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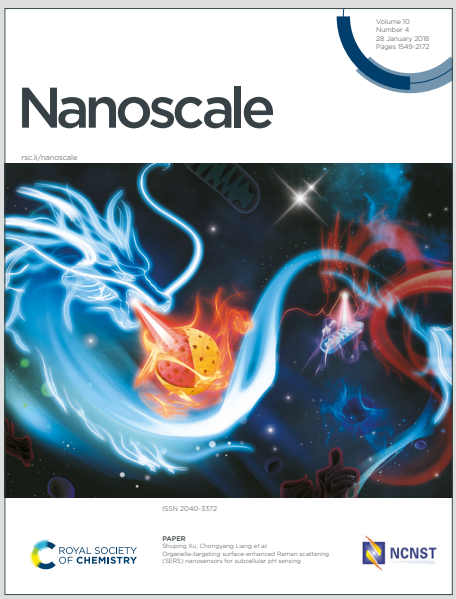

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Clinical Transformation of Afterglow Luminescence Imaging in Precision Surgery of Tumors: Opportunities and Challenges

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Abstract

The afterglow luminescence imaging technology, as an emerging tool for precise tumor diagnosis and treatment, is providing intraoperative navigation and postoperative monitoring methods for surgeons. From a clinical perspective, this article systematically reviews the current application status, clinical transformation opportunities, and challenges of afterglow luminescent materials in tumor resection surgeries. From the perspective of a surgeon, it emphasized the future development needs and called for the establishment of a cross-disciplinary collaboration platform to jointly promote the application of the afterglow luminescence imaging from the laboratory to the clinic.

Keywords: Afterglow luminescence imaging; Tumor surgery; Clinical translation

Introduction

Surgical resection remains the primary treatment approach for solid tumors. The high postoperative recurrence rate is the main factor restricting the overall survival rate[1, 2]. Therefore, achieving precise diagnosis and treatment of tumors and achieving radical resection is of great significance for improving the overall survival rate[3, 4]. To address the issue, the current area of active research is the use of near-infrared (NIR) fluorescent groups during the surgical procedure to achieve tumor visualization[5-7]. Thanks to the great efforts of researchers, so far, two NIR fluorescent groups have been approved by the FDA for use in image-guided surgery: indocyanine green (ICG) and methylene blue[8].

However, in addition to their advantages, the fluorescent groups cannot fully meet the current clinical needs for precise tumor diagnosis and treatment. Non-specific binding is the main limitation of ICG and methylene blue navigation surgeries that has been identified[9]. This situation has further given rise to the issue of false positives and the challenge of real-time identification of microscopic residual lesions during surgical procedures[10]. For instance, in liver cancer surgeries, the false positive rate can reach up to 40%[11, 12]. Similarly, in surgeries for malignant tumors of the ear, nose, and throat system, 25% of patients exhibit positive margins[13]. Furthermore, the fluorescence signal exhibits a low signal-to-noise ratio (SNR)[14]. It necessitates continuous external excitation and is highly vulnerable to attenuation caused by environmental factors, including light, temperature, and other relevant conditions. This characteristic of the fluorescence signal poses challenges in academic research, especially when precise and stable measurements are required[15].

In response to the existing problems of fluorescence navigation, researchers have been actively exploring a range of emerging optical imaging strategies. Among these, afterglow luminescence has gained increasing attention due to its distinct advantages, such as negligible background noise and the absence of real-time excitation. Moreover, afterglow luminescent materials have a large specific surface area and can be surface-modified through methods such as silica coating, polymer cross-linking, and biological molecule coupling, and are widely used in cell tracking, biosensing, and tumor diagnosis and treatment fields[16, 17].

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In this review, we discuss the latest advancements in afterglow luminescence imaging for tumor imaging, as well as the potential opportunities and challenges in its clinical application. This would provide researchers with a multidisciplinary understanding across various fields and a broad perspective.

