Nanomed Res J 7(2):124-139, Spring 2022

REVIEW PAPER

Oral cancer: Nanoparticles as a new horizon in the diagnosis and phototherapy-based therapies

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ARTICLE INFO

Article History:
Received 07 February 2022
Accepted 22 April 2022
Published 01 May 2022

Keywords:
oral cancer
diagnostic
therapeutic
nanotechnology
photothermal therapy (PTT)
photodynamic therapy (PDT)

ABSTRACT

Oral cancer has affected the health of people by causing an unacceptable high rate of mortality and has the sixth place among the most common types of malignant cancer. In addition, the /available clinical approaches for the diagnosis and treatment of this disease (e.g., magnetic resonance imaging, computed tomography, surgery, and chemoradiotherapy) proved to have a long way to reach an ideal state. Therefore, there is a pressing need for the discovery of effective and feasible early diagnostic and therapeutic strategies in regards to oral cancer. The distinctive features of nanotechnology and nanoparticles, such as small size, surface to volume ratio, etc. that induce many changes in electrical, optical, and magnetic properties, can help in providing early detection and designing a more applicable treatment. Although surgery, radiotherapy, and chemotherapy are included among the most common treatments of oral cancer, yet there are disadvantages to their usage that indicate the need for novel methods with superior therapeutic benefits. One of the new approaches in this field is phototherapy-based therapies that involve photothermal therapy (PTT) and photodynamic therapy (PDT) as the major methods. Despite their advantages, some of the limited potentials of these therapies can be possibly surpassed through the application of nanotechnology.

How to cite this article
Fallahnia N., Ansari L., Mohammadkhani H., Mousazadeh F., Mohammadi khah M., ketabchi G. Oral cancer: Nanoparticles as a new horizon in the diagnosis and phototherapy-based therapies. Nanomed Res J, 2022; 7(2): 124-139. DOI: 10.22034/nmrj.2022.02.002

INTRODUCTION

2% to 3% of cancer cases are caused by Oral cavity squamous cell carcinoma (OCSCC), which is also responsible for the occurrence of almost half of every malignancies in the head and neck that involves 5% of tumor cases. The data of Surveillance, Epidemiology, and End Results Program predicted the yearly diagnosis and addition of 28,900 new cases of oral cancer, as well as 7400 deaths, in United States. This disease has the sixth place in the causes of cancer-related mortality in United States, with one fatality per hour [1, 2]. Oral cancer as a type of malignant neoplasia that grows on lips or within the mouth, the traditional definition of oral cancer is squamous cell carcinoma (OSCC)

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since 90% of malignancies in the dental area are histologically generated in squamous cells. This disorder implicates a diversity of differentiation levels and a propensity for lymph node metastases [3]. In most of the ethnic groups, the infection rate of men is two to three times higher than women. The most recent data of the International Agency for Research on Cancer (IARC) reported the overwhelmed worldwide annual incidence of oral cancer, including the lips, tongue, gingiva, mouth floor, parotid, and salival glands, which implicate the diagnosis of over 300.000 cases and 145,000 deaths per year[4, 5]. However, the presence of some notable risk factors such as smoking and alcohol in 90% of cases can be considered as a synergistic impact on this preventable type of cancer [6, 7]. Additionally, human papillomavirus (mostly linked to oropharyngeal cancer) and ultraviolet radiation stand as the other risk factors (UV). In conformity to evidences, the contribution of HPV to carcinogenesis is completed through two virus-encoded proteins as the following: E6 advocate the degradation of tumour suppressor gene product p53, whereas E7 advances the degradation of tumour suppressor gene product pRb (retinoblastoma protein), leading to the disruption of cell cycle control and causing the overexpression of cyclin dependent kinase inhibitor p16Ink4a [8-10]. Prior to treatment, diagnostic confirmation can be achievable only by the results of biopsy and histological analysis, with probable prior cytological evidence, which simply delays the initiation of treatment. Nonetheless, the late diagnosis of oral cancer causes a delay in the start of therapy and results in a lower survival rate for patients [11-15]. For a variety of cancer indications, the safety of light-activated, photosensitizer-based therapies as the modalities of tumor ablation were proved, which include the two basic methods of photodynamic and photothermal therapies. There are certain fundamental challenges that limited the clinical usage of notable progresses that were made in the development of phototherapeutic medications and devices as cancer treatments over the last few decades. In this regard, different approaches were trialed to enhance therapeutic impacts, which included the design, identification, fabrication, and application of nanotechnology-based systems. The interest of many was focused on the usage of nanoparticles due to their unique light-to-thermal energy conversion efficiency, as well as their capabilities in loading and delivering various anticancer drugs [16, 17]. This work presented the recent developments of nanoparticle platforms that include the integration of inorganic nanostructures (photothermal therapy) with photosensitizers (photodynamic therapy) in order to combine their phototherapeutic impacts and provide aid in the diagnosis of oral cancer.

