-encapsulation of docetaxel and cisplatin allows for accurate exposure of the tumor site to both drugs. Comparatively, free drug dosing may lead to variations in tumor drug exposure, reducing potency. **(b)** Free drug and nanoparticle formulation *in vivo* efficacy in 344SQ and H460 murine xenograft models. Mice were treated with combinations of either the free drugs, singly loaded nanoparticles, or dually loaded nanoparticles. Tumor microenvironment-responsive nanoparticles. Reproduced with permission from **[164]**. **(c)** pH responsive nanoparticle of varying stability influence overall anticancer activity. (d) tumor growth and resistance in murine EL4 T-cell lymphoma treated with micellar doxorubicin conjugates. Reproduced with permission from **[165]**.

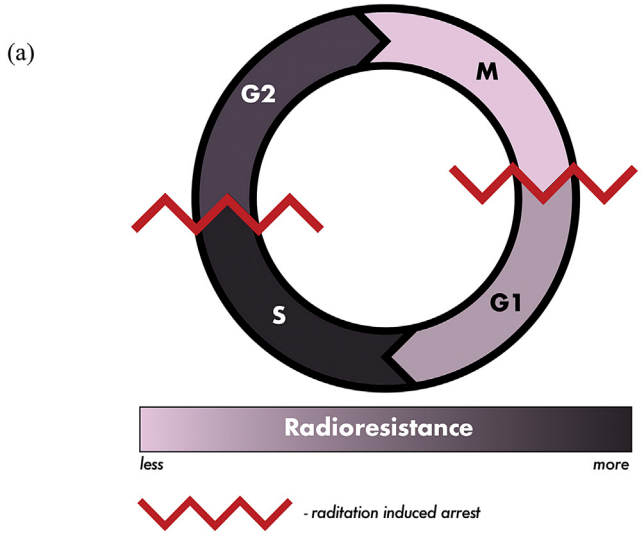
formulated an X-ray triggered liposomal platform by co-embedding photosensitizers and gold nanoparticles within the lipid bilayer [174]. Upon irradiation, the generation of ROS results in oxidation of the lipids, subsequently destabilizing the lipid membrane. *In vivo* studies revealed significantly reduced tumor growth upon administration of the X-ray triggered liposomes and IR compared to either agent alone.

While limited, several reports employed solely polymeric-based nanoparticles through the incorporation of Se—Se bonds. These selenium-containing polymers exhibit high sensitivity to low concentrations of oxidants, enhancing release of the therapeutic payload [175]. Despite the innovative concept of stimuli-responsive nanoparticle formulations, particularly for X-ray responsive nanoparticles, limited preclinical research is available regarding therapeutic relevance. In general, many of these technologies remain at the proof-of-concept state often requiring conditions beyond those allowable by current clinical conditions to demonstrate functionality. For instance, nanoparticles are commonly administered *via* intratumoral injections to enhance therapeutic efficacy by allowing administration of the entire therapeutic dose. As these types of accessible tumors are normally surgically excised, the application of these platforms may be limited. In addition, these reports often do not account for factors such as PK, release, or biodistribution. Unfortunately, this results in a limited understanding regarding whether tumoral nanoparticle accumulation is sufficient to elicit a therapeutic response upon external stimulus. Ultimately, to establish a clearer picture, more work must be done to investigate how various radiation schemes affect the pharmacokinetics, accumulation, and the release of drug from different nanoparticle formulations.

4.5.5. Therapeutic mechanism of action

In order to effectively eradicate malignant cells, cytotoxic compounds must be combined with RT to overcome efficacy-restricting variables, such as tumor hypoxia. Chemotherapy agents, including antimetabolites, platinum agents, topoisomerase inhibitors, and taxanes, can directly interact with DNA *via* distinct mechanisms in hypoxic cells to help overcome radioresistance. However, radiosensitization effects of chemotherapeutic agents often vary based on their mechanism of action leading to differences in the optimal administration sequence.

Mechanism of action plays a particularly important role in the case of cell cycle inhibitors. Fig. 10a outlines the cell cycle phases where the therapeutic agent may be most effective when used in combination with RT. For instance, there is evidence that cells damaged by alkylating agents will arrest in G_2 of the cell cycle [176]. G_2 and mitosis are considered radiosensitive phases of the cell cycle, so there is justification for early administration of alkylating agents to induce DNA damage and cause cells to arrest before or during radiation. Alternatively, antimetabolites are often most effective during S phase and shown to be extremely sensitive to drug timing and schedule [177]. Concurrent CRT exploits differential cell cycle radiosensitivity as is the case when utilizing taxanes, which promote cell cycle arrest or synchronization, at the G2 and M phases (the most radiosensitive phases). Administering radiation when cells have synchronized increases radiation sensitivity of these cells. Furthermore, the requirement of ideal timing strategies is no unique to cell cycle influencing agents, as factors such as mechanism of action and fractionation may influence the timing required of other therapeutic drugs. Table 2 lists the classes of chemotherapeutics, with specific examples, that are commonly used in combination with RT including alkylating agents, antimetabolites, plant alkaloids, and platinum-based therapeutics. These categories of chemotherapeutics are important to consider as they all have different interactions with cells that may influence the timing of drug and radiation administration. For instance, chemotherapy may also eradicate cells in S-phase, the most radioresistant portion of mitosis, effectively enhancing the number of cells in more sensitive phases which will thus be exposed to IR [88,91]. Additionally, agents such as mitomycin C and tirapazamine function as bioreductive prodrugs which are preferentially activated within hypoxic environments to confer enhanced radiosensitivity and cytotoxicity [91]. However, even within the drug class these effects can vary, so personalization of the treatment with each compound is still necessary. Of further importance, as noted by Coleman *et. al*, the mechanism of action may change when an agent is utilized in combination with radiation rather than alone to target a specific tumor pathway



Phase of Cell Cycle	Classes of Drugs Most Effective
All Phases	Alkylating Agents, Anthracyclines, Platinum Based
S Phase	Antimetabolites
G_2/M Phase	Antitumor Antibiotics, Plant Alkaloids

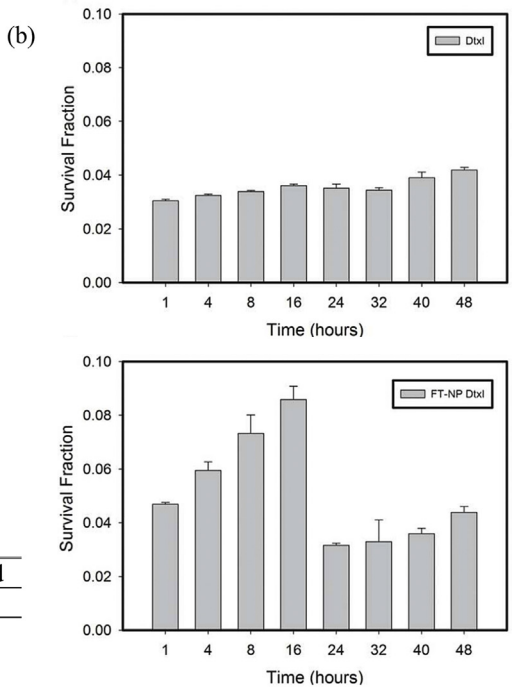


Fig. 10. (a) Radioresistance and the cell cycle. Cellular radioresistance varies depending on the stage of cell cycle with mitosis being the least radioresistant and synthesis being the most radioresistant. Due to their mechanism of action, classes of radiosensitizers are more effective at different cell cycle phases, demonstrated here. Red jagged lines depict cell cycle checkpoints that are triggered when DNA is damaged by radiation. (b) Timing plays an important role in the optimal combination of RT and nanoparticle delivered chemotherapeutics. KB cells treated with docetaxel, a plant alkaloid which induces G2/M phase arrest, (Dxtl) (top) or FT-NP Dtxl (bottom) irradiated with 4 Gy at the indicated times and evaluated for clonogenicity. Adapted with permission from **[15]**.

[178]. Thus, evaluating the specific interaction between therapeutic agents and RT rather than relying on documented mechanisms is critically important to enhancing the success of such combinations.

4.5.6. Dose/fractionation/timing/sequence

Recently, studies have begun to highlight the importance of different variables when considering MMRT. Although not inclusive, important variables include the dose of radiation, how and if radiation is fractionated, the dose of drug administered, the time of drug exposure, and the sequence of exposure to both agents. While organic-based drug-carrier nanoparticles for MMRT remain the focus of this review, the importance of timing and schedule is not unique to this nanoparticle-RT application. A report by Paunesku et al. using inorganic nanoparticles for dose enhancement found that the sequence of nanoparticle and radiation administration can play a crucial role in therapeutic outcome [179]. Similarly in immunoradiotherapy, which like nano-RT is in its infancy, there is no consensus regarding the optimal dose, fractionation, or timing for inducing the optimal immune response. Multiple reports have explored the variability that exists in this area and implored research to continue to uncover the optimal parameters [180,181]. In view of small molecule therapeutics, mechanism of action is a major determinant of optimal agent delivery time and therefore timing may bear even greater consequence. Further obstacles arise when considering the complex interplay between therapeutic agent and radiation, with the parameters mentioned above and others influencing the optimal combination schedule and dosing. Particularly for targeted agents, drug exposure time may be a major determinant of therapeutic success, as Verhagen *et. al* demonstrated when combining olaparib (PARPi) and radiotherapy [182]. Here, administration of olaparib over short periods rather than continuously resulted in lower radiation doses required for radiosensitization. Furthermore, the combination exhibited considerable synergy with overall stronger effects than administration of either agent alone, at lower doses [183]. As an increase in the therapeutic index may be derived from radiosynergy, care should be taken to properly evaluate administration schedules. Additionally, studies may need to account for alterations in PK and release of nanoparticle payloads when utilizing a new carrier.