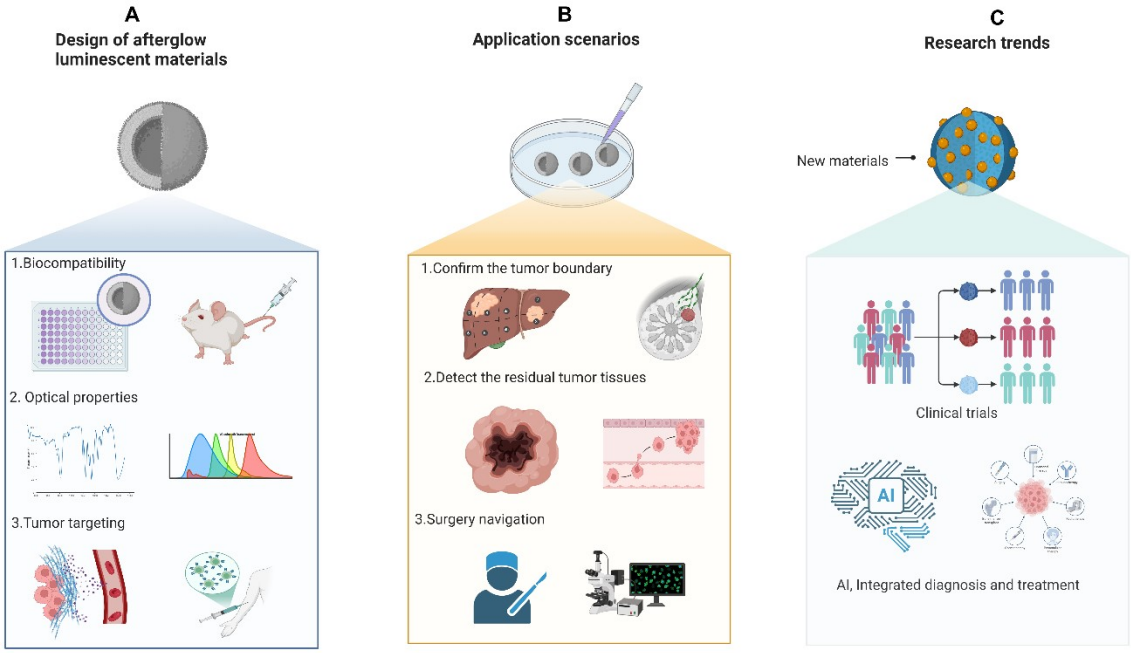

Figure 1. Overview framework

(A) Design principles of afterglow luminescent materials in tumor surgery; **(B)** Application scenarios of afterglow luminescent materials in tumor surgery; **(C)** The research trend of new material design towards clinical application.

Clinical demand-driven design of afterglow luminescent materials

Driven by clinical scenarios in tumor diagnosis and treatment, significant advancements have been achieved in the design and application of afterglow luminescent materials, positioning them at the forefront of biomedical research. These materials exhibit persistent luminescence after the cessation of excitation light sources, effectively circumventing the issue of tissue autofluorescence interference inherent in traditional fluorescence imaging, thereby offering unique advantages for deep tissue imaging and prolonged monitoring[18-20]. According to clinical requirements, the design of afterglow materials needs to comprehensively take into account the following key factors.

The biocompatibility of the material is the primary consideration factor,

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directly affecting its safe application in vivo[21]. The ideal afterglow materials should possess excellent biocompatibility, be non-toxic and non-immunogenic, be able to remain stable in the body, and eventually be safely metabolized[22, 23]. The afterglow materials can be classified into inorganic, organic and hybrid types[24]. They each have distinct characteristics in terms of biocompatibility, optical properties and metabolic behavior, and are suitable for different biomedical scenarios. Inorganic afterglow materials can regulate luminescent properties by doping different rare earth ions and transition metal ions. Jin et al. reported the design and synthesis of Mn^{2+}-doped hexagonal $CsCdCl_3$ MHP crystals with excellent X-ray scintillation and X-ray induced afterglow for more than 300 min. The afterglow emission can be rejuvenated effectively by 870 nm stimulus or heating even after 72 h of decay[25]. Most inorganic afterglow materials exhibit prolonged afterglow durations, typically ranging from several minutes to tens of hours, along with readily tunable optical properties. However, their slow degradation kinetics raise concerns regarding potential long-term retention in vivo, which may lead to persistent biological toxicity. Compared with inorganic materials, organic afterglow materials have better biocompatibility and degradability[26]. Traditional organic fluorescent molecules are encapsulated in the bovine serum albumin matrix. The afterglow emission can be significantly enhanced by 10 times, enabling tumor imaging and the detection of metastatic nodules[27]. However, hybrid materials exploit the tunable structure and easy processing of organic molecules, as well as enhanced spin-orbit coupling and intersystem crossing processes involving heavy atom dopants, to achieve excellent afterglow performance[28]. For instance, Pan et al. developed a zinc phthalocyanine-linked periodic mesoporous organic silicon nanoparticles, which served as a biodegradable photosensitizer for photodynamic therapy[29]. At the application level, inorganic materials are suitable for optical monitoring scenarios that require long-term duration and high SNR due to their persistent high-brightness luminescence properties; organic materials, with their excellent biological safety and degradability, are more suitable for short-term diagnosis and treatment that demands high biological compatibility and rapid metabolism; while hybrid materials, through the synergy of organic and inorganic components, demonstrate outstanding design flexibility and functional integration potential in combined therapy and multimodal imaging. Future research should focus on optimizing the balance between the material's metabolic safety, signal duration and

