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# 1 **Clinical Transformation of Afterglow Luminescence Imaging in Precision** 2 **Surgery of Tumors: Opportunities and Challenges**

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## 20 **Abstract**

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

30 **Keywords:** Afterglow luminescence imaging; Tumor surgery; Clinical translation

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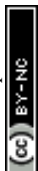
## 32 Introduction

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

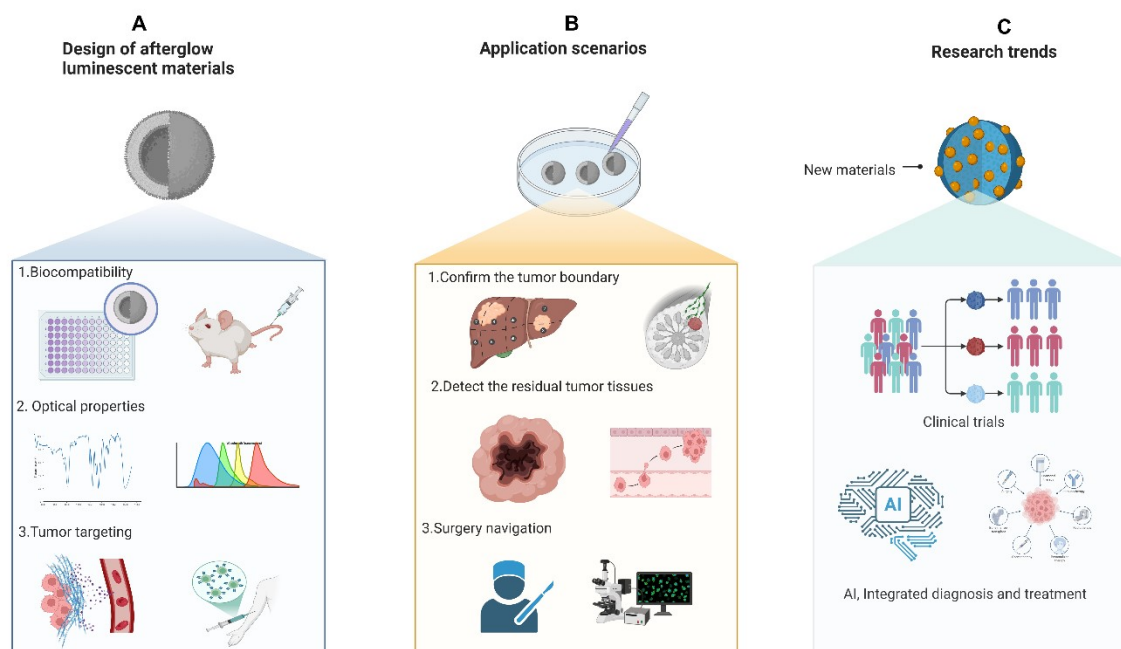
42 However, in addition to their advantages, the fluorescent groups cannot fully  
43 meet the current clinical needs for precise tumor diagnosis and treatment.  
44 Non-specific binding is the main limitation of ICG and methylene blue navigation  
45 surgeries that has been identified<sup>9</sup>. This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

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



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

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75 **Figure 1. Overview framework**