Recent studies utilizing different particle systems delivering taxanes for CRT have noted that the extent of radiation sensitization was dependent on both the sequence and timing. To determine the optimal time in which albumin-bound paclitaxel should be administered, Wiedenmann et al. tested a range of times from 9 h to 5 days prior to radiation. Interestingly, albumin-bound paclitaxel was determined to be most effective when administered 2 to 3 days prior to radiation [14]. In another study, Werner et al. demonstrated that folate-targeted polymeric nanoparticles carrying docetaxel were most effective in combination with RT administered 24 (*in vitro*) or 12 (*in vivo*) hours after nanoparticles. In comparison, free docetaxel had optimal efficacy when RT was administered 1 h (*in vitro*) after drug, emphasizing the difference between free and encapsulated drugs (Fig. 10b) [15]. Overall, both groups emphasized the importance of investigating the optimal administration sequence to determine the maximum response. Both docetaxel and paclitaxel induce G_2/M phase arrest, which in conjunction with altered drug release, may explain the increased efficacy of radiation delivered at later timepoints [184,185]. Theoretically, slower drug release would increase the time required for the appropriate concentration to accumulate at the tumor site and induce the cell cycle arrest, however, further investigation is required. The studies outlined above highlight the importance of timing and sequence, both parameters that should be considered as nanoparticles are investigated for their use in MMRT.

Currently, it is unclear what role fractionation plays on the success of MMRT. Some evidence implies that altered fractionation schedules (*i.e.* hypofractionated or accelerated) alone are equivalent to concurrent MMRT (conventionally fractionated), but without the MMRT associated toxicities RT [186]. However, given the importance of drug exposure timing, without further research, no definitive claim should be made that RT alone is superior to MMRT. To that end, studies evaluating concurrent therapy administered during accelerated or conventional

fractionation are underway. Regardless, if toxicity is higher albeit equally efficacious, utilization of proper drug delivery carriers during the optimal fractionation schedule may tip the scales giving an advantage to these combinations.

Although the efficacious doses of both IR and drug will likely be reduced during MMRT, this does not directly translate to increased, or equivalent patient tolerability. For example, when temozolomide (a DNA alkylating agent) was combined with various PARP inhibitors, the PARPi *in vivo* maximum tolerated dose (MTD) was reduced by a factor of ~3–10. A drop in MTD of this magnitude is critically important, as unnoticed and dosed at single agent levels this could lead to life-threating adverse events and possibly death. These findings emphasize the importance of thorough pre-clinical tolerability evaluation as inadequate evaluation could result in rejection of promising MMRT strategies due to adoption of therapies that produce previously undiscerned and unacceptable toxicity [187]. Furthermore, it is important to note, a difference in mechanism of action may be observed when lower dose combination therapy is utilized [188].

Considering the evidence discussed in the preceding sections, the sequence of administration of chemotherapy and radiotherapy is an important determining factor to treatment outcome. While concurrent CRT has proven to be superior to other timing schedules in several cancer types, this represents only one consideration to determining optimal treatment timing with nano-chemoradiotherapy.

4.6. Critical considerations for preclinical studies

In vitro and *in vivo* experiments are an integral component in the development of nanomedicine and radiation therapy, as they remain essential for the continued understanding of basic, fundamental bio-nano and bio-radiation interactions and responses. Recently, scientists in both fields have published papers highlighting the value of consistency among investigations and reports, as irreproducibility has been a major limiting factor to drug development and translation [178,189,190]. Unfortunately, a gap often remains between the laboratory and human clinical trials with limited prediction value from the former. At the intersection of these fields there are likely additional variables to be considered, yet many are persistently important in both disciplines. Reports in both the nanoparticle and radiation fields have noted the importance of justification of biological model. Early in the development pipeline, rodent allograft or human xenograft models are often employed to evaluate treatment efficacy. Choices in the disease model are often limited by resources and practicality, however many have unique benefits and drawbacks which should be considered. Additionally, choices must be made regarding radiation parameters which ultimately may influence study results. Importantly, both fields consistently agree that experimental protocol details and results should be clearly laid out, so study comparisons can be made, and meta-analyses conducted. The following sections present some of the most important considerations to be made when integrating nanomedicine into chemoradiotherapy regimens.

4.6.1. Limitations and progress for In Vitro studies

In vitro cell-based assays represent the first line in assessing cytotoxicity and cellular response. However, it is important to recognize the limitations of these studies and the specific biological function being assessed in the context of a multifaceted treatment such as CRT. A common oversight in *in vitro* assays is the disregard of the influence of local factors when evaluating the efficacy of RT. For instance, Kahn et al. noted that *in vitro* systems rely on the assumption that tumor cells in culture behave the same way they would *in vivo* and that the microenvironment is of minimal influence on radiation outcomes [191]. Additionally, the translation to an *in vivo* model is not always straightforward and translatable. To more accurately mimic tumor biology *in vitro*, improved assays such as 3-D cell culture and microfluidic culture environments are now being developed and more widely applied. Promising results have been observed with "organs-on-chips" that consist of living cells arranged to simulate tissue and organ-level physiology that is not feasible with conventional cell culture methods [192]. Moving forward, utilization of these complex models is highly recommended where feasible.

4.6.2. In Vivo study design

Selection of a disease model is critical in the development of novel treatments. Optimally, use of genetically engineered mouse models is preferred, but the cost and time associated with these models remains a significant limitation. Among more widely available models, the utilization of a syngeneic mouse model is beneficial in studies which aim to evaluate the radiation-immune interaction as murine cancer cells can be transplanted in mice with intact immune systems. Comparatively, human xenografts require transplantation into immune-suppressed mice to develop. As such, any radiation response will be assessed in an artificial setting of immunodeficiency [63]. It has been noted, however, that the radiation response may be fundamentally different in rodent and human cells regarding which specific molecules regulate the DNA damage response [191]. In either scenario, studies may sacrifice one aspect of a typical human cancer response, whether it be the immune system or the DNA damage response system. An additional consideration is the timeline required for tumor development in a rodent model compared to human cancer. Murine cancers may develop a significant tumor burden within a month or less while human cancers may go undetected for years, growing slowly over time [193]. Regardless of the model, some variables will likely be compromised to evaluate the response of the others.

In a subcutaneous model, tumor endpoints may be growth delay curves or Kaplan-Meier survival curves. However, in an orthotopic model, if the tumor is not accessible for measurement and imaging tools are unavailable, Kaplan-Meier survival curves may be the only tool to assess efficacy. While tumor cure, or TCD_{50} values (dose of IR required to cure 50% of animals), is an endpoint that may be utilized to evaluate treatment efficacy, it is an intensive, costly process that may not elucidate the true clinical response of new MMRT options [63]. Sharma et al. suggest that pre-clinical testing of new MMRT regimens should be performed in a minimum of two pre-clinical models, with a fractionated RT schedule, and consideration given to the sequence of agent administration [63].

Furthermore, the choice of tumor location is another challenging consideration which necessitates compromise. Tumors may be implanted subcutaneously on the flank or orthotopically at the site of origin of a particular tumor cell line [194]. Implanting subcutaneous tumors on the hind leg can prove beneficial for irradiation due to the greater distance from at risk organs. However, these tumors types are not representative of spontaneous tumors as they lack the proper tumor microenvironment [191]. Comparatively, orthotopic tumor models are more representative of the true tumor microenvironment but they require implantation at the origin site, often requiring surgery. Ultimately, this approach proves challenging due to procedural risks, detrimental tumor locations, difficulty monitoring growth, and complicated RT treatment. As *in vivo* models are complex and may elicit various types of compromise, it is important to report reasons for utilizing a specific model alongside the limitations of the model.

4.6.3. Pre-clinical radiotherapy physics parameters

Clinical radiation involving X-rays, gamma radiation, and electrons, have low linear energy transfer (LET) compared with higher LET energy particle radiation. LET is the amount of energy that is deposited along a specific length of track. Intuitively, while the higher LET would seem more biologically effective at damaging DNA, the opposite is true. Within low LET radiation, low energies have been demonstrated to have higher radiobiologic effectiveness *in vitro*. At lower energy, the importance of indirect action for DNA damage is much more important, accounting for around 80% of the cell killing at energies below 100 keV and

32% of cell killing at 2.1 MeV [195]. Clinically, it becomes less clear what the major mechanism of cell killing is based on energy dependence. As such, it is unclear which pre-clinical energies may best mirror a clinical tumor response. Furthermore, as most laboratory irradiators deliver IR with energies less than 1 MV, this is a significant difference compared to clinically utilized linear accelerators which range from 4 to 25 MV. Aside from the differences in radiobiologic effectiveness mentioned above, a crucial factor of lower energy IR is the loss of penetration depth. Thus, utilization of lower energies may mean that the RT dose will not be homogenous throughout the entire tumor mass, particularly in orthotopic models [196]. As noted by others, the variability in response to RT based on such parameters makes it imperative that radiation parameters including dose, dose rate, energy, fractionation schedule, and equipment are documented when publishing results [178,190]. Furthermore, consideration of clinical radiation schedules and equipment should be considered and implemented where possible.

4.6.4. Translation of nanomedicines

The potential challenges associated with selecting a model and testing a new MMRT *in vivo* may ultimately hinder the commercialization of nanomedicines. A report by Agrahari et al. noted that commercialization failures of nanomedicine are often attributed to issues associated with scale up, reproducibility, and production costs. Furthermore, biological failures due to issues with safety, stability, and differences between pre-clinical models and patients are common [197]. This notion is supported when considering radiation studies, as the irreproducibility of pre-clinical data may be responsible for clinical trials that which did not meet their objectives [178]. Faria *et. al* emphasized the importance of material characterization and reporting using standardized procedures and equipment, citing that a major hurdle for translation is a lack of standardization and benchmarks for new therapeutics. Defining these hurdles and standardizing characterization and reporting for the combination of nanomedicine and radiation therapy is critical to the successful translation of nanomedicines in the field.

