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The application of nano-hybrid hydrogels in post-surgical tumor recurrence

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Abstract. Surgical resection is one of the main methods for treating solid tumors, but incomplete removal of tumor cells after surgery often leads to tumor recurrence and metastasis. At the same time, the wounds formed during open surgery are susceptible to bacterial infections due to exposure. Therefore, there is an urgent need for an effective method that can be applied to postoperative wounds to suppress tumor recurrence. Hydrogels, as a three-dimensional network crosslinked material with good biocompatibility, possess excellent drug-loading capabilities. Smart hydrogels can respond to stimuli and control drug release through structural changes, promoting wound healing. Integrating tumor therapy with hydrogels can further achieve the clearance of in situ cancer cells and the inhibition of distant cancer recurrence. This article introduces the composition and characteristics of anti-tumor smart hydrogels, their application in drug delivery, and analyzes strategies to suppress tumor recurrence. With in-depth research on nano-hydrogels, it is believed that this platform is poised to significantly contribute to the prevention of tumor recurrence following surgical procedures.

Keywords: hydrogels, stimulus-response,local drug delivery, tumor recurrence, tumor therapy.

1. Introduction

According to the World Health Organization's "Global Cancer Report 2020," there were 19.3 million new instances of cancer diagnosed globally in 2020, resulting in nearly 10 million fatalities. The report also forecasts a concerning trend, projecting that the annual count of new cancer cases worldwide could escalate to 27 million by the year 2040.[1]. At present, the surgical removal of tumors continues to be a primary therapeutic approach for the clinical management of solid tumors. However, despite improvements in surgical techniques, surgeons cannot ensure the removal of all malignant cells during

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surgery. Incompletely removed tumor cells have a high propensity to cause local recurrences and distant metastases, causing great harm to patients [1]. Adjuvant systemic chemotherapy or local radiotherapy after surgical resection is the current main strategy for preventing cancer recurrence. However, chemotherapy drugs have issues such as drug resistance and are prone to causing damage to normal tissues. At the same time, the loss of postoperative tissue is prone to bacterial infections, leading to poor wound healing after surgery. Hence, there is an immediate requirement to develop new postoperative adjuvant treatments to achieve local residual tumor cell clearance and promote wound healing [2].

Due to their excellent water retention and excellent biocompatibility, hydrogels are widely used in the biomedical field. The advantages of hydrogels, such as controllable swelling behavior and flexibility, make them widely used in targeted drug delivery for cancer, wound injury and inflammation treatment, bone and cartilage regeneration, and biosensors [2]. Among them, injectable hydrogels have garnered widespread attention due to their local sustained drug release and the ability to visualize and monitor wound filling. On the one hand, t hydrogels' high water content and their resemblance to the extracellular matrix (ECM) make them recognized as the most ideal wound dressings, which can adapt to irregular tissue defects and seamlessly integrate with the wound[3-4]. On the other hand, due to their porous structure, drugs can be easily encapsulated within the gel. The polymers of the hydrogel respond to external stimuli by reversibly changing their conformation, solubility, or hydrophilic/hydrophobic balance. According to the source of the stimulus, these stimuli can be divided into physical (temperature, light, ultrasound), chemical (pH, redox potential), or biological (enzymes, glucose) stimuli. Subsequently, by adjusting the drug release rate and the drug loading, degradation, and swelling behavior of the hydrogel, the drug is released in a controllable and stable manner. This method allows the drug to retain a high concentration locally, reducing side effects on surrounding healthy tissues [5].

Despite the potential significance of smart hydrogels in clinical applications, there is a lack of focused discussion on postoperative cancer prognosis[6-8]. Hence, by integrating a vast array of academic research in this field[9-12], this study aims to review the characteristics of smart hydrogels and proposes new trends in personalized postoperative cancer prognosis based on hydrogel technology. By so doing, our study contributes to the rebalancing of local drug delivery and wound healing studies by synthesizing insights into smart hydrogels.