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light emission intensity.

To achieve deep tissue imaging, materials with emission wavelengths in the near-infrared region are usually selected, as the light in this wavelength band has better penetration ability in biological tissues[30]. Yuan et al developed an ultrasound-activated NIR-II afterglow luminescence probe (NPs-Ce4-SN) emitting afterglow luminescence with a peak at 1100 nm[31]. Wang et al reported the design and imaging performance of nanoparticles made of electron-rich trianthracene derivatives that, on excitation by room light at ultralow power, emit afterglow luminescence at 500 times those of commonly used organic afterglow nanoparticles. The nanoparticles' ultrabright afterglow allowed for deep-tissue imaging (up to 6 cm)[32]. High brightness, long afterglow time and near-infrared emission wavelength are the key performance indicators for achieving high-quality deep tissue imaging. Related studies have made significant progress in enhancing brightness and penetration depth through the design of new materials and excitation strategies. However, these performance indicators are often interrelated and mutually restrictive in actual material systems. For instance, prolonging the afterglow time may come at the expense of instantaneous brightness, and shifting the emission wavelength to the near-infrared region may also affect the intensity and stability of the luminescence. Therefore, how to achieve the optimal balance among these key parameters through ingenious chemical design molecular aggregation control and physical regulation is one of the core challenges for the practical application of afterglow materials in biomedicine.

In order to enhance the accuracy of diagnosis and treatment, it is necessary to functionalize the afterglow materials so that they can target tumor tissues or respond to specific stimuli in the tumor microenvironment[33]. Targeting ligands (such as antibodies, peptides, aptamers, etc.) can be modified on the surface of the afterglow materials to enhance the targeting ability of the materials to tumor tissues[34-36]. It is also possible to introduce responsive groups that are sensitive to the tumor microenvironment (such as pH-sensitive groups, redox-sensitive groups, enzyme-sensitive groups, etc.), which can enable the specific activation and drug release of the afterglow materials at the tumor site[37]. In order to obtain more comprehensive diagnostic information, it is common to combine the afterglow

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materials with techniques such as magnetic resonance imaging, computed tomography, and ultrasound imaging to achieve multimodal imaging and improve the accuracy of diagnosis[38]. Functionalization of afterglow materials through strategies such as targeting ligand modification, introduction of microenvironment-responsive groups, and integration of multimodal imaging techniques is a key approach to enhancing their tumor recognition specificity, release controllability, and diagnostic information integrity. These designs collectively aim at a core objective: to advance afterglow imaging from "visible" to "precise", providing important technical support for achieving safer and more efficient integrated diagnosis and treatment.