THE MOST COMMON METHODS OF DIAGNOSING ORAL CANCER AND THEIR LIMITATIONS

Expressed as OSCC (squamous cell carcinoma), oral cancer is a life-threatening illness that involves the genomic route and inducement of changes in the genome, which result in altering the expression of proteins, chemical mediators, and enzymes. OSCC usually leads to the occurrence of cell proliferation and annihilation upon disruption as a result of oncogene activation and tumor suppressor gene inactivation. Gene amplification, oncogene overexpression, mutations, deletions, and hypermethylation are among the genetic changes that cause the inactivation of some specific genes including p53 tumor suppressor gene[18, 19]. The aggressive behavior of oral cancer primarily affects oral epithelial cells, which may progress into metastasis and even death. The produced tumors can invade the tongue, buccal, floor of mouth, alveolar, and hard palate mucosa, while the tongue stands as the most common subsite with a poor prognosis[20-22]. The development of oral cancer implicates a complex and multistep procedure. There are a number of oral potentially malignant disorders (OPMD) including oral leukoplakia, oral erythroplakia, oral lichen planus, oral submucous fibrosis, actinic keratosis, and discoid lupus erythematosus. These factors express the importance of achieving the early diagnosis of OPMD and oral cancer in regards to illness prognosis [23, 24]. In prior to consulting with oral and maxillofacial surgeons and oral medicine specialists, these lesions may be initially noticed/ suspected by dental practitioners. However, scalpel biopsy and histological examinations remain as the gold standard diagnostic routes for determining the possible malignant and malignant lesions in an oral situation .The frequent invasive manner of biopsy method can cause concerns and discomfort for the patients. The selection of resection margins is largely based on histopathological assessments, while the quality of specimens and pathologists' subjective judgments can effect the obtained outcomes.

Furthermore, the disability of examinations in recording the small numbers of genetically defective cells near the edges may lead to the possibility of recurrence[25-28]. There are a number of non-painful diagnostic methods available. The possibly cancerous lesions can be detected through non-invasive visual methods including toluidine blue (TB) staining, autofluorescence (VELscope), and chemiluminescence (ViziLite) that can be performed alone or in combination[25, 29, 30]. Oral cancer stages and treatment strategies are often established by the usage of radiographic imaging modalities similar to magnetic resonance imaging (MRI), computed tomography (CT), cone beam computed tomography (CBCT), and positron emission tomography (PET). The identification of malignant lesions from normal oral mucosa is done through a number of typical optical diagnostic techniques including raman spectroscopy, elastic scattering spectroscopy, diffuse reflectance spectroscopy, narrow-band imaging, and confocal reflectance microscopy [31-34]. However, there are some drawbacks to the usage of these noninvasive methods. Furthermore, the low sensitivity of traditional detection methods is incapable of tracking biomarkers with low quantities in tissue samples or body fluids .Despite the fact that imaging technologies can reveal the morphology of real-time cancer cells, their inadequate sensitivity for perceiving small, early intraepithelial lesions is undeniable [27, 30, 35]. As a result, there are demands for novel diagnostic methods with the ability to surpass these limitations along with providing certain benefits such as the accurate prediction of malignant risk of OPMDs, specific detection of oral cancer based on molecular targeting, facilitate ultrasensitive detection approaches at nano-scale, and design real-time recommendations for determining the depth of surgical resection margins and keeping track of oral cancer prognosis in the course of the therapy[36].