2. Hydrogel Mechanisms for Post-surgical Cancer Treatment

Hydrogels, characterized by their porosity, biocompatibility, and biodegradability, are extensively utilized in the biomedical field because of these distinctive attributes. Injectable hydrogels can respond to environmental stimuli, such as pH, temperature, and ultrasound, and achieve controlled drug release at the target location. As a new drug carrier, injectable hydrogel has been widely used in tumor drug delivery. Local delivery of anticancer drugs at the target site by injecting hydrogels can mitigate the severe side effects associated with systemic delivery, enhance the concentration of drugs within tumor tissues, and ultimately lead to improved drug therapeutic efficacy. Here, we discuss the role of hydrogels with different mechanisms of action in cancer treatment, as well as the design ideas and strategies of stimulus-response hydrogels in the latest case study of cancer postoperative treatment hydrogels.[14-16]

2.1. pH-Sensitive Hydrogels

The core principle behind the design of pH-sensitive hydrogels is that the extracellular pH value in the tumor microenvironment is between 5.5 and 7.5, which is an acidic environment, providing a theoretical basis for the degradation of hydrogels in tumor cells and the release of drugs at specific points [16].

The pH responsiveness of hydrogels is achieved by protonation (proton absorption) and deprotonation (proton release) of weakly basic or polyacid copolymers, or by breaking of chemical bonds at different pH conditions. Hydrogels may swell or desswell at different pH environments, resulting in drug release at different pH values[16].

In recent years, Yang[17] et al. designed an acid dissociation temperature sensitive block polymer hydrogel pop. The pH value at the tumor site is about 6.0, the ortho ester bond in pop hydrogel polymer is unstable in the acidic environment and breaks, and the gel network will gradually collapse and degrade,

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to realize the stable and lasting release of doxorubicin (DOX), prolonging the action time of DOX and improve its bioavailability. Cimen[18] et al designed an injectable, self-healing, pH responsive hybrid gel. The amines of the gel absorb protons (-NH3+) under acidic conditions in the body. In a series of subsequent biological and solid tumor tests, the hydrogel showed pH-dependent chemotherapy drug DOX release behavior.

Especially in the field of tumor postoperative treatment, Zhou[19] et al. designed a nanocomposite hydrogel Col-APG-Cys@HHD. Col-APG-Cys@HHD hydrogels control drug release at pH gradients (6.5 ~ 5.5). This showed that the hydrogel was able to swell in the tumor's acidic environment and subsequently deliver the nanoparticles into the tumor cells and release docetaxel (DTX). The hydrogel material has certain application potential in the field of preventing postoperative tumor recurrence.

2.2. Thermosensitive Hydrogels

The mechanism of action of thermosensitive hydrogel is sol-gel phase transition. Negative thermosensitive hydrogels dissolve in water at low temperatures, because hydrogels form hydrogen bonds between their hydrophilic groups and water molecules. Upon reaching the critical solution temperature (LCST) or higher, the solution gelates because hydrophobic interactions between hydrogels' hydrophilic groups are enhanced and hydrogen bonds are broken[20-21].

Because the thermosensitive hydrogel can achieve sol-gel phase transition, it can be injected in vitro when it is convenient for injection in the sol state, and then changed into the gel state due to body temperature after entering the body, and then stay around the tumor for local drug release. For example, Liao[22] and colleagues developed an injectable heat-sensitive microsphere hydrogel composite system that, due to its heat-sensitivity, can deliver local drugs in vivo around tumors. Compared with the simple combination of free drugs, the targeted sustained-release property cleared the hepatocellular carcinoma (HCC) immune microenvironment more effectively. Ma[23] et al. designed an injection thermosensitive hydrogel system MDR@SHDS. The drug can act on a specific site. Once heating up, the hydrogel is injected into the tumor tissue in the form of a colloidal state. Upon entering the physiological environment, it transitions to a gel state, from which the encapsulated drug is progressively released.

Temperature triggered the hydrogel to turn into a gel state, which was conducive to the release of drugs. At the same time, the self-reaction of the internal substances of the hydrogel and other trigger mechanisms work together to further the effect. She[24] et al. designed an injectable TCPP-CAT CS/GP thermal-sensetive hydrogel as a method to amplify the therapeutic effect of repeated sonodynamic therapy (SDT). Once the precursor solution was administered into the tumor site, the body temperature initiated its transition from a liquid to a gelatinous state, and the gel was retained as TCPP-CAT at the target location. Under the action of ultrasound, TCPP-CAT generates ROS and triggers the decomposition of endogenous H2O2. The oxygen generated by decomposition can continuously change the hypoxic state of tumor cells and further promote the efficacy of SDT. This hydrogel treatment system can effectively eradicate tumors.