On the clinical side, the setting in which these therapeutic agents are tested proves critical to their successful approval and subsequent marketing and adoption [198]. This becomes strikingly clear upon evaluation of the approval path for Opaxio, where this product failed to demonstrate enhanced safety or efficacy in initial testing as a first-line therapy for non-small cell lung carcinoma. However, a pivot in clinical strategy has proven fruitful for Opaxio as clinical efforts have focused on its combination with radiation following preclinical demonstration of its efficacy as a radiosensitizer [198]. Since these pre-clinical studies, an FDA orphan designation was announced for glioblastoma and many clinical trials have been initiated on the combination of Opaxio and radiation. It should also be noted that patients with advanced stage disease who have failed conventional therapy and exhausted other treatment options are often enrolled. The implications of their exposure to and subsequent failure on prior therapeutics is not fully appreciated. Many therapeutic options that would be superior first-line therapies for early-stage patients may be overlooked due to their initial testing in these circumstances. While the variables presented here are worth considering, it is important to note that these are not the only factors to be considered in the testing novel MMRT regimens.

4.6.5. Collaboration

In clinical practice, the complexity and toxicity of MMRT requires careful multidisciplinary coordination for optimal treatment. For example, upon diagnosis of head and neck cancer, patients are evaluated by a surgeon, medical oncologist, and radiation oncologist to discuss their respective specialties' roles and treatment options [199]. For efficient care, many institutions coordinate multidisciplinary care conferences and clinics where all specialists determine a consensus treatment plan. Furthermore, pretreatment interventions such as gastrostomy tube placement, ensuring continued nutrition during CRT-induced oral mucositis, are coordinated between otolaryngology and radiation oncology with critical help from gastroenterology and speech pathology. Similar coordination of care is utilized for lung and gastrointestinal malignancies, although this coordination is pervasive in the setting of MMRT.

As evidenced in Fig. 11, the clinical implementation of multimodal therapy is extremely intricate and complex. Therefore, it is imperative that drug delivery researchers working toward clinical translation of

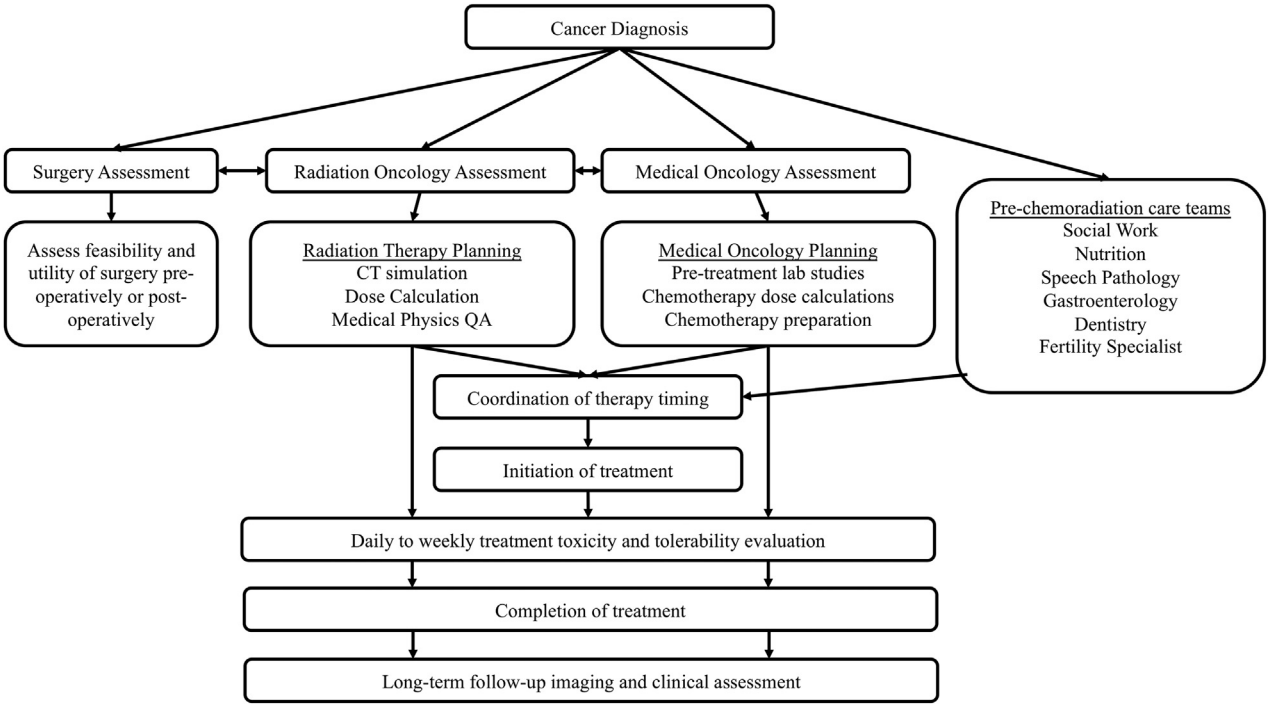


Fig. 11. A detailed flow chart detailing the intricate treatment plan that underlies each therapeutic regimen in oncology. Interdisciplinary collaboration between a multitude of medical teams is necessary for optimal patient experiences and outcomes.

nanomedicines for MMRT are embracing collaborative environments with clinicians who will be the end users of their technology. Ideally, this process would begin during idea conception, as clinicians are likely aware of the specific unmet needs and current limitations of RT. To that end, interest in bringing clinical observations to the benchtop for investigation and speeding up the bench to bedside translation has been growing in recent years [200]. A comprehensive study of European cancer research acknowledged that enhanced collaboration between cancer research centers is required in order to share translational research infrastructure and enable accelerated advancement.

In the Netherlands, a recent publication reported that a barrier to implementation when considering translation was the increase in workload and complexity of the procedure [201]. Consultation with the physicians implementing treatment protocols is crucial as adoption is more likely with simplified protocols. Furthermore, collaboration between academia and industry are critical to the successful implementation of new MMRT strategies [63].

5. Considerations and conclusions

The combination of nanomedicine and RT has resulted in significant increases in treatment therapeutic efficacy, however, significant opportunity for improvement remains. Further investigation of the influence of these clinically-relevant parameters on nanoparticle-based efficacy will aid in resolving the current state of ambiguity. As discussed in this review, parameters which we believe to be influential include; sequence of agent administration, specific fractionation schedule, total radiation dose, dose per fraction, and timing of agent administration. In terms of non-radiation dependent variables, researchers should consider utilizing more complex *in vitro* models, identify the benefits and limitations of chosen *in vivo* models, and integrate clinical radiation equipment, schedules, and doses where possible. Furthermore, outlining standards of reporting for both material characterization and radiation physics parameters will only aid to enhance reproducibility and translational success. While not all inclusive, this work aimed to identify areas of research opportunities for the academic research community and highlight important considerations which must be made. Excitingly, we are on the precipice of greater understanding regarding the larger interactions between radiation and the tumor microenvironment, and its impact regarding nano-based MMRT. Further understanding of these standardized clinical practices will lead to innovative approaches toward decreasing the translational gap between benchtop to bedside, thus proving transformative for the future of nanomedicine.