Nanotechnology in the diagnosis of oral cancer

The manipulation of matter at molecular and atomic levels is known as nanotechnology. Nanomaterials, which contain components in sizes smaller than 100 nm in at least one dimension, include atom clusters, grains, fibers, films, nanoholes, and composites. The one dimension nanomaterials are referred to as sheets, while nanowires and nanotubes contain two dimensions and quantum dots are composed of three dimensions. The special properties of these materials differ from others due to their extended surface area and quantum effects. The small sizes of nanomaterials provide a substantially higher surface area per unit mass when compared to larger particles, while leading to the alteration of their electrical, optical, and magnetic properties [37-40]. Nanotechnologies have been used in a variety of fields in recent decades, particularly in medicine. One of its most significant medical usages was to provide the diagnosis of diseases, especially cancer, which has the potential for identifying cancer and monitoring its metastasis progression. The diagnosis of oral cancer is commonly completed once the cancer cells have progressed enough to behave aggressive and resistant toward treatment, which is an untreatable stage. Therefore, the early detection of this illness is mandatory in order to improve the survival rate [41-43]. In this regard, these demands can be addressed by the application of nanotechnology for clinical diagnostics due to their ability to provide higher sensitivity and earlier illness diagnosis. The power of nanotechnology caused a revolution in cancer diagnosis and therapy by offering the capabilities of detecting even a single malignant cell in the body and delivering highly toxic chemicals directly to the diseased cells. Individual cancer cells can be located through the exertion of particular crosslinkers including specific antibodies against cancer cells [38, 44, 45]. NPs can specifically target cancer biomarkers and cancer cells, which would facilitate diagnostics with higher sensitivity, early identification with minimum tissue, long-term monitoring of therapy and tumour burden, and the annihilation of only cancer cells [46, 47] (Fig. 1). The similar sizes of nanoparticles to that of proteins or cells provides the ability to perform biotagging or labelling in living organisms. Meanwhile, the parts of cells were observed to be significantly smaller and measure in the range of sub-micron, while proteins contain an even smaller mean size of just 5 nm that is in corresponding to the dimensions of smallest artificial nanoparticles. According to this clear size analogy, nanoparticles have the potential of acting as very small probes in the course of spying on cellular machinery while inducing the least amount of interference. Having a tight control over the average particle size, as well as a narrow variation of sizes, can create highly effective fluorescent probes with the ability to emit narrow light in a wide range