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

### 79 **Clinical demand-driven design of afterglow luminescent materials**

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

89 The biocompatibility of the material is the primary consideration factor,



90 directly affecting its safe application in vivo<sup>21</sup>. The ideal afterglow materials  
91 should possess excellent biocompatibility, be non-toxic and non-immunogenic, be  
92 able to remain stable in the body, and eventually be safely metabolized<sup>22, 23</sup>. The  
93 afterglow materials can be classified into inorganic, organic and hybrid types<sup>24</sup>.  
94 They each have distinct characteristics in terms of biocompatibility, optical  
95 properties and metabolic behavior, and are suitable for different biomedical  
96 scenarios. Inorganic afterglow materials can regulate luminescent properties by  
97 doping different rare earth ions and transition metal ions. Jin et al. reported the  
98 design and synthesis of Mn<sup>2+</sup>-doped hexagonal CsCdCl<sub>3</sub> MHP crystals with  
99 excellent X-ray scintillation and X-ray induced afterglow for more than 300 min.  
100 The afterglow emission can be rejuvenated effectively by 870 nm stimulus or  
101 heating even after 72 h of decay<sup>25</sup>. Most inorganic afterglow materials exhibit  
102 prolonged afterglow durations, typically ranging from several minutes to tens of  
103 hours, along with readily tunable optical properties. However, their slow  
104 degradation kinetics raise concerns regarding potential long-term retention in vivo,  
105 which may lead to persistent biological toxicity. Compared with inorganic  
106 materials, organic afterglow materials have better biocompatibility and  
107 degradability<sup>26</sup>. Traditional organic fluorescent molecules are encapsulated in the  
108 bovine serum albumin matrix. The afterglow emission can be significantly  
109 enhanced by 10 times, enabling tumor imaging and the detection of metastatic  
110 nodules<sup>27</sup>. However, hybrid materials exploit the tunable structure and easy  
111 processing of organic molecules, as well as enhanced spin-orbit coupling and  
112 intersystem crossing processes involving heavy atom dopants, to achieve excellent  
113 afterglow performance<sup>28</sup>. For instance, Pan et al. developed a zinc  
114 phthalocyanine-linked periodic mesoporous organic silicon nanoparticles, which  
115 served as a biodegradable photosensitizer for photodynamic therapy<sup>29</sup>. At the  
116 application level, inorganic materials are suitable for optical monitoring scenarios  
117 that require long-term duration and high SNR due to their persistent  
118 high-brightness luminescence properties; organic materials, with their excellent  
119 biological safety and degradability, are more suitable for short-term diagnosis and  
120 treatment that demands high biological compatibility and rapid metabolism; while  
121 hybrid materials, through the synergy of organic and inorganic components,  
122 demonstrate outstanding design flexibility and functional integration potential in  
123 combined therapy and multimodal imaging. Future research should focus on  
124 optimizing the balance between the material's metabolic safety, signal duration and

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125 light emission intensity.

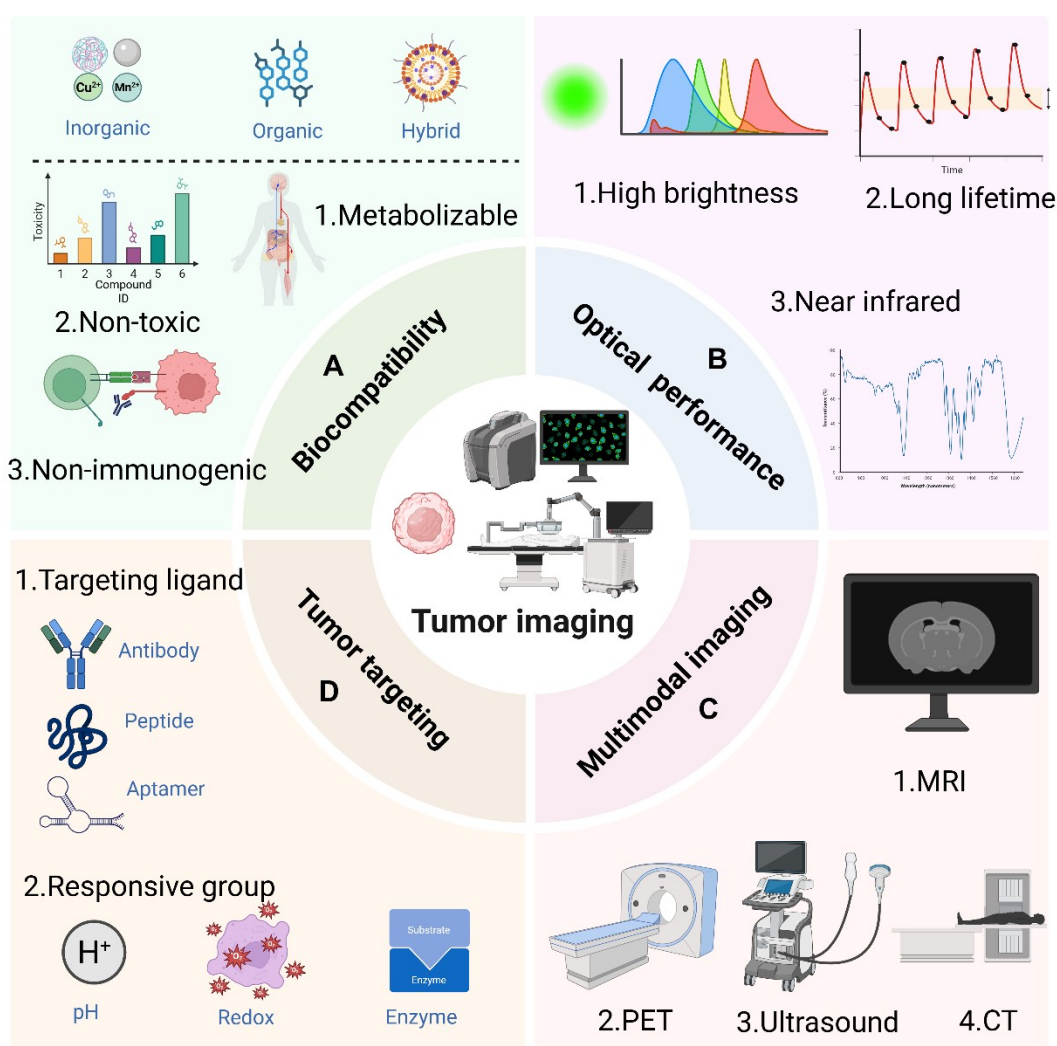
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126 To achieve deep tissue imaging, materials with emission wavelengths in the  
127 near-infrared region are usually selected, as the light in this wavelength band has  
128 better penetration ability in biological tissues<sup>30</sup>. Yuan et al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