2.3. Ultrasound-Sensitive Hydrogels

Ultrasound-sensitive hydrogels are frequently integrated with other stimulus-responsive hydrogels such as temperature sensitive, pH sensitive, and other triggers. The basic principle of their synergy is that the implanted hydrogel is activated and ruptured by interacting with ultrasound, so that the drug load is released into the target tissue. Different from pH sensitive hydrogel and text sensitive hydrogel, ultrasound is often used as an exogenous stimulus in the action of ultrasound sensitive hydrogel[26].

In local tumor treatment, ultrasonic hydrogels allow drug release or directly increase drug release by diffusion. Meng[27] with the team developed an ultrasonic hydrogel platform for providing a nanovaccine against breast cancer. In immunotherapy in vivo, in vitro ultrasound action can lead to a phase transition of the hydrogel, converting it into a sol state, which in turn facilitates the release of the vaccine.

At present, there are many successful cases of in vitro ultrasound hydrogel drug delivery system. Balci[28] et al. developed a polyvinyl alcohol (PVA) hydrogel, which released DOX drug under

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ultrasound is about twice that without ultrasound stimulation. Maria[29] and colleagues have engineered a drug delivery system that incorporates a hydrogel made from a simple protein, designed to address intestinal inflammation. This innovative platform is capable of imaging the target area and initiating the release of therapeutic agents at that specific site, utilizing conventional ultrasound imaging technology.

3. Hydrogel applications for post-surgical cancer treatment

3.1. The loading of Immunotherapy drugs

The activation of the immune system to enhance the tumor microenvironment and combat cancer has been a central focus in the fields of immunology and oncology. Immunotherapeutic hydrogels have emerged as a significant tool, capable of invoking both the body's innate and adaptive immune reactions to detect and neutralize any lingering cancer cells. Compared to traditional chemotherapy, immunotherapy has fewer side effects, more durable therapeutic effects, and can spontaneously improve the poor prognosis caused by tumor invasiveness. Studies conducted in both preclinical and clinical settings have shown that the suppression of immune activity following surgery can be reversed. Interventions applied during the perioperative period can strengthen the immune system's responses, thereby reducing the chances of cancer recurrence[28-30] . Therefore, immunotherapeutic hydrogels are considered an ideal strategy for preventing cancer recurrence.

Modulating immune checkpoints to boost the body's immune response to tumors has shown promising clinical results. Currently, PD-1 and PD-L1 are the most widely studied immune inhibitory checkpoints. The strategy of blocking the PD-1/PD-L1 interaction is frequently employed to bolster the immune system's fight against tumors. By inhibiting the interaction between PD-1 and PD-L1, the activity of T cells can be rejuvenated, empowering them to identify and combat tumor cells[31-32]. To better break the constraints of the immunosuppressive tumor microenvironment, anti-PD-L1 antibodies (αPD-L1) are often used in conjunction with immune pathway blocking strategies to trigger local and even systemic anti-tumor immune responses. Chu[34] and the team utilized anti-PD-L1 antibodies(αPD-L1) along with the hedgehog signaling inhibitor vismodegib to proficiently regulate the immune reactions in the sentinel lymph node(SLN), while also promoting the infiltration and activation of the T cells[35](Fig. 1.A-D), successfully inhibiting tumor growth. Similarly, Zhou[36] and colleagues loaded Anti-PD-L1 mAb with doxorubicin conjugates (P-DOX) and CXC chemokine receptor 4 (CXCR4) antagonist conjugates [P-(LV)6] on a hydrogel. The study points out that even if surgery can remove most of the tumor, the pre-metastatic niches (PMN) of tumor cells may have already established in distant organs[36-37]. After surgery, the activation of the CXCR4-CXCL12 signal enhances immune suppression and is associated with an increase in PD-L1 levels in tumors. Employing a CXCR4 antagonist can curtail the migration of immunosuppressive cells to the tumor, thereby inhibiting the distant metastasis of tumor cells.(Fig. 1.E). At the same time, a small amount of DOX can induce tumor immunogenic cell death (ICD)[39]. Compared with other immunotherapeutic hydrogels, this hydrogel toolkit not only achieves in situ delivery of immunotherapeutic drugs but also disrupts the pre-metastatic microenvironment to reduce the risk of distant metastasis, thoroughly preventing tumor recurrence.