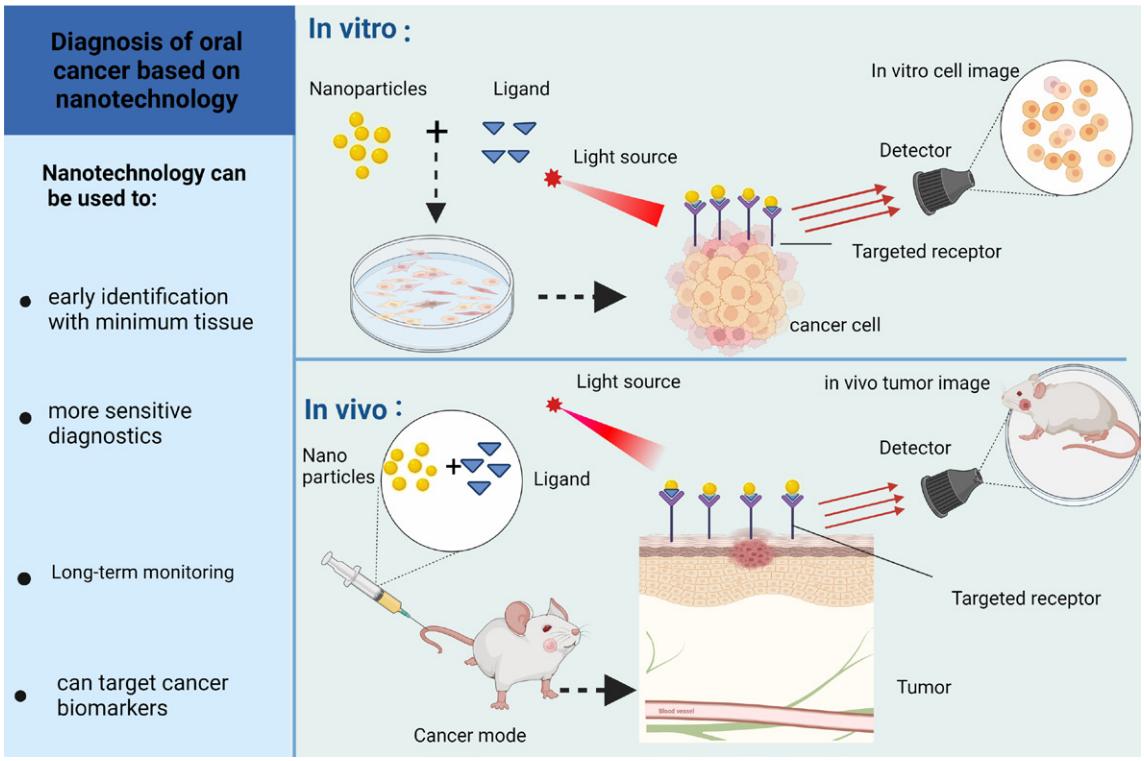

Fig. 1. usage of nanoparticles in the diagnosis of oral cancer

of wavelengths. This discovery can facilitate the production of biomarkers with a variety of distinct colours[48-50].

Next to bioconjugated particles and technologies, researches also attempted to assess the topic of early cancer detection in body fluids such as blood and serum, which function on the basis of selectively catching cancer cells or target proteins. The frequent coating of these sensors with a cancer-specific antibody or other biorecognition ligands leads to the production of an electrical, mechanical, or optical signal that can be detected upon the capture of cancer cells or target proteins. The exertion of nanoparticles in detecting and analyzing circulating tumor cells and biomarkers in blood/serum samples is another promising field of research. Apparently, the combination of nanoparticles can improve their capability of catching and examining these unique circulating cancer cells [51, 52]. The in vitro detection of tumor cells in a qualitative or quantitative behavior can be facilitated by the application of Nps, since they can concentrate and protect a marker against degradation while increasing the sensitivity of analysis. In contrast to fluorescent organic markers, the encapsulation of inorganic biomarkers is performed through another route. They proved to be more appropriate and sensitive for qualitative and quantitative detection due to being more photostable , which can not be affected by the intrinsic fluorescence (background signal) released by cells and tissues. The physicochemical features of NPs (particle size, surface charge, surface coating, and stability) can successfully redirect and concentrate the applied marker at the targeted site. Furthermore, labeled colloidal particles can be employed as radio diagnostic agents. However, nonlabeled colloidal systems are being already exerted and evaluated in the form of contrast agents in diagnostic procedures including computed tomography and nuclear magnetic resonance imaging, optical coherence tomography (OCT), photoacoustic imaging, surface plasmon resonance scattering, surface-enhanced raman spectroscopy, and diffusion reflection imaging[36, 53]. Table 1 demonstrates the utilization of nanotechnology throughout for in vitro and in vivo bioimaging of oral cancer.

Table 1. application of nanoparticles for in vitro and in vivo bioimaging of oral cancer

Nanoparticles	Ligand	Imaging technique	The role of nanoparticles	References
Liposome	64Cu	PET	-detect early tumors	[54]
Dendrimer	DNA	electrochemical sensors	- detecting biomarkers of oral cancer, such as interleukin-8 RNA, interleukin-8 protein, and interleukin-1β protein	[55]
gold nanorods	anti-EGFR monoclonal antibodies	Optical imaging	- discriminate benign from premalignant and malignant oral lesions	[56]
gold Nanorods	EGFR	Air scanning electron microscopy (airSEM)	- evaluate the SCC(squamous cell carcinoma) margins	[57]
upconversion nanoparticles (UCNPs)+ AuNPs	Matrix metalloproteinases (MMPs)	Fluorescent biosensor	- cell viability analysis in head and neck cancer cells	[58]
nanospheres and gold nanorods	anti-EGFR antibody	dark-field microscopy	- as plasmon scattering probes for dark-field multiplex imaging of live oral squamous cell carcinoma cell	[59]
plasmonic Au nanoclusters (Au NCs)	-	optical coherence tomography (OCT)	- disclosing early-stage cancer	[60]
gold nanoparticles	-	surfaceenhanced Raman scattering (SERS)	- Surface improved Raman spectroscopy (SERS) assessment of saliva for oral cancer diagnosis	[61]
gold nanoparticles	-	surfaceenhanced Raman spectroscopy (SERS)	-surface-enhanced Raman spectroscopy (SERS) of blood serum to distinguish the tumor stages and histologic classification of OSCC	[62]
gold nanoparticles-reduced graphene oxide (AuNPs-rGO) composite	Anti-IL8	electrochemical immunosensor	-label-free and noninvasive disclose of salivary oral cancer biomarker interleukin-8 (IL8)	[63]