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References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA Cancer J. Clin. 69 (2019) 7–34.
[2] K.D. Miller, R.L. Siegel, C.C. Lin, A.B. Mariotto, J.L. Kramer, J.H. Rowland, K.D. Stein, R. Alteri, A. Jemal, Cancer treatment and survivorship statistics, 2016, CA Cancer J. Clin. 66 (2016) 271–289.
[3] A. Palacios Eito, S.G. Cabezas, P.F. Ugalde, E.R. del Campo, A.O. Romero, M.P. del Martín, J.M.R. Arjona, M.M. Paredes, Characterization and adequacy of the use of radiotherapy and its trend in time, Radiother. Oncol. 106 (2013) 260–265.
[4] G. Delaney, S. Jacob, C. Featherstone, M. Barton, The role of radiotherapy in cancer treatment, Cancer. 104 (2005) 1129–1137.
[5] M.H. Barcellos-Hoff, C. Park, E.G. Wright, Radiation and the microenvironment – tumorigenesis and therapy, Nat. Rev. Cancer 5 (2005) 867–875.
[6] S. Braunstein, J.L. Nakamura, Radiotherapy-induced malignancies: review of clinical features, pathobiology, and evolving approaches for mitigating risk, Front. Oncol. 3 (2013).
[7] T.S. Lawrence, B.G. Haffty, J.R. Harris, Milestones in the use of combined-modality radiation therapy and chemotherapy, J. Clin. Oncol. 32 (2014) 1173–1179.
[8] A.Z. Wang, J.E. Tepper, Nanotechnology in radiation oncology, J. Clin. Oncol. 32 (2014) 2879–2885.
[9] K. Cho, X. Wang, S. Nie, Z. Georgia Chen, D.M. Shin, Therapeutic nanoparticles for drug delivery in cancer, Clin. Cancer Res. 14 (2008) 1310–1316.
[10] A.Z. Wang, R. Langer, O.C. Farokhzad, Nanoparticle delivery of Cancer drugs, Annu. Rev. Med. 63 (2012) 185–198.
[11] D.S. Chang, F.D. Lasley, I.J. Das, M.S. Mendonca, J.R. Dynlacht, Therapeutic Ratio, in: Basic Radiother. Phys. Biol. Springer International Publishing, New York, 2014 277–282.
[12] D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, Nanocarriers as an emerging platform for cancer therapy, Nat. Nanotechnol. 2 (2007) 751–760.
[13] M.E. Davis, Z. Georgia Chen, D.M. Shin, Nanoparticle therapeutics: an emerging treatment modality for cancer, Nat. Rev. Drug Discov. 7 (2008) 771–782.
[14] N. Wiedenmann, D. Valdecanas, N. Hunter, S. Hyde, T.A. Buchholz, L. Milas, K.A. Mason, 130-nm albumin–bound paclitaxel enhances tumor Radiocurability and therapeutic gain, Clin. Cancer Res. 13 (2007) 1868–1874.
[15] M.E. Werner, J.A. Copp, S. Karve, N.D. Cummings, R. Sukumar, C. Li, M.E. Napier, R.C. Chen, A.D. Cox, A.Z. Wang, Folate-targeted polymeric nanoparticle formulation of docetaxel is an effective molecularly targeted radiosensitizer with efficacy dependent on the timing of radiotherapy, ACS Nano 5 (2011) 8990–8998.
[16] C. Garibaldi, B.A. Jereczek-Fossa, G. Marvaso, S. Dicuonzo, D.P. Rojas, F. Cattani, A. Starzyńska, D. Ciardo, A. Surgo, M.C. Leonardi, R. Ricotti, Recent advances in radiation oncology, Ecancermedicalscience. 11 (2017) 785.
[17] J. Bernier, E.J. Hall, A. Giaccia, Radiation oncology: a century of achievements, Nat. Rev. Cancer 4 (2004) 737–747.
[18] S. Gianfaldoni, R. Gianfaldoni, U. Wollina, J. Lotti, G. Tchernev, T. Lotti, An overview on radiotherapy: from its history to its current applications in dermatology, Open Access Maced. J. Med. Sci. 5 (2017) 521–525.
[19] R.C. Bast Jr., C.M. Croce, W.N. Hait, W.K. Hong, D.W. Kufe, M. Piccart-Gebhart, R.E. Pollock, R.R. Weichselbaum, H. Wang, J.F. Holland, Holland-Frei Cancer Medicine, John Wiley & Sons, New Jersey, 2017.
[20] C.M. Hartshorn, M.S. Bradbury, G.M. Lanza, A.E. Nel, J. Rao, A.Z. Wang, U.B. Wiesner, L. Yang, P. Grodzinski, Nanotechnology strategies to advance outcomes in clinical Cancer care, ACS Nano 12 (2018) 24–43.
[21] T. Gupta, C.A. Narayan, Image-guided radiation therapy: Physician's perspectives, J. Med. Phys. Assoc. Med. Phys. India. 37 (2012) 174–182.
[22] K.A. Ahmed, C.R. Correa, T.J. Dilling, N.G. Rao, R. Shridhar, A.M. Trotti, R.B. Wilder, J.J. Caudell, Altered fractionation schedules in radiation treatment: a review, Semin. Oncol. 41 (2014) 730–750.
[23] G.C. Barnett, C.M.L. West, A.M. Dunning, R.M. Elliott, C.E. Coles, P.D.P. Pharoah, N.G. Burnet, Normal tissue reactions to radiotherapy, Nat. Rev. Cancer 9 (2009) 134–142.
[24] F. Pajonk, E. Vlashi, W.H. McBride, Radiation resistance of cancer stem cells: the 4 R's of radiobiology revisited, Stem Cells 28 (2010) 639–648.
[25] E.J. Hall, A.J. Giaccia, Radiobiology for the Radiologist, Lippincott Williams & Wilkins, 2006.
[26] R. Baskar, J. Dai, N. Wenlong, R. Yeo, K.-W. Yeoh, Biological response of cancer cells to radiation treatment, Front. Mol. Biosci. 1 (2014) 24.
[27] H. Rodney Withers, Biological basis of radiation therapy for cancer, Lancet 339 (1992) 156–159.
[28] E.H. Grubbé, Priority in the therapeutic use of X-rays, Radiology. 21 (1933) 156–162.
[29] N.-Y. Ma, W. Tinganelli, A. Maier, M. Durante, W. Kraft-Weyrather, Influence of chronic hypoxia and radiation quality on cell survival, J. Radiat. Res. (Tokyo). 54 (Suppl. 1) (2013) i13–i22.
[30] J.-Y. Tsai, F.-H. Chen, T.-Y. Hsieh, Y.-Y. Hsiao, Effects of indirect actions and oxygen on relative biological effectiveness: estimate of DSB induction and conversion induced by gamma rays and helium ions, J. Radiat. Res. (Tokyo). 56 (2015) 691–699.
[31] B.M. Kim, Y. Hong, S. Lee, P. Liu, J.H. Lim, Y.H. Lee, T.H. Lee, K.T. Chang, Y. Hong, Therapeutic implications for overcoming radiation resistance in Cancer therapy, Int. J. Mol. Sci. 16 (2015) 26880–26913.
[32] M. Lavine, The early clinical X-ray in the United States: patient experiences and public perceptions, J. Hist. Med. Allied Sci. 67 (2012) 587–625.
[33] G. Song, L. Cheng, Y. Chao, K. Yang, Z. Liu, Emerging nanotechnology and advanced materials for Cancer radiation therapy, Adv. Mater. 29 (2017) 1700996.
[34] P. Retif, S. Pinel, M. Toussaint, C. Frochot, R. Chouikrat, T. Bastogne, M. Barberi-Heyob, Nanoparticles for radiation therapy enhancement: the key parameters, Theranostics. 5 (2015) 1030–1044.
[35] S. Bhattacharyya, R.A. Kudgus, R. Bhattacharya, P. Mukherjee, Inorganic nanoparticles in Cancer therapy, Pharm. Res. 28 (2011) 237–259.
[36] E.J. Moding, M.B. Kastan, D.G. Kirsch, Strategies for optimizing the response of cancer and normal tissues to radiation, Nat. Rev. Drug Discov. 12 (2013) 526–542.
[37] S.L. Liauw, P.P. Connell, R.R. Weichselbaum, New paradigms and future challenges in radiation oncology: an update of biological targets and technology, Sci. Transl. Med. 5 (2013) 173sr2.
[38] S.M. Bentzen, Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology, Nat. Rev. Cancer 6 (2006) 702–713.
[39] G. Gordon Steel, M.J. Peckham, Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity, Int. J. Radiat. Oncol. 5 (1979) 85–91.
[40] P.P. Connell, S. Hellman, Advances in radiotherapy and implications for the next century: a historical perspective, Cancer Res. 69 (2009) 383–392.
[41] Meta-Analysis Group, Medical Research Council Clinical Trials Unit, London, UK, Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials, J. Clin. Oncol. 26 (2008) 5802–5812.
[42] P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van B Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J.

Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J.S. Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, A. van der Gaast, Preoperative chemoradiotherapy for esophageal or junctional cancer, N. Engl. J. Med. 366 (2012) 2074–2084.
[43] P.J. Loehrer, Y. Feng, H. Cardenes, L. Wagner, J.M. Brell, D. Cella, P. Flynn, R.K. Ramanathan, C.H. Crane, S.R. Alberts, A.B. Benson, Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic Cancer: An eastern cooperative oncology group trial, J. Clin. Oncol. 29 (2011) 4105–4112.
[44] R. Sauer, T. Liersch, S. Merkel, R. Fietkau, W. Hohenberger, C. Hess, H. Becker, H.-R. Raab, M.-T. Villanueva, H. Witzigmann, C. Wittekind, T. Beissbarth, C. Rödel, Preoperative versus postoperative Chemoradiotherapy for locally advanced rectal Cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years, J. Clin. Oncol. 30 (2012) 1926–1933.
[45] L.L. Gunderson, K.A. Winter, J.A. Ajani, J.E. Pedersen, J. Moughan, A.B. Benson, C.R. Thomas, R.J. Mayer, M.G. Haddock, T.A. Rich, C.G. Willett, Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent Chemoradiation involving fluorouracil/Mitomycin versus fluorouracil/cisplatin, J. Clin. Oncol. 30 (2012) 4344–4351.
[46] C. Sawyers, Targeted cancer therapy, Nature. 432 (2004) 294–297.
[47] R. Fisher, L. Pusztai, C. Swanton, Cancer heterogeneity: implications for targeted therapeutics, Br. J. Cancer 108 (2013) 479–485.
[48] J.S. Lopez, U. Banerji, Combine and conquer: challenges for targeted therapy combinations in early phase trials, Nat. Rev. Clin. Oncol. 14 (2017) 57–66.
[49] Z. Liu, B. Delavan, R. Roberts, W. Tong, Lessons learned from two decades of anticancer drugs, Trends Pharmacol. Sci. 38 (2017) 852–872.
[50] A. Cheung, H.J. Bax, D.H. Josephs, K.M. Ilieva, G. Pellizzari, J. Opzoomer, J. Bloomfield, M. Fittall, A. Grigoriadis, M. Figini, S. Canevari, J.F. Spicer, A.N. Tutt, S.N. Karagiannis, Targeting folate receptor alpha for cancer treatment, Oncotarget. 7 (2016) 52553–52574.
[51] C. Chargari, R.A. Toillon, D. MacDermed, P. Castadot, N. Magné, Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? Lancet Oncol. 10 (2009) 53–60.
[52] S. Sathornsumetee, D.A. Reardon, A. Desjardins, J.A. Quinn, J.J. Vredenburgh, J.N. Rich, Molecularly targeted therapy for malignant glioma, Cancer. 110 (2007) 13–24.
[53] C.R. Parish, Cancer immunotherapy: the past, the present and the future, Immunol. Cell Biol. 81 (2003) 106–113.
[54] Timeline of Progress, Cancer Res. Inst. https://www.cancerresearch.org/immunotherapy/timeline-of-progress 2019.
[55] R.S. Riley, C.H. June, R. Langer, M.J. Mitchell, Delivery technologies for cancer immunotherapy, Nat. Rev. Drug Discov. 18 (2019) 175–196.
[56] L.M. Weiner, R. Surana, S. Wang, Monoclonal antibodies: versatile platforms for cancer immunotherapy, Nat. Rev. Immunol. 10 (2010) 317–327.
[57] T.R. Cushman, D. Gomez, R. Kumar, A. Likacheva, J.Y. Chang, A.P. Cadena, S. Paris, J.W. Welsh, Combining radiation plus immunotherapy to improve systemic immune response, J. Thorac. Dis. 10 (2018) S468–S479.
[58] M. Beyzadeoglu, G. Ozyigit, C. Ebruli, Clinical Radiation Oncology, in: Basic Radiat, Oncol, Springer, Berlin, Heidelberg, 2010 145–173.
[59] X. Li, D. Dai, B. Chen, H. Tang, X. Xie, W. Wei, Efficacy of PI3K/AKT/mTOR pathway inhibitors for the treatment of advanced solid cancers: a literature-based meta-analysis of 46 randomised control trials, PLoS One 13 (2018), e0192464.
[60] P.J. Tofilon, K. Camphausen (Eds.), Increasing the Therapeutic Ratio of Radiotherapy, Springer International Publishing, Switzerland, 2017.
[61] P. Hoskin, External Beam Therapy, Oxford University Press, Oxford, UK, 2012.
[62] A.C. Begg, F.A. Stewart, C. Vens, Strategies to improve radiotherapy with targeted drugs, Nat. Rev. Cancer 11 (2011) 239–253.
[63] R.A. Sharma, R. Plummer, J.K. Stock, T.A. Greenhalgh, O. Ataman, S. Kelly, R. Clay, R.A. Adams, R.D. Baird, L. Billingham, S.R. Brown, S. Buckland, H. Bulbeck, A.J. Chalmers, G. Clack, A.N. Cranston, L. Damstrup, R. Ferraldeschi, M.D. Forster, J. Golec, R.M. Hagan, E. Hall, A.-R. Hanauske, K.J. Harrington, T. Haswell, M.A. Hawkins, T. Illidge, H. Jones, A.S. Kennedy, F. McDonald, T. Melcher, J.P.B. O'Connor, J.R. Pollard, M.P. Saunders, D. Sebag-Montefiore, M. Smitt, J. Staffurth, I.J. Stratford, S.R. Wedge, on behalf of the N.Ctr.A.-P.J.W. Group, Clinical development of new drug–radiotherapy combinations, Nat. Rev. Clin. Oncol. 13 (2016) 627–642.
[64] M. Baumann, M. Krause, J. Overgaard, J. Debus, S.M. Bentzen, J. Daartz, C. Richter, D. Zips, T. Bortfeld, Radiation oncology in the era of precision medicine, Nat. Rev. Cancer 16 (2016) 234–249.
[65] G.S. Higgins, S.M. O'Cathail, R.J. Muschel, W.G. McKenna, Drug radiotherapy combinations: review of previous failures and reasons for future optimism, Cancer Treat. Rev. 41 (2015) 105–113.
[66] J. Shi, P.W. Kantoff, R. Wooster, O.C. Farokhzad, Cancer nanomedicine: progress, challenges and opportunities, Nat. Rev. Cancer 17 (2017) 20–37.
[67] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat. Rev. Clin. Oncol. 7 (2010) 653–664.
[68] V.J. Venditto, F.C. Szoka, Cancer nanomedicines: so many papers and so few drugs! Adv. Drug Deliv. Rev. 65 (2013) 80–88.
[69] M. Björnmalm, M. Faria, F. Caruso, Increasing the impact of materials in and beyond bio-Nano science, J. Am. Chem. Soc. 138 (2016) 13449–13456.
[70] D.K. Chatterjee, T. Wolfe, J. Lee, A.P. Brown, P.K. Singh, S.R. Bhattarai, P. Diagaradjane, S. Krishnan, Convergence of nanotechnology with radiation therapy—insights and implications for clinical translation, Transl. Cancer Res. 2 (2013) 256–268.
[71] M. Overchuk, G. Zheng, Overcoming obstacles in the tumor microenvironment: recent advancements in nanoparticle delivery for cancer theranostics, Biomaterials. 156 (2017) 217–237.
[72] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (2015) 941–951.
[73] T. Li, M. Zhang, J. Wang, T. Wang, Y. Yao, X. Zhang, C. Zhang, N. Zhang, Thermosensitive hydrogel co-loaded with Gold nanoparticles and doxorubicin for effective Chemoradiotherapy, AAPS J. 18 (2016) 146–155.
[74] J.D. Rocca, M.E. Werner, S.A. Kramer, R.C. Huxford-Phillips, R. Sukumar, N.D. Cummings, J.L. Vivero-Escoto, A.Z. Wang, W. Lin, Polysilsesquioxane nanoparticles for triggered release of cisplatin and effective cancer chemoradiotherapy, Nanomedicine 11 (2015) 31–38.
[75] A.Z. Wang, K. Yuet, L. Zhang, F.X. Gu, M. Huynh-Le, A.F. Radovic-Moreno, P.W. Kantoff, N.H. Bander, R. Langer, O.C. Farokhzad, ChemoRad nanoparticles: a novel multifunctional nanoparticle platform for targeted delivery of concurrent chemoradiation, Nanomed. 5 (2010) 361–368.
[76] X. Tian, M. Nguyen, H.P. Foote, J.M. Caster, K.C. Roche, C.G. Peters, P. Wu, L. Jayaraman, E.G. Garmey, J.E. Tepper, S. Eliasof, A.Z. Wang, CRLX101, a nanoparticle–drug conjugate containing Camptothecin, improves rectal Cancer Chemoradiotherapy by inhibiting DNA repair and HIF1α, Cancer Res. 77 (2017) 112–122.
[77] X. Zhang, H. Yang, K. Gu, J. Chen, M. Rui, G.-L. Jiang, In vitro and in vivo study of a nanoliposomal cisplatin as a radiosensitizer, Int. J. Nanomedicine 6 (2011) 437–444.
[78] X. Tian, H. Lara, K.T. Wagner, S. Saripalli, S. Nabeel Hyder, M. Foote, M. Sethi, E. Wang, J.M. Caster, L. Zhang, A.Z. Wang, Improving DNA double-strand repair inhibitor KU55933 therapeutic index in cancer radiotherapy using nanoparticle drug delivery, Nanoscale. 7 (2015) 20211–20219.
[79] M.I. Koukourakis, K. Romanidis, M. Froudarakis, G. Kyrgias, G.V. Koukourakis, G. Retalis, N. Bahlitzanakis, Concurrent administration of docetaxel and stealth® liposomal doxorubicin with radiotherapy in non-small cell lung cancer : excellent tolerance using subcutaneous amifostine for cytoprotection, Br. J. Cancer 87 (2002) 385–392.
[80] M.I. Koukourakis, S. Koukouraki, A. Giatromanolaki, S.C. Archimandritis, J. Skarlatos, K. Beroukas, J.G. Bizakis, G. Retalis, N. Karkavitsas, E.S. Helidonis, Liposomal doxorubicin and conventionally fractionated radiotherapy in the treatment of locally advanced non–small-cell lung Cancer and head and neck Cancer, J. Clin. Oncol. 17 (1999) 3512–3521.
[81] H. Varveris, S. Kachris, M. Mazonakis, E. Lyraraki, A. Markouizou, S. Karabekios, A. Tzedakis, K. Perisinakis, J. Damilakis, M. Vlachaki, Pegulated liposomal doxorubicin and cisplatin given concurrently with conventional radiotherapy: a phase I dose-escalation trial for patients with squamous cell carcinoma of head and neck and lung, Oncol. Rep. 12 (2004) 473–481.
[82] M.I. Koukourakis, G. Patlakas, M.E. Froudarakis, G. Kyrgias, J. Skarlatos, I. Abatzoglou, G. Bougioukas, D. Bouros, Hypofractionated accelerated Radiochemotherapy with Cytoprotection (chemo-HypoARC) for inoperable non-small cell lung carcinoma, Anticancer Res. 27 (2007) 3625–3631.
[83] M.I. Koukourakis, J. Manavis, C. Simopoulos, V. Liberis, A. Giatromanolaki, E. Sivridis, Hypofractionated accelerated radiotherapy with cytoprotection combined with trastuzumab, liposomal doxorubicine, and docetaxel in c-erbB-2-positive breast cancer, Am. J. Clin. Oncol. 28 (2005) 495–500.
[84] . D.I. Rosenthal, S.S. Yom, L. Liu, M. Machtay, K. Algazy, R.S. Weber, G.S. Weinstein, A.A. Chalian, L.K. Mille, K. Rockwell, M. Tonda, E. Schnipper, D. Hershock, A phase I study of SPI-077 (stealth liposomal cisplatin) concurrent with radiation therapy for locally advanced head and neck cancer, Investig. New Drugs 20 (2002) 343–349.
[85] T. Dipetrillo, L. Milas, D. Evans, P. Akerman, T. Ng, T. Miner, D. Cruff, B. Chauhan, D. Iannitti, D. Harrington, H. Safran, Paclitaxel Poliglumex (PPX-Xyotax) and concurrent radiation for esophageal and gastric Cancer: a phase I study, Am. J. Clin. Oncol. 29 (2006) 376.
[86] M.I. Koukourakis, S. Koukouraki, A. Giatromanolaki, S. Kakolyris, V. Georgoulias, A. Velidaki, S. Archimandritis, N.N. Karkavitsas, High intratumoral accumulation of stealth liposomal doxorubicin in sarcomas–rationale for combination with radiotherapy, Acta Oncol. Stockh. Swed. 39 (2000) 207–211.
[87] C. de L. Davies, L.M. Lundstrøm, J. Frengen, L. Eikenes, Ø.S. Bruland, O. Kaalhus, M.H.B. Hjelstuen, C. Brekken, Radiation improves the distribution and uptake of liposomal doxorubicin (caelyx) in human osteosarcoma xenografts, Cancer Res. 64 (2004) 547–553.
[88] G. Hariri, H. Yan, H. Wang, Z. Han, D.E. Hallahan, Radiation-guided drug delivery to mouse models of lung cancer, Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 16 (2010) 4968–4977.
[89] R.J. Passarella, D.E. Spratt, A.E. van der Ende, J.G. Phillips, H. Wu, V. Sathiyakumar, L. Zhou, D.E. Hallahan, E. Harth, R. Diaz, Targeted nanoparticles that deliver a sustained, specific release of paclitaxel to irradiated tumors, Cancer Res. 70 (2010) 4550–4559.
[90] C. Li, S. Ke, Q.-P. Wu, W. Tansey, N. Hunter, L.M. Buchmiller, L. Milas, C. Charnsangavej, S. Wallace, Tumor irradiation enhances the tumor-specific distribution of poly(l-glutamic acid)-conjugated paclitaxel and its antitumor efficacy, Clin. Cancer Res. 6 (2000) 2829–2834.
[91] T. Lammers, V. Subr, P. Peschke, R. Kühnlein, W.E. Hennink, K. Ulbrich, F. Kiessling, M. Heilmann, J. Debus, P.E. Huber, G. Storm, Image-guided and passively tumour-targeted polymeric nanomedicines for radiochemotherapy, Br. J. Cancer 99 (2008) 900–910.
[92] T. Lammers, P. Peschke, R. Kühnlein, V. Subr, K. Ulbrich, J. Debus, P. Huber, W. Hennink, G. Storm, Effect of radiotherapy and hyperthermia on the tumor accumulation of HPMA copolymer-based drug delivery systems, J. Control. Release 117 (2007) 333–341.
[93] F. Cui, R.-T. Li, Q. Liu, P. Wu, W. Hu, G. Yue, H. Ding, L.-X. Yu, X.-P. Qian, B.-R. Liu, Enhancement of radiotherapy efficacy by docetaxel-loaded gelatinase-stimuli PEG-pep-PCL nanoparticles in gastric cancer, Cancer Lett. 346 (2014) 53–62.