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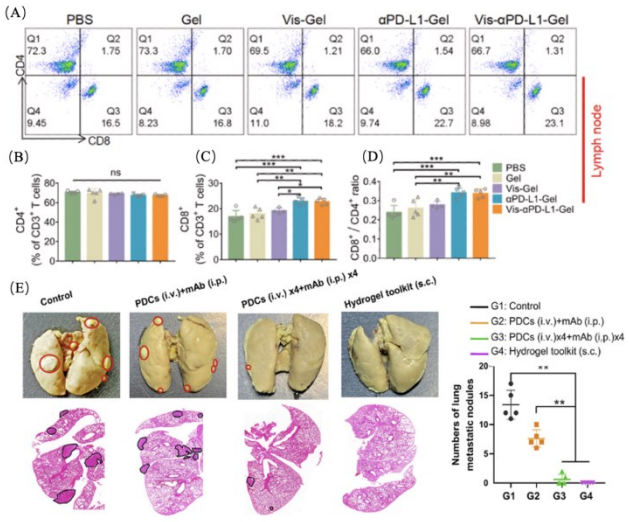

Figure 1. (A) Investigation of the T-cell activation effect of Vis-αPD-L1-Gel in osteosarcoma and sentinel lymph nodes (SLN). Flow cytometry plots represent the percentages of CD4+ T cells and CD8+ T cells among CD3+ lymphocytes in SLN samples from mice treated with different groups (n = 5 mice per group). The ratio of (B)CD4+ to CD3+ (C) CD8+cells to CD3+cells and (D) CD8+ to CD4+in the SLN after treatment [34] (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$); (E)H&E histology analysis of metastatic nodules in lung, and numbers of lung metastatic nodules in mice at the end of 2 weeks post-surgery. (scale bar Z 500 mm). Data are presented as mean ±SD (n =5); **P < 0.01 vs. indicated[36].

In addition to immune checkpoint inhibitors, stimulants that target activating immune checkpoints are also commonly used in cancer immunotherapy. STING is a protein that can activate TBK1 and IRF-3, thereby promoting the production of type I interferons and regulating anti-tumor immune responses[40]. Researchers such as Huang[41] have leveraged the characteristic of Mn2+ to trigger the cGAS-STING pathway to develop an immuno-nanohydrogel. The MnO2 coating disintegrates within the tumor's local environment, releasing Mn2+, oxygen, and doxorubicin. The Mn2+ intensifies cGAS's reaction to dsDNA, which in turn stimulates the generation of interferons and cytokines. This process facilitates the maturation and antigen presentation of dendritic cells and macrophages, stimulates CD8+ T cells and natural killer (NK) cells, and boosts the population of CD44hiCD8+ T cells[42]. Additionally, Mn2+ can collaborate with other hydrogel components to prevent the M2 polarization of tumor-associated macrophages and decrease PD-L1 expression . By integrating various immunotherapeutic agents, this strategy effectively improves the immunosuppressive state, offering a new direction for cancer immunotherapy.

3.2. The loading of photothermal agents

Photothermal therapy (PTT) is a method of treating tumors that leverages the photothermal effect. When exposed to the irradiation of near-infrared (NIR) lasers, photothermal agents convert harmless light energy into heat energy, selectively heating and killing tumor cells with minimal impact on surrounding normal tissues[43]. The advantages of PTT include its precise targeting capability, non-invasiveness, spatial and temporal controllability, and lower side effects. Moreover, the hyperthermia therapy (HTT)[44] induced by PTT can promote immunogenic cell death, which aids in activating the immune system and further inhibit tumor growth and metastasis. The characteristics of PTT make it a promising strategy in the comprehensive treatment of cancer.

