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Quantum Dots as Theranostic Probes for the Treatment of Ovarian Cancer

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Abstract. Ovarian cancer stands as a deadly gynaecological malignancy featuring a pessimistic prognosis. And low early detection rate. This proposal focuses on advancing a novel category of theranostic nano drugs, based on quantum dots modified with a Gadolinium contrast agent and Olaparib, For the diagnosis and therapy of ovarian cancer. Quantum dots (QDs), especially carbon quantum dots (CQDs), have excellent photoelectric properties. They are chosen for their advantages in biomedical applications, such as being excited by multiple wavelengths, high light stability, and good biocompatibility. Gadolinium(Gd3+) forms a stable chelate as an MRI contrast agent. Polyethylenimine (PEI) is used to modify quantum dots to improve their water solubility and biocompatibility. PARP inhibitors can be connected to modified Gd-CQDs to form a "dual-mode nanoprobe" with therapeutic effect. However, there are challenges in synthesising and modifying these nanostructures, including the purity, activity, and stability of precursors, the control of reaction conditions, the modification efficiency and stability of PEI, and the connection efficiency and specificity of PARPi. Overall, this study intends to create a potential theranostic agent for treating ovarian cancer.

Keywords: Theranostics, Biological imaging, Fluorescence imaging, Magnetic resonance imaging, Quantum dots.

1. Introduction

Among gynaecological malignancies, ovarian cancer is the one boasting the highest lethality globally. Each year, 225,000 new cases and 140,000 deaths occur worldwide. Among Chinese women, the estimated incidence of ovarian cancer is on the rise. It has surged by 30% over the past decade, and the mortality rate has ascended by 18%, with 15,000 deaths taking place annually [1]. It is expected that by 2040, worldwide, the occurrence rate of ovarian cancer among women will increase markedly by around 42%, with a total of 445,721 newly diagnosed cases resulting from this rise. In addition, the annual number of deaths caused by ovarian cancer will increase significantly. Compared with the data in 2020, it will increase by more than 50%, and it is expected to reach 313,617 deaths [2]. In the UK, the five-year survival rates for women diagnosed at stages I and IV are 90% and 4% respectively [3]. Due to subtle or non-specific symptoms, the disease is often complex to detect and diagnose early, so a comprehensive understanding of its various manifestations is required. Most ovarian cancers are diagnosed after symptoms appear, and the focus should be on the early detection of symptomatic diseases.

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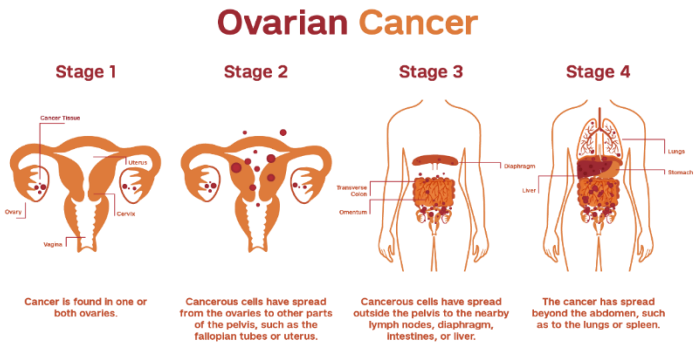

Figure 1. Ovarian cancer stages: 1 -in ovaries; 2 -to pelvis; 3 -outside pelvis; 4 -beyond abdomen [4].

Throughout ovarian cancer, it can be divided into four stages. Figure 1 accurately shows the location and severity of the four stages of ovarian cancer. When ovarian cancer is in a situation where it is localised within the ovaries (stage I), more than 90% of women can be healed through existing surgical and chemotherapy methods. Even when the disease has extended to the pelvic cavity, the survival rate can surpass 70%. Nevertheless, if the cancer spreads across the abdominal cavity or reaches outside the abdominal cavity, the cure rate dramatically declines to 20% or even lower. Due to the lack of effective screening methods, only 20% of the diseases can be diagnosed at an early stage [5].

