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Review Article

Multimodal Imaging Techniques and Theragnostic Approaches for Diagnosis and Treatment of Cancer

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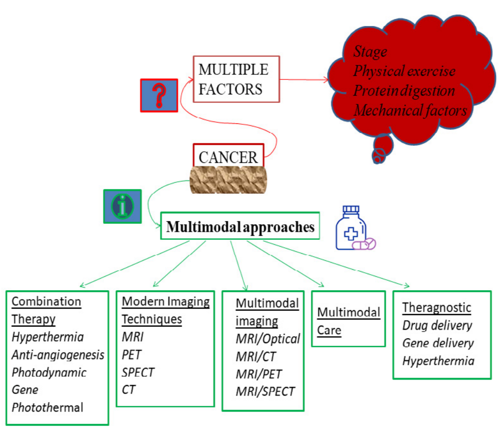
ABSTRACT

Since cancer is a complex illness, a multimodal strategy with a multidisciplinary team is necessary. Currently, chemotherapy, surgery, and/or radiation therapy are used in combination to treat cancer. Chemotherapy is currently recognized as the most effective cancer treatment despite the fact that it is known to induce severe side effects in patients due to its non-discriminatory adverse effect on both normal and malignant cells. Understanding how drugs are distributed throughout organs and creating site-specific drug delivery strategies that target cancer cells are primary challenges in cancer and other complex chemotherapeutic diseases. Thus, it is essential to create innovative methods for the traceable and targeted delivery of anticancer drugs. This review article aims to provide an overview of current tumor therapy methods and discuss their potential benefits in a multimodal approach. There is growing optimism that significant improvements in illness diagnosis and treatment may result from the use of nanotechnology in medicine. Additionally, this review article offers an overview of multifunctional nanostructures used in medication delivery and cancer therapy.



GRAPHICAL ABSTRACT

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Introduction

One of the deadliest illnesses that affects people is cancer, the precise cause of which is yet unknown. Since cancer is currently the leading cause of mortality worldwide, it poses a significant risk to human hygiene. Every year, almost 10 million people receive a cancer diagnosis. Cancer begins as a localized illness before spreading to other parts of the body and becomes incurable. In general, multistage malignancy processes that link cellular functional organizations, such as compartmental motion, are very complex and incomprehensible, resulting in cell death. Cancer's morbidity and mortality have skyrocketed, drawing attention to the need to discover alternative therapeutic approaches in order to lessen the disease's impact.[1]

Traditional cancer operations and treatments can be limited by inadequate human visualization since they rely significantly on the physician's eye-hand coordination. Moreover, the human eye may not be able to differentiate many infiltrating, malignant tumors, such as those in the lung or brain, from nearby normal tissue. Therefore, intraprocedural outcomes are extremely difficult due to the inability to discriminate between tumor borders and related anatomic structures. The human eye may not be able to view 3D functional or morphological data concerning tumors and even less observe perfusion, metabolism, or tissue temperature, all of which are necessary for the accurate release of treatment. Hence, imaging may reveal a novel and vital function in controlling these discrepancies and achieving an ideal target description, which is a prerequisite for all efficacious surgeries or interventions. The patient undertakes a set of diagnostic imaging tests before all such procedures. These photographs were then used to practice different behaviors and transformed into 3D models and images, demonstrating the patient's anatomy as well as the disease. An imaging probe may locate cancer cells and provide data regarding the tumor in targeted cancer imaging.

Numerous scientists and researchers are working to determine the precise cause, mechanism, and course of treatment for a particular type of cancer. Chemotherapy is one of the oldest treatments for cancer and is thought to be the only option. Despite its numerous drawbacks, such as drug delivery to all tissues, including healthy tissues, drug resistance, low bioavailability, etc., chemotherapy is currently the only proven treatment for cancer. Cancer patients require targeted and efficient treatment because of the disease's severity and localization. Therefore, a medication that simultaneously monitors the therapeutic response and incorporates a diagnostic agent is required.[2]

Nanoparticles (NPs) have the capability to extend the period of drug circulation, accept more hydrophobic drugs, boost drug accumulation to tumor tissues *via* improved permeability and retention, and minimize adverse effects. As a result, numerous nanoparticle (NP) preparations have been recommended, including liposomes, magnetic NPs, and micelles, and it has been demonstrated that they enhance the therapeutic effects of many anticancer treatments and strategies.[3] Additionally, NPs are being actively developed for targeted medication delivery, cancer biomarker biomolecular profiling, and *in-vivo* tumor imaging.[4] It has been established that these forms enhance the therapeutic benefits of various anticancer therapies and systems.[5]