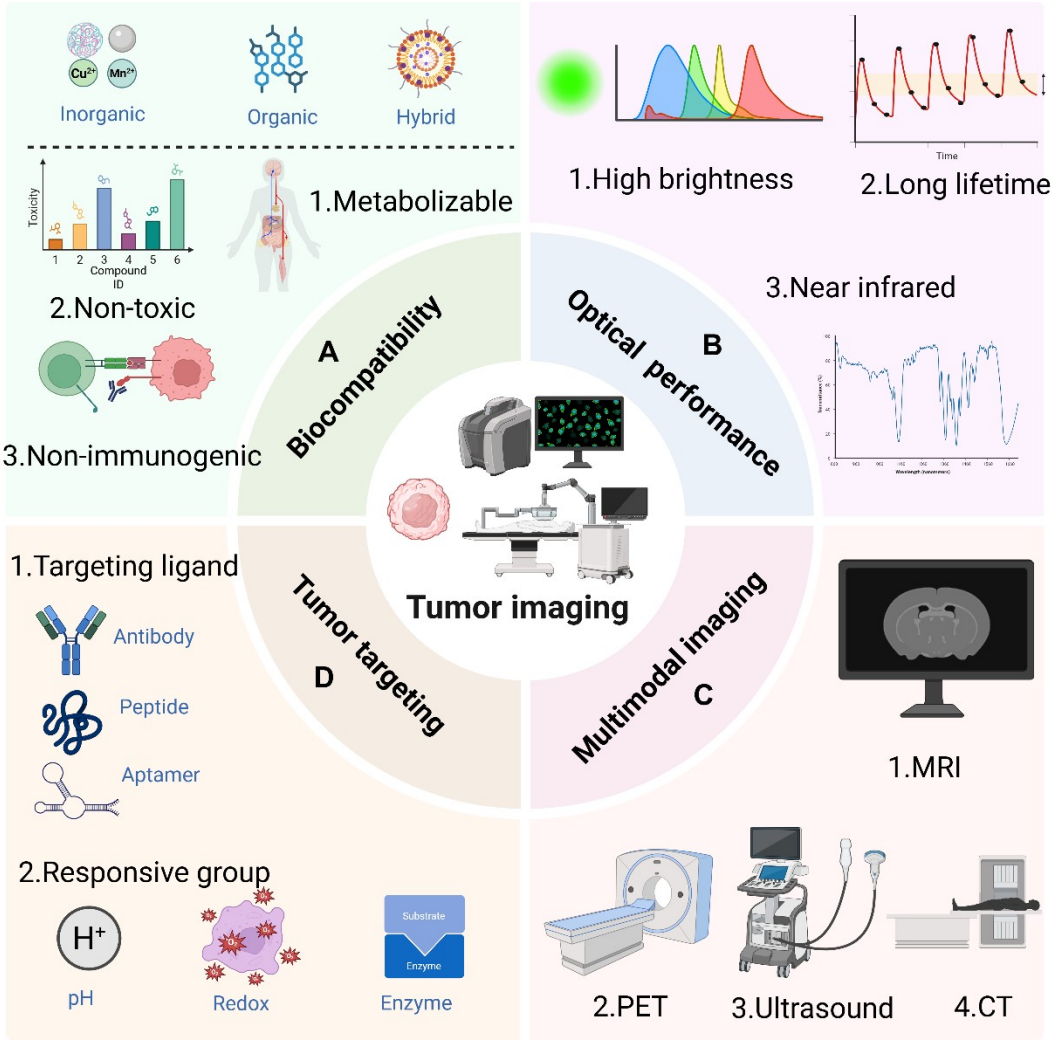

Figure 2. Clinical requirements for postoperative afterglow luminescent materials

(A) Biocompatibility requires metabolizability, non-toxicity and lack of immunogenicity; **(B)** Optical performance requires high brightness, long lifetime

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and near-infrared characteristics; **(C)** Integration of multimodal imaging (MRI、PET、Ultrasound and CT); **(D)** Connecting targeting ligand or responsive group confers tumor targeting properties.

The application scenarios of afterglow luminescent materials in tumor surgery

The afterglow luminescent materials do not require continuous light excitation, avoiding the interference of spontaneous fluorescence and scattered light from biological tissues. This enhances the imaging SNR and penetration depth, giving them unique advantages in deep tissue imaging, long-term real-time monitoring, and tumor treatment. The afterglow luminescent materials can achieve long-term real-time imaging, which is helpful for continuous monitoring of tumors during the surgery[39].

In tumor resection surgeries, accurately identifying the tumor boundaries is crucial for achieving complete removal. By combining the afterglow luminescent materials with moieties that target tumor cells (such as antibodies, peptides, etc.), they can specifically accumulate in tumor tissues, thereby achieving precise marking of the tumor boundaries[40]. Secondly, through strategies that respond to the tumor microenvironment, the luminescence performance of the afterglow luminescent materials is enhanced in the tumor tissue, thereby enabling the distinction of tumor boundaries. Studies have reported that an activatable nanoprobe (SAN-MO) is customized for simultaneously activatable fluoro-photoacoustic and afterglow imaging of peroxynitrite (ONOO-). precise image-guided resection of tiny metastatic tumors, which is unattainable for fluorescence imaging[41]. What's even more interesting is that Li et al developed a GSH-activatable afterglow probe (Q-TPP-DO NPs) for ultrasensitive detection of subcutaneous tumor with the smallest tumor volume of 0.048 mm^3, demonstrating the high potential for early diagnosis and imaging-guided surgical resection of tumors[42]. Furthermore, by combining the afterglow luminescent materials with traditional fluorescent dyes, the long-lasting background signal provided by the afterglow luminescence is utilized, while the fluorescent dyes offer the advantage of high sensitivity for tumor signals, enabling the precise display of tumor boundaries[43].