In cancer treatment, metals and their sulfides are commonly used photothermal materials. Chen[45] and colleagues designed a multifunctional CA-AuAgNPs-gel leveraging PTT. The Pluronic F127 hydrogel is an ideal material for local treatment as a temperature-sensitive hydrogel[46]. It attaches to

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the tumor site in a gel state in response to thermal fluctuations, promoting drug enrichment at the tumor site. Under NIR laser irradiation, AuNPs serve as a photothermal agent, inducing tumor apoptosis and enhancing the gelation of the hydrogel through hyperthermia and immunogenic cell death. Through in vitro hydrogel antitumor effect experiments, the mice treated with NIR-irradiated CA-AuAgNPs-Gel exhibited stronger tumor suppression than other groups. Moreover, after 6 minutes, the temperature of the CA-AuAgNPs-Gel-NIR group had risen apparently more than in the other groups, indicating that resulting hydrogel has potent antitumor effects due to photothermal capabilities(Fig. 2.A) In the study of the immunogenic cell death(ICD), there was a marked rise in the levels of CD4+ and CD8+ T cells within the group treated with CA-AuAgNPs-Gel under NIR laser irradiation. This confirmed that AuNPs in the hydrogel induce tumor apoptosis and enhance the immune response to suppress tumors under NIR irradiation through hyperthermia and ICD effects. (Fig. 2.B) To better assess the clinical performance of the hydrogel, researchers simulated clinical postoperative infections. (Fig. 2.C, E) Compared with other groups, under NIR irradiation, this hydrogel showed an extremely strong ability to promote postoperative wound healing and antitumor capabilities. This scheme provides a novel strategy for inhibiting postoperative tumor recurrence, employing hyperthermia and immunogenic cell death induced by PTT to suppress tumor recurrence and enhance wound healing without chemical antineoplastic drugs.

Based on these experiments, hydrogels loaded with photothermal agents are typically thermosensitive. These hydrogels leverage the heat generated by the photothermal agents to achieve controlled drug release and to induce changes in the physical state of the hydrogel. Liu[47] and colleagues loaded the photothermal agent IR820 and the chemotherapeutic drug curcumin (Cur) onto a thermosensitive hydrogel. Under NIR laser irradiation, the Cur@IR820 nanoparticles exhibited significant photothermal activity, which both ablated residual tumor cells and colonizing bacteria, and facilitated the sol-gel transition that promotes wound healing. (Fig. 2.D,F)

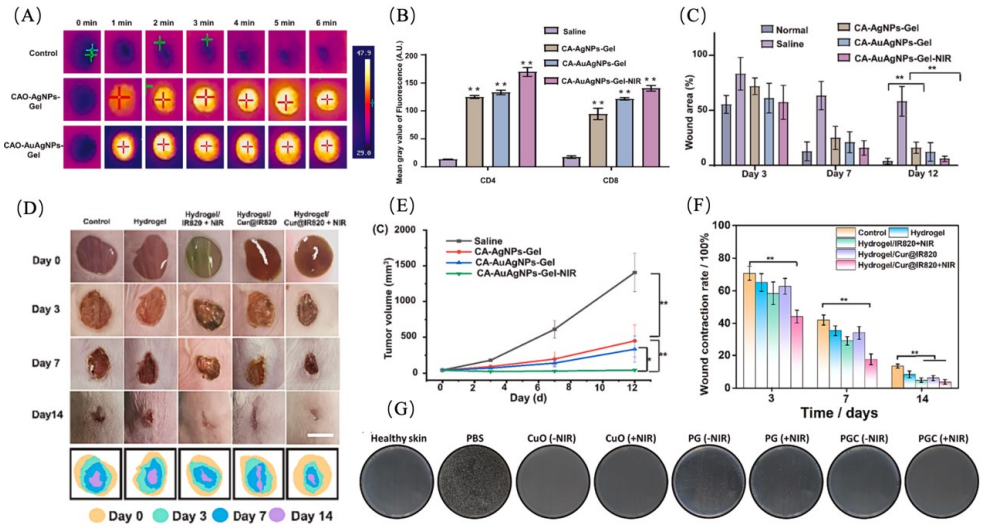

Figure 2. (A)Under 1.0 W cm-2 of NIR irradiation, the infrared thermography of mice with different treatments within 6 minutes. [45]; (B)Semi-quantitative detection of immunogenic cell death induced by different treatment groups through the average fluorescence values of CD4 and CD8; (C)Wound healing performance different treatment groups in vivo. (Data are shown as mean ±SD. *P <0.05, **P <0.01 vs Saline group) [45]; (D)Representative images of wounds post various treatments at different time points. Scale bar: 5 mm[47]; (E)The changes of tumor volume showing anti-tumor recurrence of different treatment groups in vivo[45]; (F)Wound healing rates post various treatments at different time points. Scale bar: 5mm (n = 3).(*P < 0.05, **P < 0.000) [47]; (G)Photographs of MRSA bacterial colonies from tissue samples collected under different treatments and cultured in vitro after 13 days of treatment. [49]