For cancer treatment, theragnostic (or theranostic) is a novel strategy that combines medicines and diagnostics.[6-10] The results of investigative evaluations are connected to specific treatment in this case. Novel diagnostic assays have emerged as a result of the innovative data on proteins, biomarkers, and genes generated by advances in proteomics, informatics, and genomics. While an anticancer agent is delivered precisely to the targeted cancer site with the aid of suitable targeting ligands, such as small molecules, peptides, peptide mimetics, antibodies, and aptamers, the results of investigative evaluations are utilized in theragnostics to plan and implement targeted treatments effectively. As a result, diagnosis and treatment are complementary to each other. Monitoring and improving medication efficacy and safety as well as therapy response, is the primary goal of theragnostic. Additionally, tremendous effort has been made to cultivate substances that could likely be used for targeted therapy and tumor imaging.

Moreover, cancer cases have changed body image that influences their relationships, emotions and community working. Further, cancer patients become isolated and restricted and compounded by health repair specialists and cares. However, factors of cancer in patients like age, physical activity and mechanism of protein metabolism can assist in anabolic blockade.

Modern Imaging Techniques

The major objective is to develop cancer imaging probes that are biocompatible, highly specific, provide a greater signal-to-noise ratio, have enhanced sensitivity, and exhibit optimal pharmacodynamic and pharmacokinetic profiles. Various aiming ligands, such as antibodies, peptides, small molecules, and aptamers, may be utilized to create goal-specific imaging probes. Several techniques used for imaging cancer are magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), ultrasound, X-ray imaging, and optical imaging.[11-13] The benefits and drawbacks of important imaging methods are depicted in Table 1.[14]

MRI

In the clinical field, it is a helpful analytical instrument for solving difficulties, as it has higher longitudinal resolution and contrast in soft tissue compared to other imaging

Table 1: The benefits and drawbacks of important imaging methods

S. No.	*Imaging modality*	*Advantages*	*Disadvantages*
1	MRI	Good soft tissue divergence Greater longitudinal determination Provides functional and anatomical information	Requires expensive equipment Low sensitivity Long acquisition time
2	PET	High sensitivity 3D imaging Provides biochemical information Monitor changes in drug biodistribution and tumor metabolism	Requires expensive equipment Requires specialized equipment Requires radio-nucleotide facilities Limited anatomical information
3	SPECT	In contrast to PET detect multiple probes simultaneously	Lower resolution Lower sensitivity as compared with PET
4	CT	3D image High sensitivity anatomical imaging	Requires expensive equipment Restricted efficient data Deprived soft tissue divergence
5	Optical (Bioluminescence & fluorescent)	Extensive applicability Relatively inexpensive Concurrently screen various molecular actions	Decreased sensitivity by enhanced imaging deepness Provides limited anatomical information

modalities. Furthermore, these protons originate from water molecules that are present in our body tissue. The resonance frequency that is a radiofrequency produced at a specific frequency may flip the spin of a proton. The proton spins reverse to a unique level when the electromagnetic field is turned off and generates a radiofrequency signal. Such a procedure is known as relaxation. The receiver coil measures this relaxation and transforms it into a picture through a computer algorithm.[15] MRI contrast mediators can be used to alter relaxation rates at times T_1 or T_2. T_1 contrast agents like gadolinium chelator enhance positive signal on T_1 weighed pictures while T_2 contrast mediators like superparamagnetic iron oxide NPs (SPION) supported contrast mediators decrease indicator strength on T_2 weighed images.

PET

It is suitable for cancer imaging and highly sensitive non-invasive technology.[16] Radiolabeled tracers are injected to acquire 3D images that display the location and concentration of the tracer of interest. The molecules of curiosity may be characterized by an isotope that is capable of emitting two gamma rays by releasing a positron from its nucleus. The most commonly used PET tracer is fluorodeoxyglucose (FDG), which offers a versatile approach for cancer imaging. Currently, the majority of clinical PET studies utilize FDG, with general mean specificity and sensitivity across several applications.