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Real-time navigation surgery is an emerging surgical technique. It uses imaging technology to display the tumor tissue in real time during the operation, guiding the surgeon to perform precise removal. The afterglow luminescent materials can provide long-lasting imaging signals, thereby ensuring the visualization of tumor tissues during the surgery. Li et al. developed a tumor microenvironment-activated afterglow nanoprobe FMCR. It continuously catalyzes the generation of oxygen from hydrogen peroxide within tumors through its CuRu nanozyme component, significantly enhancing and prolonging the afterglow luminescence. It was successfully used to guide the resection of abdominal metastases with diameters as small as 2-4.5 mm[44]. Traditional fluorescence imaging requires a continuous external excitation light source. Surgical operations may affect the irradiation of the excitation light, thereby impacting the imaging quality[45]. However, afterglow luminescence imaging does not require external excitation and can reduce the influence of surgical operations on imaging[46]. Furthermore, current research has combined the afterglow luminescence imaging technology with surgical robots, enabling more precise surgical operations and enhancing the completeness of tumor removal. Surgical robots can improve the accuracy and stability of the surgery, reduce human errors, and when combined with afterglow luminescence imaging, it can further enhance the surgical outcome[47].

Even when operated on by experienced surgeons, there may still be tiny residual tumor tissues after the surgery. These residual tissues are a significant cause of tumor recurrence. The afterglow luminescent materials have long residual luminescence duration, even when the content of tumor tissues is relatively low, they can still provide clear imaging signals. This means that even if only a small amount of tumor cells remain, they can be detected through afterglow luminescence imaging[48]. Moreover, near-infrared afterglow luminescent materials can penetrate deeper tissues, thus enabling the localization of residual tumor tissues at a deeper level[49]. This is particularly important for tumor remnants located in deep tissues. Ni et al. designed and synthesized a type of near-infrared afterglow luminescent nanoparticles AGL AIE dots, which are used for intraoperative imaging-guided tumor resection. These nanoparticles have a high tumor/liver signal ratio, can effectively distinguish tumor tissues from normal tissues, and can be used for precise image-guided cancer surgery, helping to

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display the tumor boundary during the operation and locate the residual tumor tissues after the operation[50].

The residual tumor tissues can be located using the afterglow luminescent materials. At the same time, it can be combined with photodynamic therapy, radiotherapy, chemotherapy and other methods to treat the remaining tissues, thereby reducing the risk of tumor recurrence[51]. Loading photosensitizers into the afterglow luminescent materials and using the afterglow luminescence to activate the photosensitizers can generate cytotoxic substances, thereby killing tumor cells. This method can achieve treatment of deep tumor tissues while reducing damage to normal tissues[52]. Radiotherapy is a treatment method that uses high-energy rays to kill tumor cells. However, it may also cause damage to normal tissues. Loading radioactive nuclides or radiosensitizers into phosphor materials that produce afterglow luminescence can improve the accuracy of radiotherapy by using afterglow luminescence imaging for guidance[53]. By loading chemotherapy drugs or antineoplastic drugs into the afterglow luminescent materials, it is possible to achieve targeted drug delivery and controlled release of the drugs[54, 55]. The above research has confirmed that the researchers have gradually integrated the afterglow luminescent materials with various diagnostic and therapeutic methods to achieve the integration of tumor diagnosis and treatment, and constructed a multifunctional nanoscale diagnostic and therapeutic platform.