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Phototherapy also has certain advantages in antimicrobial treatment. Under near-infrared (NIR) laser irradiation, the heat energy converted by photothermal agents triggers protein denaturation and changes in membrane permeability within bacteria, while the reactive oxygen species (ROS) generated interact with bacterial components to kill the bacteria[48]. Nosrati-Siahmazgi[49] and colleagues designed a tumor treatment-antibacterial platform. Under NIR, CuO as a photothermal agent not only induces photothermal therapy but also exerts an inherent antibacterial effect. Additionally, the maleic acid in the hydrogel has an auxiliary antibacterial effect. (Fig. 2.G)This approach successfully prevents microbial infections during the postoperative wound treatment of tumors, demonstrating the potential of photothermal materials in synergistic antibacterial strategies for postoperative tumor treatment.

3.3. The loading of antineoplastic drugs

Chemotherapy is a primary cancer treatment method. Although there are dozens of commonly used chemotherapy drugs, their common action is to interfere with the replication of DNA and destroy its integrity, preventing the proliferation, infiltration, and metastasis of cancer cells until they ultimately kill cancer tissue[50]. Postoperative chemotherapy can not only eliminate residual cancer cells that surgery may not have completely removed, but also circulate throughout the body to combat cancer cells that may have metastasized to distant sites through the blood or lymphatic system.

Due to the low selectivity of most chemotherapy drugs, which often cause toxic side effects on normal tissues, responsive carriers are usually required to assist in controlled drug release and targeting[51]. Docetaxel (DTX) is a first-line anticancer drug used for combating a range of cancers such as those of the head、breast and stomach[52]. Zhou[53] and colleagues developed a hydrogel loaded with DTX to prevent peritoneal adhesions and tumor recurrence after abdominal surgery. This hydrogel is designed to specific release DTX upon encountering acidic pH of the tumor microenvironment, achieving target drug delivery. Due to the complexity of tumors, it is often necessary to use a combination of multiple drugs in chemotherapy to target multiple cellular pathways simultaneously, improving treatment outcomes, and reducing drug resistance. Chen[54] and colleagues constructed a temperature-sensitive hydrogel co-delivering 5-fluorouracil (5-FU) and cisplatin DDP for the treatment of gastric cancer. 5-FU is a first-choice chemotherapy drug for gastric cancer, and DDP increases the intracellular content of tetrahydrofolic acid, enhancing the sensitivity to 5-FU[55].The combined use of these two drugs can enhance the inhibition of cell proliferation and promote apoptosis, offering acceptable levels of drug-related toxicity, and elevate survival rates of gastric cancer patients[55-56]. In a mouse model with residual tumors after gastric cancer surgery, the dual-drug loaded hydrogel outperformed the one with just a single drug (Figure 3.A-C), validating the dual-drug loaded hydrogel system as a rational and effective approach, providing a valuable option for clinical postoperative management.