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



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



179 **Figure 2. Clinical requirements for postoperative afterglow luminescent**  
 180 **materials**

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



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

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## 186 **The application scenarios of afterglow luminescent materials in tumor** 187 **surgery**

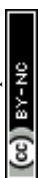
188 The afterglow luminescent materials do not require continuous light  
189 excitation, avoiding the interference of spontaneous fluorescence and scattered  
190 light from biological tissues. This enhances the imaging SNR and penetration  
191 depth, giving them unique advantages in deep tissue imaging,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

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



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

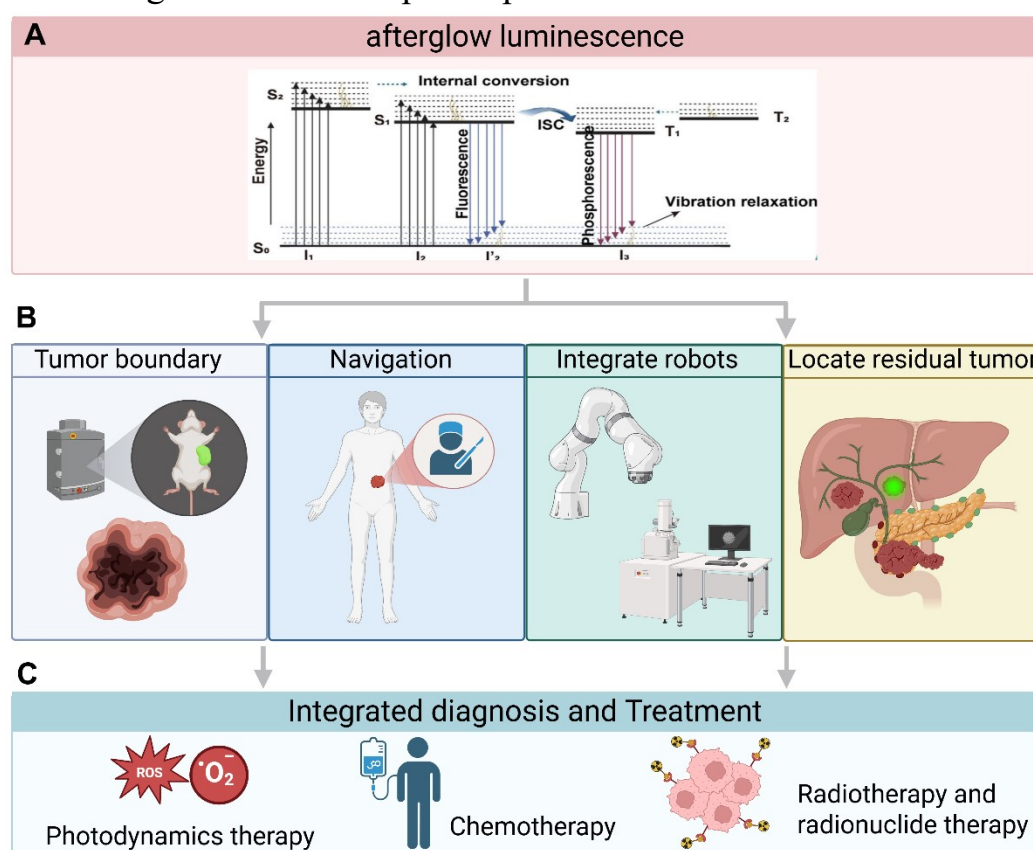
235 Even when operated on by experienced surgeons, there may still be tiny  
236 residual tumor tissues after the surgery. These residual tissues are a significant  
237 cause of tumor recurrence. The afterglow luminescent materials have long residual  
238 luminescence duration, even when the content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



249 display the tumor boundary during the operation and locate the residual tumor  
 250 tissues after the operation<sup>50</sup>.