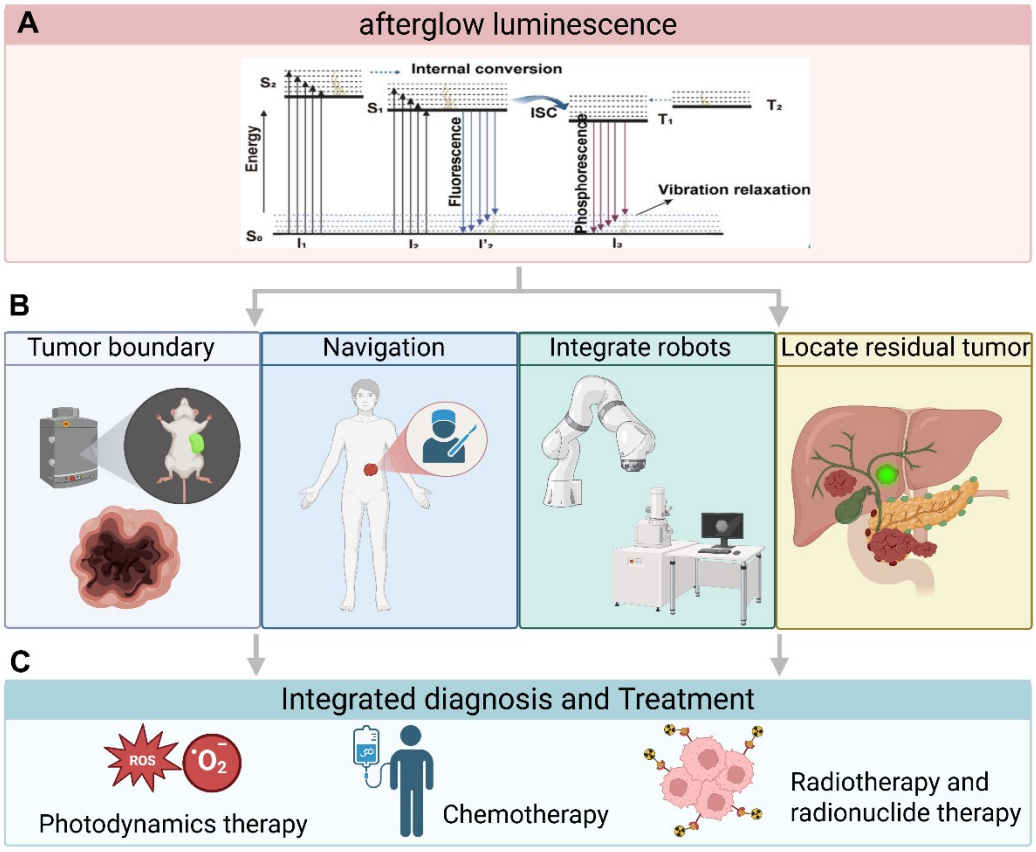

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Figure 3. Afterglow luminescence imaging in tumor surgery

(A) Jablonski diagram; **(B)** Application scenarios of afterglow luminescent materials in tumor surgery; **(C)** Integrated tumor diagnosis and treatment.

Clinical translation challenges of afterglow luminescent materials

Clinical translation refers to the process of applying laboratory research results to actual clinical treatment. Afterglow luminescent materials, as an emerging biomedical material, demonstrate great potential in biological imaging, drug delivery, and disease treatment. However, converting it from laboratory research success to clinical application still faces many challenges. And these challenges are concentrated in areas such as biological safety, targeting, luminescent performance, production standardization, regulatory oversight, and ethical considerations.

The afterglow luminescent materials usually exist in the form of nanoparticles, and their potential nano-toxicity is the primary concern in the clinical transformation process. Nanoparticles may enter the human body through various pathways and interact with biological molecules, interfering with cellular functions and even causing cell death. The composition, size, shape, surface charge and modification of nanoparticles can all affect their toxicity[56]. For instance, certain metal oxide nanoparticles may release toxic metal ions, causing damage to organs such as the liver and kidneys. After entering the body, they may be recognized by the immune system as foreign substances, thereby activating immune responses and leading to adverse reactions such as inflammation, allergies, and even immune rejection[57, 58]. Currently, research on the long-term biological effects of afterglow materials is still relatively lacking. The metabolic, degradation and excretion pathways of these materials in the body are not yet fully understood. Long-term retention in the body may cause chronic inflammation, tissue fibrosis, and even long-term risks such as tumors.