The occurrence of ovarian cancer usually has no apparent symptoms and may be confused with menstrual pain. Although current screening techniques, surgery, and chemotherapy have developed, most ovarian cancers are only discovered at stage III or IV. As of now, Cancer Antigen 125 (CA125) is the biomarker most commonly employed for the detection of ovarian cancer. However, this approach exhibits low specificity. and still has no acceptable accuracy in population-based ovarian cancer screening [6].

Around 10% to 15% of ovarian cancers are associated with genetic elements. BRCA is the abbreviation of Breast Cancer Susceptibility Gene. BRCA1 and BRCA2 are two vital tumour suppressor genes. When certain specific mutations occur in these two genes, the risk of an individual developing breast cancer, ovarian cancer, and other cancers will significantly increase. The BRCA genes primarily exert a crucial function in the significant DNA damage repair pathway of Homologous Recombination Repair. When severe damage such as double-strand breaks occurs in intracellular DNA, BRCA proteins coordinate the activities of a series of molecules, promoting the exchange and recombination of homologous chromosomal fragments, thereby accurately repairing the damage and maintaining genomic stability. Suppose mutations in the BRCA gene cause functional defects. In that case, it will damage this homologous Recombination Repair mechanism, making DNA damage unable to be effectively repaired, thereby increasing the risk of cancer (such as ovarian cancer) [7].

2. Applications

Poly ADP-ribose Polymerase inhibitors (PARPi) have shown great potential in the field of cancer treatment. As a critical enzyme in the cell nucleus, PARP is involved in various DNA repair pathways. PARP is mainly responsible for the repair of single-strand DNA breaks (SSB). In normal cells, once a single-strand DNA break occurs, PARP quickly intervenes for repair to prevent it from further developing into a double-strand break, As shown in Figure 2 [8]. If BRCA1/2 in the cells mutates, resulting in damage to the HR repair pathway, and then the function of PARP is inhibited because both of these essential repair mechanisms have problems, the cells will have difficulty effectively repairing DNA damage. The absence of either of the two genes is not fatal by itself, but the simultaneous inactivation of both will lead to cell death. This phenomenon is called "synthetic lethality" and is of great significance in cancer treatment [9]. For example, for tumour cells with BRCA mutations, the use of PARP inhibitors can selectively kill tumour cells while having a relatively small impact on normal cells.

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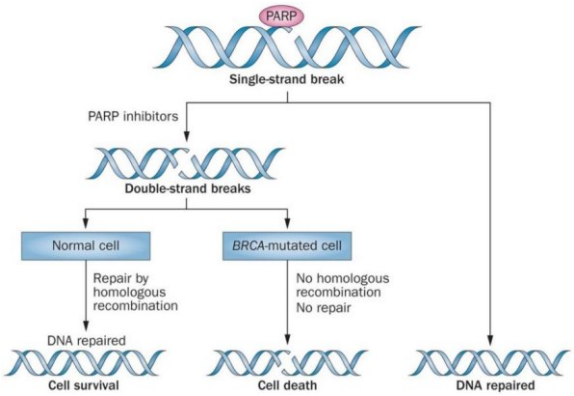

Figure 2. PARP inhibitors lead to double-strand breaks. Normal cells repair; BRCA-mutated cells without homologous recombination die [10].

Today, many PARP inhibitors, such as Niraparib, Rucaparib, Fluzoparib, Pamiparib and Olaparib (see Figure 3), have been approved for marketing. They have performed well in treating tumours with BRCA gene mutations, achieving sound therapeutic effects and showing broad application prospects [11]. For example, in some ovarian cancer cases, the use of Olaparib significantly prolongs the relapse-free survival of patients and enhances lifestyle quality. Niraparib has also shown significant effects in inhibiting tumour growth and metastasis in specific breast cancer treatments [12]. In conclusion, the emergence of PARP inhibitors has brought new hope to cancer treatment and provided more treatment options for patients. However, during the use process, it is still necessary to closely monitor the negative effects of the drugs and the individual differences of patients to achieve precise, safe, and effective treatment.