Continued Table 1. application of nanoparticles for in vitro and in vivo bioimaging of oral cancer

Nanoparticles	Ligand	Imaging technique	The role of nanoparticles	References
super-paramagnetic iron oxide nanoparticles (SPIONs)	-	Magnetic resonance imaging (MRI)	- Resonance imaging (MRI) contrast agents in cancer diagnosis	[64]
magnetic nanoparticles (MNPs)	-	Magnetic resonance imaging (MRI)	- in the form of contrast agents in magnetic resonance imaging and as a therapeutic system in conjunction with hyperthermia	[65]
quantum dots (QDs)	FITC	confocal microscopy	- Double labeling and comparing the fluorescence intensity and photostability among quantum dots and FITC in oral tumors	[66]
quantum dots	EGFR monoclonal antibody	in-vivo visible imaging	- to assess in-vivo visible imaging of oral squamous cell carcinoma (OSCC)	[67]
quantum dots	-	visible imaging	- Diagnosis Expression of Caveolin-1 in tongue squamous cell carcinoma	[68]
quantum dots	-	visible imaging	- o evaluate the relation of oral squamous cell carcinoma with human papillomavirus (HPV) using quantum dots (QD) in situ hybridization (ISH)	[69]
quantum dots	DNA	electrochemical sensors	- early diagnosis of oral cancer	[70]
PLGA nanoparticles	chemokine SDF-1	photoacoustic imaging	- targeted photoacoustic imaging and photothermal therapy of metastatic lymph nodes in tongue squamous cell carcinoma	[71]
Chitosan-Based Nanoparticles	folic-acid+ Succinate	fluorescent endoscopic	- detecting primary oral lesions during endoscopy	[72]
carbon nanotube	CIP2A	electrochemical immunosensor	- rapid cancer screening tests at the point-of-care (POC) such as for the early-stage diagnosis of oral cancer at a dentist's office	[73]

COMMON TREATMENTS FOR ORAL CANCER AND THEIR LIMITATIONS

The fundamental goal of oral cancer treatment is to cure the patients through the removal of primary tumor and prevent the spreading of disease to finally achieve a disease-free state. However, the treatment goal of incurable illnesses changes to increasing the quality of patients lives until death. Over the last century, the great expansion of management options resulted in enhancing the illness control and survival rates along with the quality of patients lives. The main treatment approaches include solitary surgery, combined surgery with postoperative radiotherapy, solitary radiotherapy,