In terms of targeting, the tumor microenvironment(TME) is a complex ecosystem. The heterogeneity of the TME leads to an uneven distribution of the afterglow luminescent materials in the tumor tissue, affecting their imaging and

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therapeutic effects[59]. For brain tumors, the afterglow luminescent materials need to penetrate the blood-brain barrier (BBB) to reach the tumor tissue. This severely limits their application in brain tumor diagnosis and treatment[60]. More importantly, when the afterglow luminescent materials circulate in the body, they are easily engulfed by macrophages in organs such as the liver and spleen, resulting in a decrease in their accumulation in the tumor tissue[61]. In terms of luminescence performance, the luminescence intensity of afterglow luminescent materials directly affects their imaging sensitivity and therapeutic effect. The luminescence intensity of many afterglow luminescent materials is still relatively low, making it difficult to meet the requirements of clinical applications. Secondly, there is a limitation on the luminescence wavelength. The ideal biological imaging wavelength should be in the near-infrared region. However, the luminescence wavelengths of many afterglow luminescent materials currently deviate from the near-infrared region, restricting their application in deep tissue imaging.

The production process of afterglow luminescent materials is complex and difficult to achieve large-scale production, resulting in high costs and limiting their clinical application. At the same time, the quality of these materials directly affects their imaging and therapeutic effects[62]. Currently, there is a lack of unified quality control standards for afterglow luminescent materials, leading to significant performance differences among different batches of materials. Moreover, during storage and transportation, afterglow luminescent materials are prone to agglomeration, degradation, and other phenomena, which affect their performance. As a new type of biomedical material, the clinical application of afterglow luminescent materials requires a strict approval process. Currently, the approval procedures for afterglow luminescent materials vary among different countries, resulting in a long clinical transformation cycle. The lack of safety standards for afterglow luminescent materials leads to risks in their clinical application. It is necessary to establish a complete safety evaluation system for afterglow luminescent materials to provide guarantees for clinical application. The research and development of afterglow luminescent materials require a large amount of financial and human resources investment. Strengthening the protection of afterglow luminescent materials intellectual property rights can motivate enterprises and research institutions to increase their research and development efforts, promoting their clinical transformation.

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Currently, the majority of research on afterglow luminescent materials still focuses on in vitro and in vivo preclinical stages, concentrating on demonstrating the feasibility of their principles and efficacy in small animal models. Only a very few studies have begun to systematic safety assessments. Overall, this field is still in the early stage of transitioning from "proof of concept" to "product development", and there is still a long way to go before widespread clinical applications can be achieved. Transforming afterglow luminescent materials from laboratory research to clinical application is a complex and lengthy process, facing numerous challenges. Only by fully understanding these challenges and actively seeking solutions can the clinical transformation of afterglow luminescent materials be ultimately achieved, contributing to human health. With the continuous development of fields such as nanotechnology, materials science, and biomedical engineering, it is believed that in the near future, afterglow luminescent materials will play an increasingly important role in clinical tumor diagnosis and treatment.