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



277

278

### Figure 3. Afterglow luminescence imaging in tumor surgery

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

### 281 Clinical translation challenges of afterglow luminescent materials

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

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

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

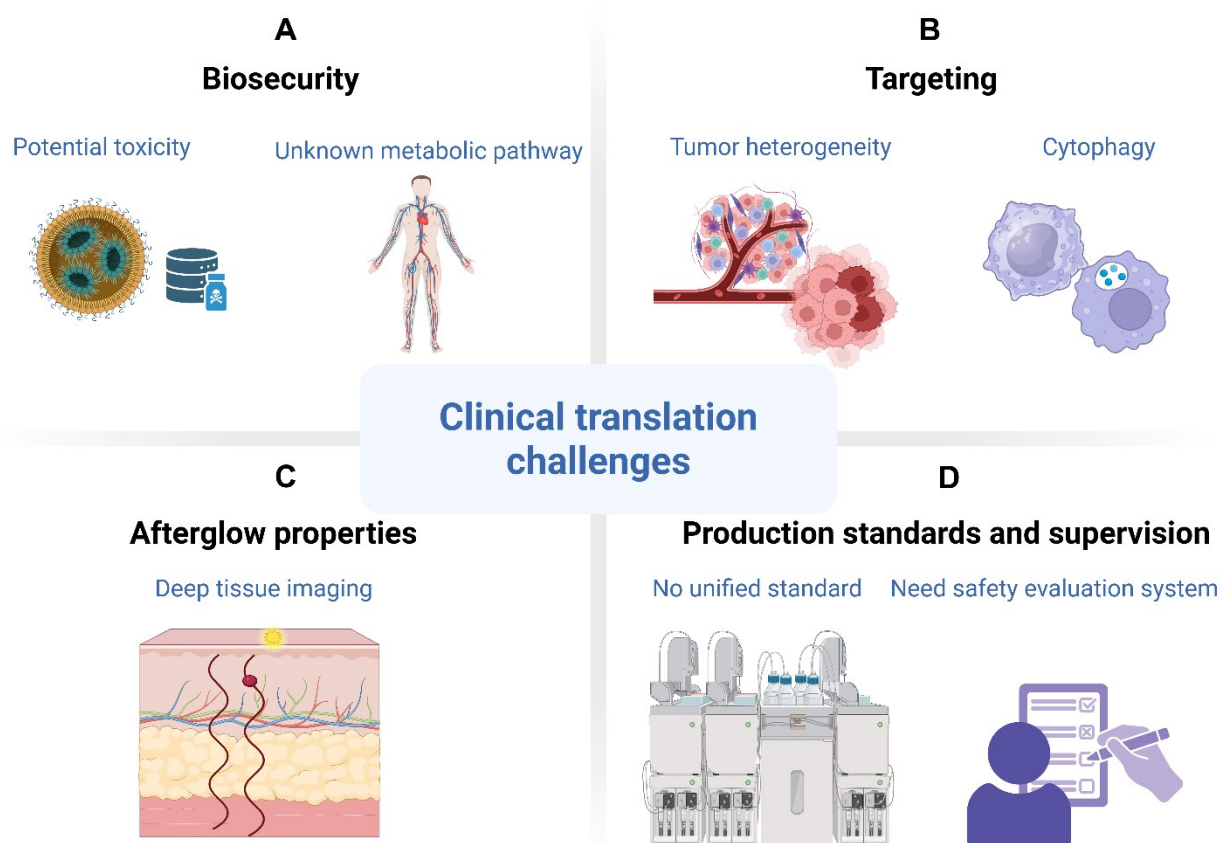


308 therapeutic effects<sup>59</sup>. For brain tumors, the afterglow luminescent materials need to  
309 penetrate the blood-brain barrier (BBB) to reach the tumor tissue. This severely  
310 limits their application in brain tumor diagnosis and treatment<sup>60</sup>. More importantly,  
311 when the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

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



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



366 **Figure 4. Clinical translation challenges**

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



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

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### 371 **Surgically-Driven research trends in afterglow luminescence**

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

### 391 **Conclusion**

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

### 398 **Author contribution**



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

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## 405 **Conflicts of interest**

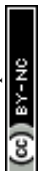
406 There are no conflicts to declare.

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## Data Availability Statement

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No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