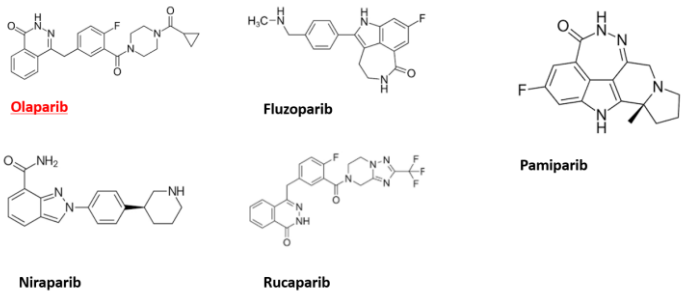

Figure 3. Structure of PARP inhibitors.

Clinical magnetic resonance imaging (MRI) is a powerful imaging means that provides adjustable soft tissue contrast and high spatiotemporal resolution without the use of ionising radiation. However, because of its low sensitivity, its application in molecular imaging is limited, and its low sensitivity application in molecular imaging is constrained [13]. Here, the magnetic resonance contrast agent can reach superior targeting exactness and a lesser radiation dose on the adjacent normal tissue and can supply a method to increase the relative biological dose further to defend the normal tissue [14].

Gadolinium (Gd^{3+}) is an element widely used in the field of medical imaging. From the chemical structure perspective, figure 4 shows that gadolinium is a paramagnetic metal ion with multiple unpaired electrons. This can substantially shorten the longitudinal and transverse relaxation time of hydrogen protons within the adjacent tissue. Based on this characteristic, Gd^{3+} is complexed with a specific ligand to form a stable chelate (Gd-CQDs), which has become a commonly used MRI contrast agent (MRI CAs) in the clinic. In MRI examination, the signal difference between normal tissue and diseased tissue is sometimes not obvious, and introducing a gadolinium-containing contrast agent can change the

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relaxation time of tissue, thus enhancing the signal contrast between tissues and making the lesion site more clearly displayed [15].

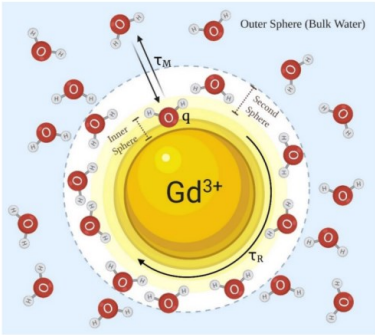

Figure 4. Structure of Gd^{3+} ion.

Quantum dots (QDs) have excellent photoelectric properties, they can be used in the most diversified uses. That is, in the medical arena, they hold great potential for various diagnostic and therapeutic purposes, compared with organic fluorescent dyes, from figure 5, QDs have the advantages of being excited by a variety of wavelengths, high light stability, and conjugate biological molecules without customised chemical modification, and QDs can be used as organic And markers of inorganic carriers, multifunctional QDs for simultaneous imaging and treatment can be combined with a variety of reagents [16]. In order to better observe the content of BRCA and the changes of BRCA in cells in vitro, we use quantum dot staining to target cells. Unique photoelectric characteristics [17]: non-zero band gap, ability to accommodate functional groups and dopants, excellent dispersion, highly adjustable characteristics, and biocompatibility, which make QDs have great application potential in many fields.

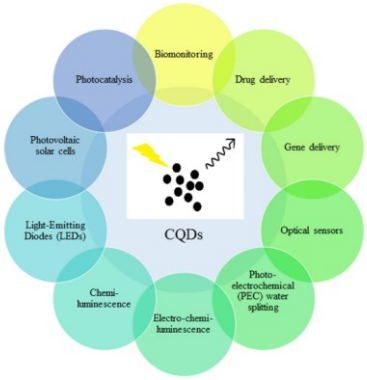

Figure 5. The advantages of the CQDs [18].

Carbon quantum dots are chosen as the fluorescent agent among many quantum dot materials. Because of its unique photoelectric characteristics [19]. CQDs represent a new kind of nanomaterial whose size is approximately less than 20 nanometers. Due to these distinctive characteristics make CQDs our current optimal quantum dot selection. The alteration of CQDs should be emphasised. These make it feasible to detect and attach many particular substances to be analysed on the surface of CQDs, which is of remarkable significance. Electrostatic forces and hydrogen bonds play essential parts here and function as platforms for specific sensing to enable this to occur [20].