[94] M.E. Werner, N.D. Cummings, M. Sethi, E.C. Wang, R. Sukumar, D.T. Moore, A.Z. Wang, Preclinical evaluation of Genexol-PM, a nanoparticle formulation of paclitaxel, as a novel Radiosensitizer for the treatment of non-small cell lung Cancer, Int. J. Radiat. Oncol. Biol. Phys. 86 (2013) 463–468.
[95] K.J. Harrington, G. Rowlinson-Busza, P.S. Uster, R.G. Vile, A.M. Peters, J.S. Stewart, Single-fraction irradiation has no effect on uptake of radiolabeled pegylated liposomes in a tumor xenograft model, Int. J. Radiat. Oncol. Biol. Phys. 49 (2001) 1141–1148.
[96] Leadient Biosciences, DepoCyt Discontinuation Letter, https://leadiant.com/wp-content/uploads/2017/08/DepoCyt-HCP-Notification-Ltr-8-7-17-PDF.pdf (2017).
[97] Galen, DaunoXome Discontinuation Letter, https://www.galen-pharma.com/uploads/documents/2016/06/2016-06-02_15-31-15-daunoxome-letter-2.pdf 2016.
[98] R. Wang, P.S. Billone, W.M. Mullett, Nanomedicine in action: An overview of Cancer nanomedicine on the market and in clinical trials, J. Nanomater. 2013 (2013).
[99] J.H. Park, S. Lee, J.-H. Kim, K. Park, K. Kim, I.C. Kwon, Polymeric nanomedicine for cancer therapy, Prog. Polym. Sci. 33 (2008) 113–137.
[100] V.P. Torchilin, Liposomes as targetable drug carriers, Crit. Rev. Ther. Drug Carrier Syst. 2 (1985) 65–115.
[101] P. Milla, F. Dosio, L. Cattel, PEGylation of proteins and liposomes: a powerful and flexible strategy to improve the drug delivery, Curr. Drug Metab. 13 (2012) 105–119.
[102] X. Tian, J.M. Caster, S.B. Warner, K.T. Wagner, P. Ohana, A. Gabizon, A.Z. Wang, Preclinical evaluation of Promitil, a radiation-responsive liposomal formulation of a Mitomycin C prodrug, for use in Chemoradiation therapy, Int. J. Radiat. Oncol. 96 (2016) S18–S19.
[103] V.P. Torchilin, Recent advances with liposomes as pharmaceutical carriers, Nat. Rev. Drug Discov. 4 (2005) 145–160.
[104] S. Marchal, A.E. Hor, M. Millard, V. Gillon, L. Bezdetnaya, Anticancer drug delivery: An update on clinically applied Nanotherapeutics, Drugs. 75 (2015) 1601–1611.
[105] M.I. Koukourakis, N. Bahlitzanakis, M. Froudarakis, A. Giatromanolaki, V. Georgoulias, S. Koumiotaki, M. Christodoulou, G. Kyrias, J. Skarlatos, J. Kostantelos, K. Beroukas, Concurrent conventionally factionated radiotherapy and weekly docetaxel in the treatment of stage IIIb non-small-cell lung carcinoma, Br. J. Cancer 80 (1999) 1792–1796.
[106] P.G. Tsoutsou, M.E. Froudarakis, D. Bouros, M.I. Koukourakis, Hypofractionated/accelerated radiotherapy with Cytoprotection (HypoARC) combined with Vinorelbine and liposomal doxorubicin for locally advanced non-small cell lung Cancer (NSCLC), Anticancer Res. 28 (2008) 1349–1354.
[107] M.I. Koukourakis, A. Giatromanolaki, M. Pitiakoudis, G. Kouklakis, P. Tsoutsou, I. Abatzoglou, M. Panteliadou, K. Sismanidou, E. Sivridis, T. Boulikas, Concurrent liposomal cisplatin (lipoplatin), 5-fluorouracil and radiotherapy for the treatment of locally advanced gastric cancer: a phase i/ii study, Int. J. Radiat. Oncol. • Biol. • Phys. 78 (2010) 150–155.
[108] S. Senapati, A.K. Mahanta, S. Kumar, P. Maiti, Controlled drug delivery vehicles for cancer treatment and their performance, Signal Transduct. Target. Ther. 3 (2018) 7.
[109] K. Ninomiya, E. Ichihara, K. Hotta, N. Sone, T. Murakami, D. Harada, I. Oze, T. Kubo, H. Tanaka, S. Kuyama, D. Kishino, A. Bessho, S. Harita, K. Katsui, M. Tanimoto, K. Kiura, Three-arm randomized trial of sodium alginate for preventing radiation-induced esophagitis in locally advanced non-small cell lung Cancer receiving concurrent Chemoradiotherapy: the OLCSG1401 study protocol, Clin. Lung Cancer. 18 (2017) 245–249.
[110] J. Nicolas, S. Mura, D. Brambilla, N. Mackiewicz, P. Couvreur, Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery, Chem. Soc. Rev. 42 (2013) 1147–1235.
[111] K.M. Au, Y. Min, X. Tian, L. Zhang, V. Perello, J.M. Caster, A.Z. Wang, Improving Cancer Chemoradiotherapy treatment by dual controlled release of Wortmannin and docetaxel in polymeric nanoparticles, ACS Nano 9 (2015) 8976–8996.
[112] A.N. DuRoss, M.J. Neufeld, M.R. Landry, J.G. Rosch, C.T. Eaton, G. Sahay, C.R. Thomas, C. Sun, Micellar formulation of Talazoparib and Buparlisib for enhanced DNA damage in breast Cancer Chemoradiotherapy, ACS Appl. Mater. Interfaces 11 (2019) 12342–12356.
[113] M. Zhang, C.T. Hagan, Y. Min, H. Foley, X. Tian, F. Yang, Y. Mi, K.M. Au, Y. Medik, K. Roche, K. Wagner, Z. Rodgers, A.Z. Wang, Nanoparticle co-delivery of wortmannin and cisplatin synergistically enhances chemoradiotherapy and reverses platinum resistance in ovarian cancer models, Biomaterials. 169 (2018) 1–10.
[114] R. Ferrari, M. Sponchioni, M. Morbidelli, D. Moscatelli, Polymer nanoparticles for the intravenous delivery of anticancer drugs: the checkpoints on the road from the synthesis to clinical translation, Nanoscale. 10 (2018) 22701–22719.
[115] S. Mignani, J. Rodrigues, H. Tomas, M. Zablocka, X. Shi, A.-M. Caminade, J.-P. Majoral, Dendrimers in combination with natural products and analogues as anti-cancer agents, Chem. Soc. Rev. 47 (2018) 514–532.
[116] S.-Y. Wu, H.-Y. Chou, C.-H. Yuh, S.L. Mekuria, Y.-C. Kao, H.-C. Tsai, Radiation-sensitive dendrimer-based drug delivery system, Adv. Sci. 5 (2018) 1700339.
[117] J.M. Caster, A.N. Patel, T. Zhang, A. Wang, Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 9 (2017), e1416.
[118] I. Ekladious, Y.L. Colson, M.W. Grinstaff, Polymer–drug conjugate therapeutics: advances, insights and prospects, Nat. Rev. Drug Discov. 18 (2019) 273.
[119] A.O. Elzoghby, W.M. Samy, N.A. Elgindy, Protein-based nanocarriers as promising drug and gene delivery systems, J. Control. Release Off. J. Control. Release Soc. 161 (2012) 38–49.
[120] A. Maham, Z. Tang, H. Wu, J. Wang, Y. Lin, Protein-based nanomedicine platforms for drug delivery, Small Weinh. Bergstr. Ger. 5 (2009) 1706–1721.