SPECT

SPECT falls under the nuclear imaging category, as it is dependent on the discovery of radioisotopes that release one or two gamma rays or positrons. Due to its sensitivity, specificity, and rapid recognition period, it is considered an excellent imaging technique. But this technique cannot display good spatial resolution. This technique utilizes gamma releasing heavy radioisotopes like ^{123}I, ^{99m}Tc and ^{133}Xe.[17]

CT

It is a further imaging technique most broadly utilized in the clinic for diagnosis of different categories of cancer. This technique utilizes X-rays to get pictures through portions of body parts. The major benefit of this method is that it creates pictures through greater longitudinal determination. The most commonly used CT contrast agents are iodine-based substances. CT contrast agent functions by lumping X-rays, delivering contrast and increasing a fraction of body. Iodine-based compounds yield various adverse outcomes like itching, vomiting as well as anaphylactic shock. Between ionic and non-ionic agents, ionic agents have been shown to be extremely injurious, particularly in patients with renal problems.[18-20] Thus, for CT, current research has emphasized on emerging a gold NP-constructed contrast agent. Gold NPs are biocompatible and capable of targeting tumors by enhanced permeability and retention (EPR) effect. This material has an X-ray absorption coefficient that makes it suitable for CT imaging. Gold provides better X-ray attenuation and contrast, as it is a metal with an elevated atomic number and thus serves as a robust candidate for CT imaging.[21]

Optical imaging has utilized the physical properties of light to penetrate tissue, and numerous optical imaging approaches are employed. These methods depend on absorption, fluorescence, reflectance or bioluminescence by means of basis of divergence. Optical imaging mainly consists of near-infrared fluorescence (NIRF), bioluminescence, and reflectance imaging. Apart from this, optical imaging is also used in several clinical and research settings. Thus, inexpensive, sensitive, versatile and non-toxic are key advantages of optical contrast agent.[22-24] Earlier, optical imaging utilized in cancer finding was dependent upon difference in the endogenous fluorescence of neoplastic tissue. Nevertheless, exogenous contrast agents were limited due to the complexity of differentiating diagnostic signal constituents from backdrop fluorescence. An NP-dependent optical contrast agent, such as a quantum dot, was thus built, which has greater imaging characteristics compared to organic counterparts. The inability to accurately enumerate image and autofluorescence of normal tissue compared to fluorescence of divergence is a major problem in optical imaging, which can impair the superiority of the image.[25]

Multimodal Imaging

Imaging modalities differ in resolution, compassion as well as measurable aptitudes. In single-modality imaging, a major dilemma is the lack of ability to guarantee conformance of diagnosis, which is considered a critical issue in deciding therapy. However, such difficulty may be resolved through multimodal imaging, as each imaging modality offers its own unique advantages. Moreover, multimodal imaging provides a grouping of methods through complementary assets, allowing for the conquest of intrinsic limitations of specific modalities.[27,28] For instance, PET images deliver high-sensitivity functional as well as biological data regarding cancer. Oppositely, MRI, as well as CT, show high-resolution images to collect anatomical data. Thus, a mixture of imaging modalities provides greater resolution and sensitivity simultaneously in addition to more detailed biological or anatomical data regarding cancer disease. For cancer theranostics, multimodal imaging is a cutting-edge method that exploits the benefits of NPs.[29,30]

MRI/optical imaging

In MRI/optical dual imaging, the progress of MRI and NIRF dye-coupled contrast mediator is a crucial research determination.[31,32] MRI is not capable of measuring functional details like protease activity as well as gene appearance. However, NIRF imaging may be utilized to visualize the practical aspects of molecular events. Thus, these techniques, when combined, increase overall imaging excellence.[33] Cyanine dye is most extensively utilized as compared with other NIRF dyes. MRI, as well as optical imaging, are well-established methods in multimodal imaging, connected by means of NIRF-dependent molecular imaging probes with a wavelength of emission ranging from 650 to 900 nm.[34] For example, MRI/optical double contrast mediators were built up for *in-vivo* tumor imaging through thermally cross connecting of SPION via Si-OH enclosing co-polymer.[35]

MRI/CT imaging

Anatomical imaging is an essential characteristic that requires the gathering of data indicating the presence of a lesion in the body. Both MRI and CT are excellent for anatomical imaging but weak in functional imaging. MRI/CT double imaging is a combination of two anatomic modalities that share equivalent functional characteristics.[36] The variation between MRI and CT is physics included in the corresponding imaging process. CT utilizes X-ray radiation to pass through tissue, and an image is noted depending on the absorption and attenuation properties of the contrast mediator. While MRI works below the pressure of a robust magnetic field and the image is examined on the basis of T_1 or T_2 contrast improvement encouraged by NPs.[37] The most commonly used CT contrast agent is gold NPs. They are grouped with SPION to produce a hybrid called gold iron oxide NPs (GION), which may be utilized as a twin contrast agent for MRI and CT.[38]