and chemotherapy[74-79]. The dominant stance of dispatching malignancies by surgery among the other treatments of oral cancers is undeniable. This method was the very first approved technique for treating tumours in general with a well-established history of over a century, with the goal of achieving a total tumor excision by surgical margins comprised of healthy tissues. Although the advancement of surgical techniques (e.g., more conservative resection and free tissue transfer from distant sites) caused an initial improvement in control rates and quality of life, however, the addition of radiotherapy and chemotherapy in the roles of adjuncts to surgical removal discredited the superiority of solitary surgery as the best treatment option for most oral cancers due to its poor outcomes[80, 81]. The development of radical neck provided the possibility of performing surgical treatments for oral malignancies with a clinically positive neck. After decades of development, modified radical neck dissections (for positive neck lymph nodes) and selective/elective neck dissections (for negative neck lymph nodes) are considered as common surgical methods in order to inhibit occult cancer metastases throughout the head and neck regions while lacking the morbidity associated with comprehensive/radical neck dissections. Although the type of neck dissection is determined by the initial presentation of patients, however, the preferred choice is typically ipsilateral neck dissections unless the existence of contralateral neck nodes is proved or the position of primary tumor is confirmed to be at/across the midline, which heightens the risk of contralateral/bilateral spread. Tumor thickness can also stand as a significant predictor of cervical nodal metastasis, since tumours with a thickness of more than 5 mm are linked to a higher risk of cervical metastasis. According to the majority of related researches, high control and survival rates are mainly associated with early lesions, while a drastic reduction is observed in both values as the stages of tumour proceeds, such as an increase in the number of positive neck lymph nodes or primary tumour size/thickness[82-87]. The common therapeutic option for the treatment of oral malignancies and tumours of the head and neck regions is surgery combined with postoperative radiotherapy. Radiotherapy is usually applied after surgery in order to ease the fibrosed situation and slow healing of surgically removed irradiated tissues. The performance of radiation at primary sites is dictated by certain parameters including large primary tumours, positive or close surgical margins, and signs of perineural/lymph/vascular invasion. However, the common procedures involve a treatment for the neck as well, particularly upon conditions that implicate positive lymph nodes with or without extracapsular spread, to inhibit potential metastasis and recurrence[88]. Radiotherapy is rarely prescribed as a sole treatment option for the cases of oral malignancies (usually involve an inoperable tumour site or the patients refusal to undergo a surgery). This method can be also applied as a palliative treatment for the patients that are reaching the advanced/terminal stages. As the most typical choice, radiation therapy is exerted in combination with surgery and/or chemotherapy for causing the rapid annihilation of dividing cancer cells by altering their DNA construction at the expense of affecting healthy cells [88, 89]. In recent years, chemotherapy has become a common adjuvant treatment for locoregionally progressed oral SCC. It's a systemic therapy that seeks to inhibit tumors from spreading and metastasizing by destroying quickly dividing malignant cells. Although it is rarely curative on its own, this technique can be conducted in prior to surgery (induction), concurrently with irradiation post surgery (chemoradiotherapy), or both for solid head and neck or oral tumors. Adjuvant chemoradiotherapy is the most commonly applied method for treating progressed head and neck malignancies. In addition, cisplatin is the most common chemotherapy drug. The availability of methotrexate, 5-fluorouracil, hydroxyurea, platinum derivatives, anthracyclines, plant alkaloids, and the most current taxoids expanded the range of applicable drugs for the treatment of oral and maxillofacial tumors in recent decades. The results of massive studies on combination chemotherapy exhibited its relatively high response rates caused by synergistic impacts, which is achieved at the cost of increased toxicity without extending the survival rates, particularly in recurring and metastatic cancer. Complications of concomitant chemoradiotherapy include a higher percentage of toxicities (up to twice the incidence) than induction chemotherapy or solitary radiation [90-92]. There are frequent reports on the adverse toxic consequences that are induced during and after the treatment of oral malignancies with radiotherapy and/or chemotherapy. Due to the nature of both therapies, every rapidly dividing cell of the body

may be affected in the course of the treatment, which include skin epithelial cells (xeroderma), haemopoietic cells (haematologic toxicity) within the bone marrow, epithelial lining of the alimentary tract that particularly involve the oral mucosa (mucositis), and hair follicles (alopecia). The severity of common side effects, such as nausea and vomiting, neurotoxicity, nephrotoxicity, and ototoxicity[93-95], can deeply affect the quality of patients lives while decrease their capacity to continue therapy and reducing the probability of a cure[96]. Next to the expected consequences (for example, salivary gland hypofunction in over 60% of patients subsequent to head and neck radiotherapy), there are other impacts, such as mucositis, renal dysfunction, neurotoxicity, and haematologic toxicities, that are quiet difficult to be foreseen and pose life-threatening dangers[97]. The prescription of antineoplastic drugs cannot be avoided for the majority of cases. Even the the advancement of combined modality therapy was incapable of extending the overall 5-year survival rate of patients with head and neck squamous cell carcinoma, which continues to be 40–50%. This fact highlights the necessity of developing non-invasive modality with a lower rate of side effects in order to inhibit and treat the lesions of patients with oral cancer[98]. Standing as promising and effective cancer treatments, Photothermal therapy (PTT) and photodynamic therapy (PDT) implicate the exogenous application of specific wavelengths of light, which initiate the heat generation of nanoparticles and lead to the activation of photosensitizer (PS) medicines[99]. The method is mediated by light, light sensitizers (PS), and reaction oxygen species (ROS), which offer unique advantages in spatial and temporal selection and minimum invasion. Nevertheless, next to the restricted tissue penetration, the hydrophobic nature of most PSs has limited their usage for therapeutic purposes[100].