The absorption of CQDs in the short-wavelength domain is owed to the π-π transition of double bonds. Typically, they exhibit intense optical absorption within the UV zone (ranging from 250 to 330 nm), and the absorption tail even stretches into the visible spectrum [21]. Generally speaking, C-dots are more capable of handling long wavelengths. The absorption properties of CQDs are different from each other con, contingent on surface passivation and the functional groups attached to the surface [22].

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In terms of the emission wavelength, the concentration of quantum dots primarily impacts the intensity of the emission peak, as shown in Figure 6. Generally speaking, when the concentration of quantum dots increases, the intensity of the emission peak will also increase accordingly. Nevertheless, the circumstance where it directly brings about a notable emission wavelength shift is relatively infrequent. However, it should be noted that if the concentration of quantum dots is overly high, it might cause a certain extent of spectral change due to the interaction between quantum dots, such as aggregation.

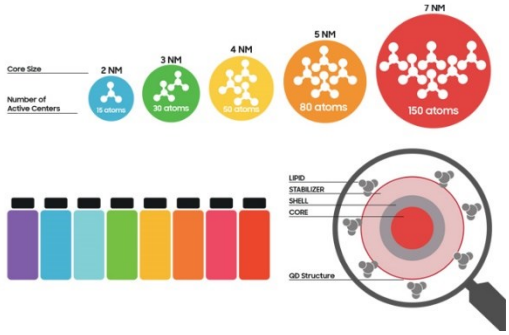

Figure 6. Core sizes (2nm, 3nm, 4nm, 5nm, 7nm) and a corresponding number of active centres (0 atoms, 15 atoms, 50 atoms, 80 atoms, 150 atoms) with lipid stabiliser, shell, and core in GD structure.

PEI is the abbreviation of Polyethylenimine(see Figure 7), which is a cationic polymer. It is an organic macromolecule with a high cationic charge density and is often used in gene transfection technology. It can wrap DNA to form a complex, prevent it from being degraded by DNAse, and then attach to the cell membrane and be endocytosed into the cell. After rupture and release, DNA enters the cytoplasm to function. It possesses good water solubility and is extremely abundant in positive charge. In the drug delivery system, PEI is capable of binding to diverse nanoparticles to deliver drugs and genes. It can have a high affinity with negatively charged cell surface receptors, resulting in a high swallowing rate, thus promoting the entry of drugs into cells. Nevertheless, PEI with high molecular weight may pose high cell toxicity, limiting its application in the biomedical field. In order to reduce toxicity, low molecular weight PEI is usually used [23]. By modifying quantum dots with low molecular weight PEI, PEI coating can improve quantum dots' water solubility and biocompatibility and protect the internal quantum dots, making them play a stronger fluorescence and making detection more sensitive.

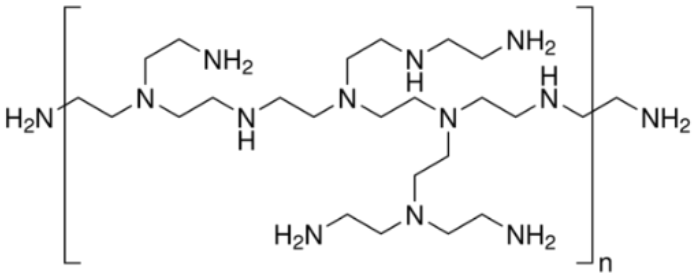

Figure 7. The structure of PEI.

3. Results

In order to detect and treat, a nano-drug was invented: Gd-CQDs-PEI-PARPi to make this drug. First, Gds-doped and nitrogen-doped quantum dots (Gd-CQDs) select suitable Gd pressures, appropriate quantum dots colour and reaction conditions to synthesise Gd-CQDs; Re-modify Gd-CQDs so that low molecular weight PEI can surface modify Gd-CQDs. PEI can improve the water solubility and biocompatibility of quantum dots; finally, connect PARPi to the modified Gd-CQDs through covalent bonds to form a "dual-mode nanoprobe" with the therapeutic effect of Gd-CQDs-PEI-PARPi.

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Researchers have utilised the thermal decomposition technique. In ordinary thermal decomposition, a material or compound undergoes chemical decomposition due to the effect of heat. The thermal reactions leading to decomposition are generally endothermic. These decomposition reactions can be either non-reversible (for instance, the breakdown of starch and protein) or reversible. The benefits of this approach consist of simplicity in use, less time expenditure, low costliness, and is appropriate for large-scale manufacturing [24].