MRI/PET imaging

MRI/PET imaging is preferred for both anatomic and functional imaging. Compared with MRI/CT, MRI/PET has the benefit of decreased radiation exposure. PET is a nuclear imaging method, like SPECT, and is grounded in nucleotide-releasing positrons. MRI gains image with increased spatial resolution thus modifying fractional volume results sourced by PET. Multimodal MRI/PET contains a radionucleotide coupled to an MRI agent, SPION.[39] Yang developed the water-soluble SPION-based nanocarrier.[40]

MRI/SPECT imaging

The benefit of SPECT is the opportunity to acquire data on molecular processes using precise radiolabels. Additionally, SPECT enables clinicians to regulate the biodistribution of radiotracer-labeled elements *in-vivo* in picomolar concentration series. Thus, MRI is utilized in conjunction with SPECT to acquire high-quality bodily images, offering both functional and structural advantages of dynamic imaging. MRI/SPECT reduces the scan periods needed for discrete imaging and discomfort associated with multiple lesions.[41] Recently, Misri and colleagues developed an MRI/SPECT twin modality imaging system for malignant mesothelioma. The significant features of multimodal imaging are depicted in Table 2.

Theragnostic

Theragnostic (or theranostic) is a new approach that combines therapeutics and diagnostics for cancer therapy.[42-46] Theranostic states to agents which mark molecular biomarkers of cancer ailment and thus supposed to subsidize to personalized medicine. In theranostic treatment, SPIONs have gained considerable consideration amongst the currently existing NPs, as they are utilized as contrast enhancement mediators for MRI and deliver therapeutic agents, such as anticancer agents and siRNA, to the disease site. Furthermore, SPION can emit continuous heat on contact with an irregular outside magnetic field (AMF) by converting electromagnetic energy into heat.[47-52]

Table 2: Significant features of multimodal imaging

Sr. No.	*Multimodal imaging*	*Advantages*	*Disadvantages*
1	MRI/optical	Useful featuring of molecular incident and decent anatomical featuring	Passive targeting
2	MRI/CT	Good anatomical detailing	No tumor targeting and poor functional imaging capability
3	MRI/PET	Tall sensitivity	Various amount of MRI and PET agents
4	MRI/SPECT	High sensitivity and functional information	-

The following are advantages, disadvantages and diverse applications of theranostic.

Advantages

Improved diagnostics and treatment

By combining the advantages of therapeutic drugs and imaging, theranostics can offer a more specific diagnostic and treatment approach.

Reduced side effects

Compared to conventional treatments, targeted therapies can decrease damage to healthy tissues, resulting in fewer and milder side effects.

Early disease detection

Theranostic enables the early detection of diseases, potentially improving patient outcomes by combining imaging and treatment agents.

Improved precision

Theranostic has the capability to advance radiation delivery accuracy while reducing collateral damage to nearby healthy tissues.

Personalized medicine

Theranostic makes it possible to customize treatment for each patient according to their unique molecular traits, resulting in more focused and effective treatments.

f. Real-time monitoring

Theranostic makes it possible to track the usefulness and reaction of treatments in real-time, which aids prompt modifications to treatment plans.

Disadvantages

Difficulties in nanomedicine

Conventional theranostic systems in nanomedicine encounter problems like poor distribution within the body, high toxicity, rapid excretion from the body, and poor picture clarity.

Complex manufacturing

Scaling up manufacturing may be problematic because of the intricate procedures required to synthesize and purify theranostic chemicals.

High costs

Theranostic agents can be costly to develop and produce, which may limit their accessibility.

Ethical issues

Theranostic rises ethical issues, including the possibility of prejudice and data confidentiality.

Applications

Drug delivery

The common therapeutic approach for fighting cancer is chemotherapy. But it causes various side effects to healthy tissues and also non-selective. Thus, magnetic NPs may be filled with an anticancer agent and act as a probable drug carrier in a novel drug delivery policy. To reduce adverse effects and increase treatment efficacy, aimed transport of therapeutics may be utilized to confine therapeutic drugs to definite tissues. Currently, a range of anticancer drugs, such as paclitaxel, methotrexate, and doxorubicin (DOX), have been combined with magnetic nanoparticles (NPs) in tumor treatment.[53] Therefore, by utilizing imaging modalities and anticancer drugs, the multifunctionality of SPION-based nanosystems was investigated. For example, Yu *et al.* effectively assessed the tumor reduction efficacy of biocompatible polymer-covered SPION filled with DOX in lung cancer.[54]

Gene delivery

Gene therapy delivers a therapeutic gene to affected tissue to replace a defective gene and treat pathological genotypes by expressing the therapeutic gene. SiRNA is a group of double stranded RNA molecules which obstruct definite protein expression at post transcriptional stage. This procedure is called RNA interference (RNAi). Genes united within SPION promote cellular internalization and endosomal release, and protect nucleic acids against enzymatic degradation. SPION is considered a brilliant medium for siRNA release, as it is biocompatible and has objective functionalization.[55] MRI evident SPION have shown a double modality function which improves observing of siRNA towards targeted area.[56] Chen *et al.*[57] synthesized the SPION functionalized by way of polyethylene grafted polyethyleneimine using CD44v6 single sequence variable part for gastric cancer as targeting agent and siRNA loaded for therapy.