Overcoming the limitations of Photothermal therapy and photodynamic therapy using nanotechnology

The two categories of phototherapy, including photothermal therapy (PTT) and photodynamic therapy (PDT), are considered as minimally invasive and efficient cancer treatment options. Photothermal agents that contain a high absorbance throughout the range of near-infrared (NIR) are commonly exerted in PTT to produce heat and result in the thermal ablation of target cells. On the other hand, PDT transmits photo energy to the surrounding oxygen molecules by the aid of photosensitizer and creates reactive oxygen species such singlet oxygen (SO) with the ability to destroy

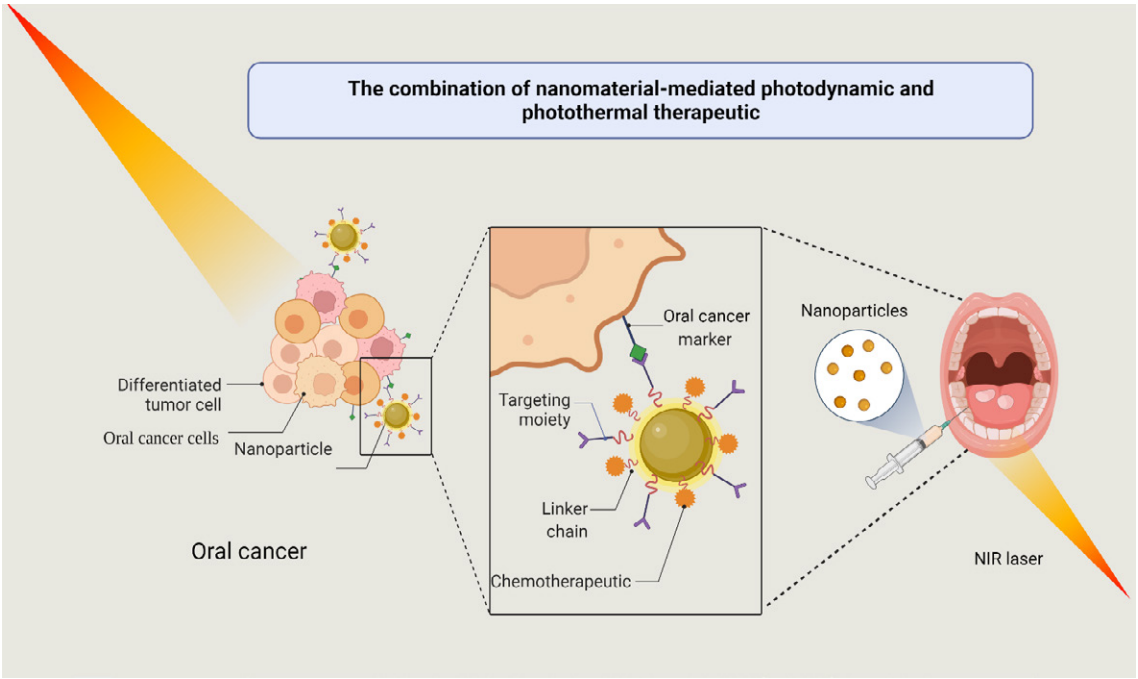

Fig. 2. Usage of nanoparticles in photodynamics and photothermal therapy

Table 2. Types of nanoparticles exerted in the form of a carrier for drug delivery or as a photosensitizer in the treatment of oral cancer