In fluorescence detection, the gadolinium-doped carbon quantum dots synthesised through the hydrothermal method present the following traits: The wavelength of the emission peak associated with their photoluminescence (PL) hinges upon the excitation wavelength. For instance, in ultraviolet-visible spectroscopy (UV-Vis), an absorption peak exists at 271 nm, and when stimulated by distinct wavelengths, spectra featuring different wavelengths of maximum emission intensity are produced. Regarding fluorescence stability, when excited by light having a wavelength of 300 nm, the CQDs can preserve the fluorescence intensity's stability at various ionic strengths and at temperatures reaching up to 65°C [25].

These nanostructures do not flicker and possess a large cross-section in two-photon excitation. Together with non-toxicity, this makes carbon quantum dots potentially possible to become nanoprobes for biological imaging. The size of carbon quantum dots is mostly below 10 nanometers, and there exist amorphous or crystalline forms, and the carbon atoms within them are sp2 hybridised. The functional groups containing oxygen on the surface of CQDs endow them with water solubility [26]. Compared with graphene quantum dots with poor water solubility, this has advantages in biomedical applications. Carbon quantum dots can be excited in the near-infrared region and emit photoluminescence (PL) in the near-infrared region. Carbon quantum dots' photoluminescence (PL) range extends from deep ultraviolet to near-infrared. By controlling their size, altering the surface and edge conditions, and doping heteroatoms, the PL emission of carbon quantum dots can be regulated.

4. Discussion

When suitable Gd predecessors are chosen for synthesising Gd-doped and nitrogen-doped quantum dots (Gd-CQDs), problems of inconsistent purity, activity and stability of the predecessors may be faced, resulting in uneven quality and performance of the synthetic Gd-CQDs. At the same time, in the process of synthesising Gd-CQDs, the control of the colour and reaction conditions of quantum dots (such as temperature, pressure, reaction time, solvent system, etc.) is very important. Suppose the reaction conditions are not accurately optimised. In that case, the uneven size distribution and irregular morphology of quantum dots may be affected, affecting their optical and magnetic properties and thus reducing the effect in imaging and treatment.

When low molecular weight PEI is used to surface modify Gd-CQDs, uneven modification may occur, resulting in an obvious improvement in the water solubility and biocompatibility of some quantum dots and affecting subsequent applications in organisms. In the modification process, the combination of efficiency and stability of PEI and Gd-CQDs is also a problem. If the binding efficiency is low, the number of subsequent PARPi connections may need to be increased. If the binding stability is poor, PEI may fall off the surface of Gd-CQDs in the complex physiological environment in the body, affecting the performance and function of nanopharmaceuticals.

If PARPi needs to be connected, it must be connected to the modified Gd-CQDs through the covalent key. This may have the problem of low connection efficiency, resulting in an insufficient load of PARPi in nanopharmaceuticals and affecting its treatment effect. Moreover, the covalent bond connection reaction may cause damage to the structure and performance of Gd-CQDs, such as reducing the fluorescence intensity of quantum dots and changing their magnetic properties. The third point is that there may also be problems in the selectivity and specificity of the connection reaction, resulting in PARPi not only being connected to the surface of Gd-CQDs but also non-specifically connected with other impurities or molecules in the reaction system, affecting the purity and performance of nanodrugs.

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5. Conclusion

This study has successfully developed a novel class of theranostic nanodrugs based on quantum dots modified with Gadolinium and Olaparib to diagnose and treat ovarian cancer. The exceptional photoelectric properties of quantum dots, particularly carbon quantum dots, make them highly suitable for biomedical applications. The integration of gadolinium as an MRI contrast agent and the modification of quantum dots using PEI demonstrate significant progress in the field. In the future, further research endeavours will be directed towards optimising these nanostructures' synthesis and modification processes. This will involve enhancing their performance and specificity and conducting extensive in vivo and clinical studies to validate their safety and efficacy. The ultimate goal is to provide a more precise and effective therapeutic strategy for ovarian cancer, thereby improving the prognosis and quality of life for patients. This work represents a promising step forward in the field of cancer nanomedicine.

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