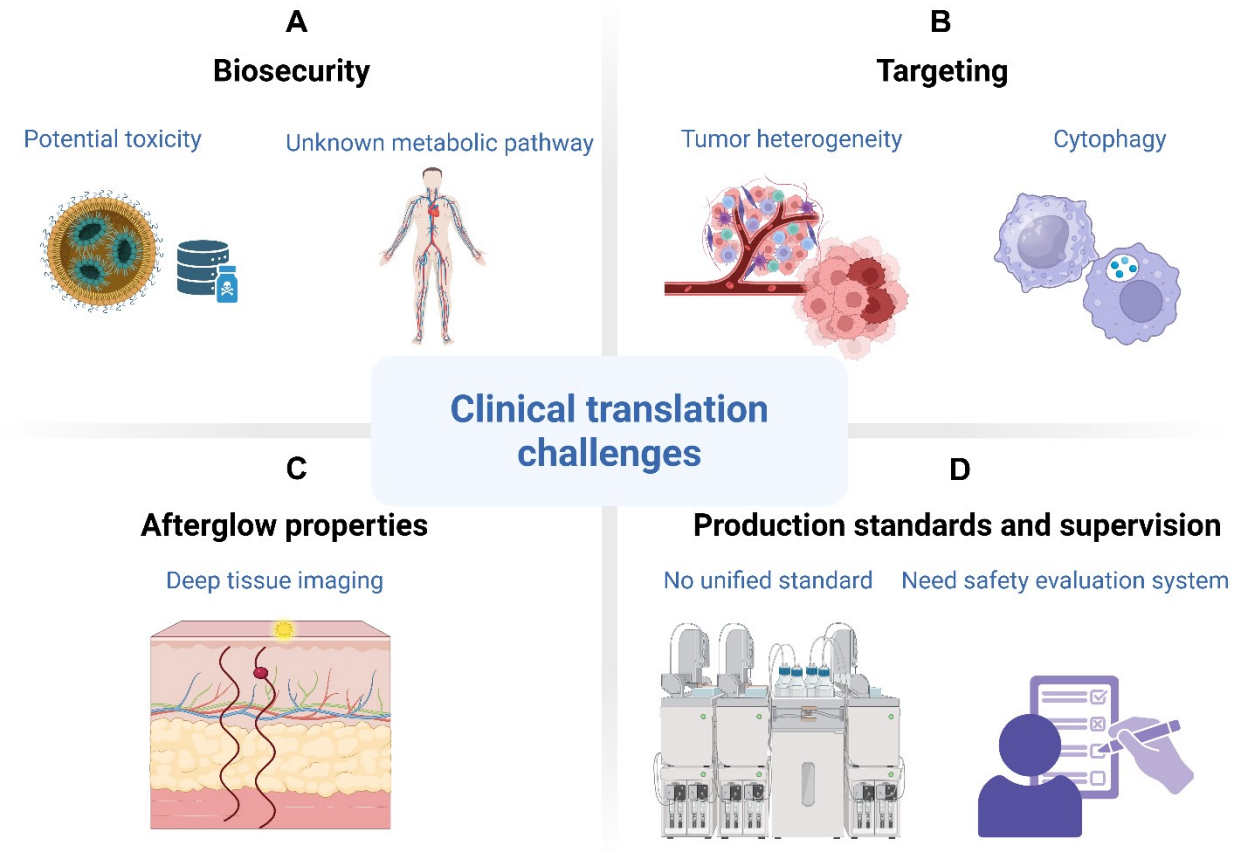

Figure 4. Clinical translation challenges

(A) Biocompatibility requires metabolizability, non-toxicity and lack of

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immunogenicity; **(B)** Tumor heterogeneity and cell phagocytosis limit targeting; **(C)** Limited deep tissue imaging; **(D)** The production process lacks unified standards and evaluation systems.

Surgically-Driven research trends in afterglow luminescence

Afterglow luminescent materials as an emerging optical diagnostic agent, due to their unique sustained luminescence properties, have shown great potential in the biomedical field, especially in tumor diagnosis and treatment. Surgeons are also showing interest in this research direction. Firstly, there is a need to develop new organic afterglow luminescent materials. By designing new organic molecular structures, the luminescent properties of afterglow luminescent materials can be precisely controlled, and their biocompatibility can be improved. Thus, several issues should be included: 1. Developing efficient targeted strategies to enhance the enrichment of Afterglow luminescent materials in tumor tissues; 2. Combining afterglow luminescent materials with other diagnostic and therapeutic methods to achieve integrated tumor diagnosis and treatment; 3. Conducting large-scale clinical trials to verify the effectiveness and safety of afterglow luminescence technology in locating residual tumor tissues after surgery; 4. Combining artificial intelligence with afterglow luminescence imaging technology to enable automated diagnosis and efficacy assessment of tumors, thereby improving the efficiency and quality of clinical diagnosis and treatment. Actually, afterglow luminescent materials have a broad application prospect in the field of tumor surgical resection. With the continuous advancement of technology, they are expected to bring new breakthroughs to the precise treatment of tumors.

Conclusion

Afterglow luminescent materials is an emerging technology in the field of tumor imaging. Their unique advantages such as no in situ excitation, deep tissue penetration, and high signal-to-noise ratio make them have great potential for application in tumor resection surgeries. However, the clinical implementation of this technology still faces many challenges, and it requires close collaboration among surgeons, radiologists, materials scientists, and regulatory agencies.

Author contribution

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The conceptual framework of this study was designed by Jinghua Li, Zhen Li and Yufeng Yuan. The literature search was performed by Liangxuan Ding, while the subsequent literature screening and data extraction were conducted by Liangxuan Ding and Weijie Ma. Jinghua Li drafted the initial manuscript, which was critically reviewed and edited by Yong He, Qianqian Li, Zhen Li and Yufeng Yuan. All authors have read and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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