Hyperthermia

In this treatment, the temperature of body tissues is elevated toward 42°C. Thus, it influences the usefulness of proteins, cell membranes, and cellular structures. Nucleic acid restores enzymes as well as encourages death of the cell. Therefore, due to lesser tolerance of an unexpected temperature variation by magnetic hyperthermia (MHT), tumor cells may be killed. Furthermore, SPIONs possess the ability to produce high temperatures through ferromagnetic resonance. Nevertheless, during MHT treatment, the heating procedure is produced by Brownian and Neel relaxations. Thus, it has been studied widely in diverse categories of cancer like cervical, glioma and head and neck cancer. Hoskins *et al.*[52] studied the opportunity of using SPION in nano heater and multimodal applications.

Multimodal Care

The roots of wasting will support multimodal treatment programmes.[58] Components of this treatment include

- Nutritional psychotherapy for patients as well as for household
- Exercise programme
- Psychological counseling
- Identification of signs of cancer patient as well as strategy to cure it
- Use of agents to stimulate appetite

This program can be implemented by an interdisciplinary team.[59,60] It is promoted by the palliative care division rather than by nutrition care. At the onset of a natural life-threatening ailment, palliative care must be applied. According to the 2002 WHO, palliative care is a style that enhances the quality of life of patients as well as their families facing life-threatening diseases, anticipating and relieving suffering through meticulous assessment and treatment of discomfort and additional difficulties, such as spiritual, physical, and psychological. Palliative attention integrates efforts to manage illness and, if possible, symptoms in 'patient-family focused care'. The 'patient-family focused care' prioritizes the importance and needs of patients and their families across symptom control, helping them to manage their individual lives. Thus, in the case of cancer disease, the patient as well as the family will be in control of attention through a professional as counselor.

Hence, exercise in multimodal therapy is a workout in palliative attention. The finest trained associates to work as a team and regulate symptoms related to food consumption, enhance purpose, and report psychological problems are palliative care experts. Therefore, palliative care serves as a sign for the conclusion of life care. However, palliative care must be applied as soon as possible in the sequence of grieving for the patient, but minute advancements have been made in this case, and thus, the symbolic associations of palliative care must be strong. The study showed that palliative care, introduced in the initial analysis of cancer, advances the quality of life of patients and results in prolonged survival.[61]

Firstly, every member of the clinical team may contribute to a multimodal approach. Multimodal attention encompasses reporting nutritional influence symptoms, such as constipation, pain, and sore throat, which hinder absorption and intake. Within the scope of all clinicians, evaluating and handling this sign is an essential part of multimodal care. However, it is not permanently feasible to discuss with an expert, and thus, unassuming applied information must become part of each respective squad member's repertoire. This may be supplemented by an assurance of inter-professional knowledge and its application. Secondly, multimodal care in tumor patients must emphasize supported self-organization and be person-centered. Treatments to maintain and improve psychological, physical, or social functioning may require behavioral alteration and must be adapted to separate and adjacent backgrounds. Furthermore, the family and social system of the patient are important in improving and intensifying care for health behavior. Additionally, in coordination with this, patient-reported results have a major character in identifying efficacious maintenance.[62,63] Thus, multimodal care may be operationalized along with pharmacological treatments.

Conclusion

Tumor recurrence and chemotherapy resistance are the main barriers to the development of effective cancer treatment regimens. These are the hardest parts of cancer to treat right now. A multimodal strategy can be used to effectively diagnose, treat and control cancer, a complex multifactorial condition. Clinicians, pharmacists, dietitians, and physiologists may be involved in this strategy, which aims to manage cancer and detect it early. This multidisciplinary team may also create a modified treatment plan that incorporates both non-pharmaceutical and pharmacological methods. Additionally, the design of nanostructures may combine multimodal treatment, enabling the imaging and destruction of cancer cells by the combination of multimodal imaging techniques and theragnostic approaches. Thus, thoughtful multidisciplinary deliberations and clinical examinations are considered cornerstones in deciding the optimum multimodality strategy for each patient. However, upcoming learnings may implement these multimodal methods to recognize the complex processes involved in the growth of cancer, malignant development, and response to treatment.

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