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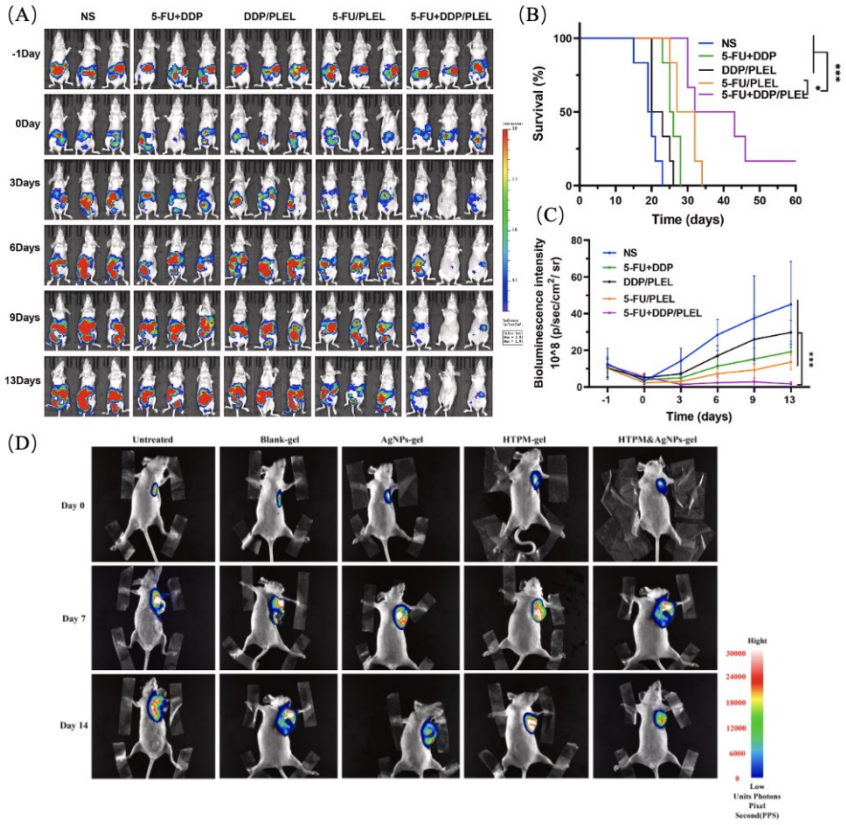

Figure 3. (A) Bioluminescence images of mice post-gastrectomy under various treatments to monitor the efficacy of the dual-drug hydrogel; (B) Quantified bioluminescence intensity in tumor-bearing mice after various treatments; (C) Survival curves of mice following various treatments. Data are presented as mean ± standard deviation (n = 5). *p < 0.05, ***p < 0.001. [25]; (D) Investigating the biodistribution of various hydrogels in postoperative TNBC nude mice bearing the MDA-MB-231-luc cell model (representative photos, n = 5, the experiment was replicated three times). [56].

To address the drug resistance of chemotherapy drugs, researchers are exploring synergistic therapies that combine chemotherapy with other treatment methods to improve the effectiveness of treatment[57-59] For example, combine immunotherapy with chemotherapy. Utilizing immunoadjuvants such as silver nanoparticles (AgNPs) and anticancer drugs like halofuginone, delivered through thermo-responsive hydrogels (such as HTPM&AgNPs-gel), allows for targeted drug release and sustained medication supply[60]. This approach not only reduces drug toxicity and resistance but also induces the body's own regulation to reduce the rate of tumor recurrence and postoperative inflammatory responses. In animal models of triple-negative breast cancer (TNBC), the synergistic therapy showed significantly better anti-tumor effects than the use of chemotherapy or immunoadjuvants alone **(Figure 3.D)**, including the inhibition of tumor metastasis, angiogenesis, and inflammatory responses.

4. Conclusion

In this article, hybrid nano-hydrogels in preventing postoperative cancer recurrence has been discussed. Hydrogels, as a novel drug carrier, have shown exhibit significant promise in cancer treatment due to their ease of application, high local drug concentration, sustained drug retention, and good biocompatibility. The three-dimensional crosslinked network structure of smart hydrogels allows them to effectively load drugs. Most importantly, they can undergo sol-gel transitions in reaction to changes in the tumor microenvironment (like pH, body temperature) or external stimuli (like ultrasound), thereby

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achieving controlled release of the drug and enhancing the precision and effectiveness of drug delivery. Loading nano-drugs on hydrogels both extends the action time of the drugs to improve therapeutic outcomes, and minimizes detrimental effects on normal tissues and organs. By integrating therapies such as immunotherapy and chemotherapy, they can eliminate residual microscopic cancer cells and combat potentially metastatic cancer cells to suppress tumor recurrence. Moreover, they can also combine antimicrobial capabilities to effectively prevent postoperative infections and accelerate wound healing. Despite challenges such as complexity in preparation, cost, and long-term biosafety, these multifunctional hydrogels are anticipated to have a substantial impact on the follow-up treatment of future cancer surgeries with the advancement of material science and nanotechnology.

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TianChen Guo and RuiYing Ji contributed equally to this work and should be considered co-first authors.

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