[121] P.E. Lammers, B. Lu, L. Horn, Y. Shyr, V. Keedy, nab-paclitaxel in combination with weekly carboplatin with concurrent radiotherapy in stage iii non-small cell Lung cancer, The Oncologist 20 (2015) 491–492.
[122] M.G. Fury, E.J. Sherman, S.S. Rao, S. Wolden, S. Smith-Marrone, B. Mueller, K.K. Ng, P.R. Dutta, D.Y. Gelblum, J.L. Lee, R. Shen, S. Kurz, N. Katabi, S. Haque, N.Y. Lee, D.G. Pfister, Phase I study of weekly nab-paclitaxel + weekly cetuximab + intensity-modulated radiation therapy (IMRT) in patients with stage III-IVB head and neck squamous cell carcinoma (HNSCC), Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 25 (2014) 689–694.
[123] Y. Kawano, T. Sasaki, H. Yamaguchi, K. Hirano, A. Horiike, M. Satouchi, S. Hosokawa, R. Morinaga, K. Komiya, K. Inoue, Y. Fujita, R. Toyozawa, T. Kimura, K. Takahashi, K. Nishikawa, J. Kishimoto, Y. Nakanishi, I. Okamoto, Phase I/II study of carboplatin plus nab-paclitaxel and concurrent radiotherapy for patients with locally advanced non–small cell lung cancer, Lung Cancer 125 (2018) 136–141.
[124] H. Tinwell, J. Ashby, Genetic toxicity and potential carcinogenicity of taxol, Carcinogenesis. 15 (1994) 1499–1501.
[125] S.R. Adams, H.C. Yang, E.N. Savariar, J. Aguilera, J.L. Crisp, K.A. Jones, M.A. Whitney, S.M. Lippman, E.E.W. Cohen, R.Y. Tsien, S.J. Advani, Anti-tubulin drugs conjugated to anti-ErbB antibodies selectively radiosensitize, Nat. Commun. 7 (2016) 13019.
[126] L. Bourillon, C. Bourgier, N. Gaborit, V. Garambois, E. Llès, A. Zampieri, C. Ogier, M. Jarlier, N. Radosevic-Robin, B. Orsetti, H. Delpech, C. Theillet, P.-E. Colombo, D. Azria, A. Pèlegrin, C. Larbouret, T. Chardès, An auristatin-based antibody-drug conjugate targeting HER3 enhances the radiation response in pancreatic cancer, Int. J. Cancer 0 (2019).
[127] S.J. Advani, H. Yang, M. Doan, M.F. Camargo, J. Aguilera, S.R. Adams, Antibody drug conjugate targeted radiosensitization of her2 tumors, Int. J. Radiat. Oncol. • Biol. • Phys. 99 (2017) S148.
[128] J. Raja, J.M. Ludwig, S.N. Gettinger, K.A. Schalper, H.S. Kim, Oncolytic virus immunotherapy: future prospects for oncology, J. Immunother. Cancer. 6 (2018) 140.
[129] D.S. Sanchala, L.K. Bhatt, K.S. Prabhavalkar, Oncolytic herpes simplex viral therapy: a stride toward selective targeting of Cancer cells, Front. Pharmacol. 8 (2017) 270.
[130] J. Fang, H. Nakamura, H. Maeda, The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect, Adv. Drug Deliv. Rev. 63 (2011) 136–151.
[131] R.K. Jain, Vascular and interstitial barriers to delivery of therapeutic agents in tumors, Cancer Metastasis Rev. 9 (1990) 253–266.
[132] S. Ferretti, P.R. Allegrini, M.M. Becquet, P.M. McSheehy, Tumor interstitial fluid pressure as an early-response marker for anticancer therapeutics, Neoplasia. 11 (2009) 874–881.
[133] D.M. McDonald, P. Baluk, Significance of blood vessel leakiness in cancer, Cancer Res. 62 (2002) 5381–5385.
[134] Y. Navalitloha, E.S. Schwartz, E.N. Groothuis, C.V. Allen, R.M. Levy, D.R. Groothuis, Therapeutic implications of tumor interstitial fluid pressure in subcutaneous RG-2 tumors, Neuro-Oncol. 8 (2006) 227–233.
[135] S. Stapleton, D. Jaffray, M. Milosevic, Radiation effects on the tumor microenvironment: implications for nanomedicine delivery, Adv. Drug Deliv. Rev. 109 (2017) 119–130.
[136] S.N. Ekdawi, J.M.P. Stewart, M. Dunne, S. Stapleton, N. Mitsakakis, Y.N. Dou, D.A. Jaffray, C. Allen, Spatial and temporal mapping of heterogeneity in liposome uptake and microvascular distribution in an orthotopic tumor xenograft model, J. Control. Release Off. J. Control. Release Soc. 207 (2015) 101–111.
[137] A.J. Clark, D.T. Wiley, J.E. Zuckerman, P. Webster, J. Chao, J. Lin, Y. Yen, M.E. Davis, CRLX101 nanoparticles localize in human tumors and not in adjacent, nonneoplastic tissue after intravenous dosing, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 3850–3854.
[138] A. Udhrain, K.M. Skubitz, D.W. Northfelt, Pegylated liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma, Int. J. Nanomedicine 2 (2007) 345–352.
[139] J.W. Nichols, Y.H. Bae, EPR: evidence and fallacy, J. Control. Release 190 (2014) 451–464.
[140] R. Vinhas, R. Mendes, A.R. Fernandes, P.V. Baptista, Nanoparticles—emerging potential for managing leukemia and lymphoma, Front. Bioeng. Biotechnol. 5 (2017) 79.
[141] A. Gabizon, H. Shmeeda, Y. Barenholz, Pharmacokinetics of pegylated liposomal doxorubicin: review of animal and human studies, Clin. Pharmacokinet. 42 (2003) 419–436.
[142] E.J. Potchen, J. Kinzie, C. Curtis, B.A. Siegel, R.K. Studer, Effect of irradiation on tumor microvascular permeability to macromolecules, Cancer. 30 (1972) 639–643.
[143] S. Stapleton, M. Dunne, M. Milosevic, C.W. Tran, M.J. Gold, A. Vedadi, T.D. Mckee, P.S. Ohashi, C. Allen, D.A. Jaffray, Radiation and heat improve the delivery and efficacy of Nanotherapeutics by modulating Intratumoral fluid dynamics, ACS Nano 12 (2018) 7583–7600.
[144] M.I. Koukourakis, S. Koukouraki, I. Fezoulidis, N. Kelekis, G. Kyrias, S. Archimandritis, N. Karkavitsas, High intratumoural accumulation of stealth® liposomal doxorubicin (Caelyx®) in glioblastomas and in metastatic brain tumours, Br. J. Cancer 83 (2000) 1281–1286.
[145] S.H. Benedict, D.J. Schlesinger, S.J. Goetsch, B.D. Kavanagh, Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy, CRC Press, 2014.
[146] M.A. Miller, R. Chandra, M.F. Cuccarese, C. Pfirschke, C. Engblom, S. Stapleton, U. Adhikary, R.H. Kohler, J.F. Mohan, M.J. Pittet, R. Weissleder, Radiation therapy primes tumors for nanotherapeutic delivery via macrophage-mediated vascular bursts, Sci. Transl. Med. 9 (2017) eaal0225.
[147] G. Multhoff, J. Radons, Radiation, inflammation, and immune responses in cancer, Front. Oncol. 2 (2012) 58.
[148] K. Stark, A. Eckart, S. Haidari, A. Tirniceriu, M. Lorenz, M.-L. von Brühl, F. Gärtner, A.G. Khandoga, K.R. Legate, R. Pless, I. Hepper, K. Lauber, B. Walzog, S. Massberg,

Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and "instruct" them with pattern-recognition and motility programs, Nat. Immunol. 14 (2013) 41–51.
[149] M. Björnmalm, K.J. Thurecht, M. Michael, A.M. Scott, F. Caruso, Bridging bio–Nano science and Cancer nanomedicine, ACS Nano 11 (2017) 9594–9613.
[150] L. Arabi, A. Badiee, F. Mosaffa, M.R. Jaafari, Targeting CD44 expressing cancer cells with anti-CD44 monoclonal antibody improves cellular uptake and antitumor efficacy of liposomal doxorubicin, J. Control. Release Off. J. Control. Release Soc. 220 (2015) 275–286.
[151] H. Jin, J. Pi, Y. Zhao, J. Jiang, T. Li, X. Zeng, P. Yang, C.E. Evans, J. Cai, EGFR-targeting PLGA-PEG nanoparticles as a curcumin delivery system for breast cancer therapy, Nanoscale. 9 (2017) 16365–16374.
[152] J.D. Byrne, T. Betancourt, L. Brannon-Peppas, Active targeting schemes for nanoparticle systems in cancer therapeutics, Adv. Drug Deliv. Rev. 60 (2008) 1615–1626.
[153] M.M. Schmidt, K.D. Wittrup, A modeling analysis of the effects of molecular size and binding affinity on tumor targeting, Mol. Cancer Ther. 8 (2009) 2861–2871.
[154] D.B. Kirpotin, D.C. Drummond, Y. Shao, M.R. Shalaby, K. Hong, U.B. Nielsen, J.D. Marks, C.C. Benz, J.W. Park, Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models, Cancer Res. 66 (2006) 6732–6740.
[155] Y. Shamay, M. Elkabets, H. Li, J. Shah, S. Brook, F. Wang, K. Adler, E. Baut, M. Scaltriti, P.V. Jena, E.E. Gardner, J.T. Poirier, C.M. Rudin, J. Baselga, A. Haimovitz-Friedman, D.A. Heller, P-selectin is a nanotherapeutic delivery target in the tumor microenvironment, Sci. Transl. Med. 8 (2016) 345ra87.
[156] D.E. Hallahan, L. Geng, A.J. Cmelak, A.B. Chakravarthy, W. Martin, C. Scarfone, A. Gonzalez, Targeting drug delivery to radiation-induced neoantigens in tumor microvasculature, J. Control. Release 74 (2001) 183–191.
[157] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity. 39 (2013) 1–10.
[158] C.T. Hagan, Y.B. Medik, A.Z. Wang, Nanotechnology Approaches to Improving Cancer Immunotherapy, in: Adv, Academic Press, Cancer Res, 2018 35–56.
[159] Y. Min, K.C. Roche, S. Tian, M.J. Eblan, K.P. McKinnon, J.M. Caster, S. Chai, L.E. Herring, L. Zhang, T. Zhang, J.M. DeSimone, J.E. Tepper, B.G. Vincent, J.S. Serody, A.Z. Wang, Antigen-capturing nanoparticles improve the abscopal effect and cancer immunotherapy, Nat. Nanotechnol. 12 (2017) 877–882.
[160] S.C. Formenti, S. Demaria, Combining radiotherapy and cancer immunotherapy: a paradigm shift, J. Natl. Cancer Inst. 105 (2013) 256–265.
[161] H.E. Barker, J.T.E. Paget, A.A. Khan, K.J. Harrington, The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence, Nat. Rev. Cancer 15 (2015) 409–425.
[162] T. Hamaguchi, K. Kato, H. Yasui, C. Morizane, M. Ikeda, H. Ueno, K. Muro, Y. Yamada, T. Okusaka, K. Shirao, Y. Shimada, H. Nakahama, Y. Matsumura, A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation, Br. J. Cancer 97 (2007) 170–176.
[163] M. Sethi, R. Sukumar, S. Karve, M.E. Werner, E.C. Wang, D.T. Moore, S.R. Kowalczyk, L. Zhang, A.Z. Wang, Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity, Nanoscale. 6 (2014) 2321–2327.
[164] J. Tian, Y. Min, Z. Rodgers, X. Wan, H. Qiu, Y. Mi, X. Tian, K.T. Wagner, J.M. Caster, Y. Qi, K. Roche, T. Zhang, J. Cheng, A.Z. Wang, Nanoparticle delivery of chemotherapy combination regimen improves the therapeutic efficacy in mouse models of lung cancer, Nanomedicine 13 (2017) 1301–1307.
[165] P. Chytil, M. Šírová, J. Kudláčová, B. Říhová, K. Ulbrich, T. Etrych, Bloodstream stability predetermines the antitumor efficacy of micellar polymer-doxorubicin drug conjugates with pH-triggered drug release, Mol. Pharm. 15 (2018) 3654–3663.
[166] S. Guo, C.M. Lin, Z. Xu, L. Miao, Y. Wang, L. Huang, Co-delivery of cisplatin and rapamycin for enhanced anticancer therapy through synergistic effects and microenvironment modulation, ACS Nano 8 (2014) 4996–5009.
[167] X. Wan, J.J. Beaudoin, N. Vinod, Y. Min, N. Makita, H. Bludau, R. Jordan, A. Wang, M. Sokolsky, A.V. Kabanov, Co-delivery of paclitaxel and cisplatin in poly(2-oxazoline) polymeric micelles: implications for drug loading, release, pharmacokinetics and outcome of ovarian and breast cancer treatments, Biomaterials. 192 (2019) 1–14.
[168] S. Uthaman, K.M. Huh, I.-K. Park, Tumor microenvironment-responsive nanoparticles for cancer theragnostic applications, Biomater. Res. 22 (2018).
[169] Y. Kato, S. Ozawa, C. Miyamoto, Y. Maehata, A. Suzuki, T. Maeda, Y. Baba, Acidic extracellular microenvironment and cancer, Cancer Cell Int. 13 (2013) 89.
[170] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science. 324 (2009) 1029–1033.
[171] J. Du, L.A. Lane, S. Nie, Stimuli-responsive nanoparticles for targeting the tumor microenvironment, J. Control. Release Off. J. Control. Release Soc. 219 (2015) 205–214.
[172] F. Liu, J. Lou, D. Hristov, X-ray responsive nanoparticles with triggered release of nitrite, a precursor of reactive nitrogen species, for enhanced cancer radiosensitization, Nanoscale. 9 (2017) 14627–14634.
[173] M. Su, K.G. Guggenheim, J. Lien, J.B. Siegel, T. Guo, X-ray-mediated release of molecules and engineered proteins from nanostructure surfaces, ACS Appl. Mater. Interfaces 10 (2018) 31860–31864.
[174] Z.B. Starkewolf, L. Miyachi, J. Wong, T. Guo, X-ray triggered release of doxorubicin from nanoparticle drug carriers for cancer therapy, Chem. Commun. 49 (2013) 2545–2547.
[175] N. Ma, H. Xu, L. An, J. Li, Z. Sun, X. Zhang, Radiation-sensitive Diselenide block copolymer micellar aggregates: toward the combination of radiotherapy and chemotherapy, Langmuir. 27 (2011) 5874–5878.
[176] J.S. Ross, D.P. Schenkein, R. Pietrusko, M. Rolfe, G.P. Linette, J. Stec, N.E. Stagliano, G.S. Ginsburg, W.F. Symmans, L. Pusztai, G.N. Hortobagyi, Targeted therapies for cancer 2004, Am. J. Clin. Pathol. 122 (2004) 598–609.
[177] A. Petrelli, S. Giordano, From single- to multi-target drugs in cancer therapy: when aspecificity becomes an advantage, Curr. Med. Chem. 15 (2008) 422–432.
[178] C.N. Coleman, G.S. Higgins, J.M. Brown, M. Baumann, D.G. Kirsch, H. Willers, P.G.S. Prasanna, M.W. Dewhirst, E.J. Bernhard, M.M. Ahmed, Improving the predictive value of preclinical studies in support of radiotherapy clinical trials, Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 22 (2016) 3138–3147.
[179] T. Paunesku, S. Gutiontov, K. Brown, G.E. Woloschak, Radiosensitization and Nanoparticles, Nanotechnol.-Based Precis. Tools Detect, Springer International Publishing, Switzerland, Treat. Cancer 2015, pp. 151–171.
[180] Y. Wang, W. Deng, N. Li, S. Neri, A. Sharma, W. Jiang, S.H. Lin, Combining immunotherapy and radiotherapy for Cancer treatment: current challenges and future directions, Front. Pharmacol. 9 (2018) 185.
[181] S.J. Gandhi, A.J. Minn, R.H. Vonderheide, E.J. Wherry, S.M. Hahn, A. Maity, Awakening the immune system with radiation: optimal dose and fractionation, Cancer Lett. 368 (2015) 185–190.
[182] M. Verheij, C. Vens, B. van Triest, Novel therapeutics in combination with radiotherapy to improve cancer treatment: rationale, mechanisms of action and clinical perspective, Drug Resist. Updat. 13 (2010) 29–43.
[183] C.V.M. Verhagen, R. de Haan, F. Hageman, T.P.D. Oostendorp, A.L.E. Carli, M.J. O'Connor, J. Jonkers, M. Verheij, M.W. van den Brekel, C. Vens, Extent of radiosensitization by the PARP inhibitor olaparib depends on its dose, the radiation dose and the integrity of the homologous recombination pathway of tumor cells, Radiother. Oncol. 116 (2015) 358–365.
[184] V. Fisi, E. Kátai, P. Bogner, A. Miseta, T. Nagy, Timed, sequential administration of paclitaxel improves its cytotoxic effectiveness in a cell culture model, Cell Cycle 15 (2016) 1227–1233.
[185] T.D. Han, D.H. Shang, Y. Tian, Docetaxel enhances apoptosis and G2/M cell cycle arrest by suppressing mitogen-activated protein kinase signaling in human renal clear cell carcinoma, Genet. Mol. Res. GMR. 15 (2016).
[186] Q.-T. Le, D. Raben, Integrating biologically targeted therapy in head and neck squamous cell carcinomas, Semin. Radiat. Oncol. 19 (2009) 53–62.
[187] E. Deutsch, J.C. Soria, J.P. Armand, New concepts for phase I trials: evaluating new drugs combined with radiation therapy, Nat. Clin. Pract. Oncol. 2 (2005) 456–465.
[188] M.A. Smith, C.P. Reynolds, M.H. Kang, E.A. Kolb, R. Gorlick, H. Carol, R.B. Lock, S.T. Keir, J.M. Maris, C.A. Billups, D. Lyalin, R.T. Kurmasheva, P.J. Houghton, Synergistic activity of PARP inhibition by Talazoparib (BMN 673) with Temozolomide in pediatric Cancer models in the pediatric preclinical testing program, Clin. Cancer Res. 21 (2015) 819–832.
[189] M. Faria, M. Björnmalm, K.J. Thurecht, S.J. Kent, R.G. Parton, M. Kavallaris, A.P.R. Johnston, J.J. Gooding, S.R. Corrie, B.J. Boyd, P. Thordarson, A.K. Whittaker, M.M. Stevens, C.A. Prestidge, C.J.H. Porter, W.J. Parak, T.P. Davis, E.J. Crampin, F. Caruso, Minimum information reporting in bio–nano experimental literature, Nat. Nanotechnol. 13 (2018) 777–785.
[190] H.B. Stone, E.J. Bernhard, C.N. Coleman, J. Deye, J. Capala, J.B. Mitchell, J.M. Brown, Preclinical data on efficacy of 10 drug-radiation combinations: evaluations, concerns, and recommendations, Transl. Oncol. 9 (2016) 46–56.
[191] J. Kahn, P.J. Tofilon, K. Camphausen, Preclinical models in radiation oncology, Radiat. Oncol. Lond. Engl. 7 (2012) 223.
[192] S.N. Bhatia, D.E. Ingber, Microfluidic organs-on-chips, Nat. Biotechnol. 32 (2014) 760–772.
[193] I. Holen, V. Speirs, B. Morrissey, K. Blyth, In vivo models in breast cancer research: progress, challenges and future directions, Dis. Model. Mech. 10 (2017) 359–371.
[194] C.-P. Day, G. Merlino, T. Van Dyke, Preclinical mouse Cancer models: a maze of opportunities and challenges, Cell. 163 (2015) 39–53.
[195] R. Hirayama, A. Ito, M. Tomita, T. Tsukada, F. Yatagai, M. Noguchi, Y. Matsumoto, Y. Kase, K. Ando, R. Okayasu, Y. Furusawa, Contributions of direct and indirect actions in cell killing by high-LET radiations, Radiat. Res. 171 (2009) 212–218.
[196] B.F. Koontz, F. Verhaegen, D. De Ruysscher, Tumour and normal tissue radiobiology in mouse models: how close are mice to mini-humans? Br. J. Radiol. 90 (2017).
[197] V. Agrahari, V. Agrahari, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities, Drug Discov. Today 23 (2018) 974–991.
[198] Y. Min, J.M. Caster, M.J. Eblan, A.Z. Wang, Clinical translation of nanomedicine, Chem. Rev. 115 (2015) 11147–11190.
[199] T.A. Chan, B. Hristov, S.N. Powell, Radiation Biology for Radiation Oncologists, in: Clin, John Wiley & Sons, Inc., Radiat. Oncol, 2017 15–61.
[200] A. Rajan, A. Berns, U. Ringborg, J. Celis, B. Ponder, C. Caldas, D. Livingston, R.G. Bristow, T.T. Hecht, T. Tursz, H. van Luenen, P. Bono, T. Helander, K. Seamon, J.F. Smyth, D. Louvard, A. Eggermont, W.H. van Harten, Excellent translational research in oncology: a journey towards novel and more effective anti-cancer therapies, Mol. Oncol. 10 (2016) 645–651.
[201] M. Jacobs, L. Boersma, F.V. Merode, A. Dekker, F. Verhaegen, L. Linden, P. Lambin, How efficient is translational research in radiation oncology? The example of a large Dutch academic radiation oncology department, Br. J. Radiol. 89 (2016).