Nanoparticles	Drug or photosensitizer	Imaging technique	The role of nanoparticles	References
Fe3O4@Au/reduced graphene oxide nanostructures	-	-	- Combination therapy involving radiotherapy (RT) and photothermal therapy (PTT)	[115]
Gold nanorods (GNRs)	rose bengal (RB) (anionic photosensitizer)	visible imaging	- nanoparticles in the form of a vehicle to conjugate with RB for enhancing the uptake efficiency by cancer cells - a diagnostic facility to perceive oral precancerous and malignant lesions	[116]
Black phosphorous nanosheets–gold nanoparticles	cisplatin (CDDP)	-	- As a carrier of cisplatin (CDDP) - superior photothermal features and the photothermal combination of photodynamic and therapy of BPNSs and AuNPs	[117]
Poly(β-amino ester) (PBAE)/poly lactic-co-glycolic acid (PLGA) blended nanoparticles	photosensitizer indocyanine green (ICG) and Nrf2-siRNA	visible imaging	- -promising OTSCC-targeted delivery system for both photosensitizer and gene - efficient synergist for amplifying PDT	[118]
anti-EGFR antibody conjugated gold nanoparticles	-	-	- Efficient conversion of strongly absorbed light - selective photothermal agents in molecular cancer cell targeting - Au nanoparticles offered a new category of selective photothermal agents	[119]
AuNFs@SiO2@mSiO2-ICG	indocyanine green (ICG)	-	- improved PDT/PTT synergistic impact to oral carcinoma - improved Cal27 cells lethality in vitro while preventing the in vivo growth of tumor	[120]
Liposomal	Diazepinoporphyrazines	-	- the highest fluorescence quantum yield - the highest singlet oxygen production quantum yield -approximately three times stronger photocytotoxicity than that of the free form	[121]

Continued Table 2. Types of nanoparticles exerted in the form of a carrier for drug delivery or as a photosensitizer in the treatment of oral cancer

Nanoparticles	Drug or photosensitizer	Imaging technique	The role of nanoparticles	References
Liposomal	Foscan, Foslip, Fospeg (as photosensitizer)+ anticancer drug bleomycin (BLM)	Fluorescence microscopy	- imrpoved the efficacy of anticancer drugs entrapped in liposomal	[122]
Liposomes	cisplatin (CDDP)	-	- potent additive impact towards chemotherapy efficacy - combination of PDT with LPC NPs improved the therapeutic achievement in human OSCC	[123]
Liposomes	zinc phthalocyanine (ZnPc) or aluminum phthalocyanine chloride (AlPc)	-	- The embedding of phthalocyanines in liposomes enhanced their phototoxicity	[124]
Upconversion Nanoparticles Conjugated with Au Nanorods	Methylene blue (MB)	-	- enhance ROS Production - enhanced PS gathering in tumor areas - Overcome short penetration depth of light and low extinction coefficient PSs	[125]
superparamagnetic iron oxide nanoparticles (SPIONPs)		laser scanning confocal microscopy (LSCM)	- good biocompatibility - the possibility of annihilating CSCs by targeted magnetic nanoparticles and an AMF, while magnetic fluid hyperthermia significantly prevented the extension of grafted Cal-27 tumors in mice	[126]
Magnetic iron oxide nanoparticles	-	-	- antibody-targeting magnetic nanoparticles with thermal ablation	[127]
superparamagnetic iron oxide	cisplatin	-	- lowering the incidence of serious cisplatin-related side effects - offering the possibility of decreasing the clinically effective dosage of cisplatin through its exertion in combination with ferucarbotran/AMF-induced hyperthermia	[128]
quantum dot+ mesoporous carbon nanospheres	-	visible imaging	- light-to-heat conversion efficiency up to 52% - substantial thermal ablation effect	[129]

Continued Table 2. Types of nanoparticles exerted in the form of a carrier for drug delivery or as a photosensitizer in the treatment of oral cancer

Nanoparticles	Drug or photosensitizer	Imaging technique	The role of nanoparticles	References
polymeric carrier (PEG-PBC-TKDOX)	doxorubicin	visible imaging	- polymeric system with enhanced efficiency for chemo-photodynamic therapy and decreased off-target toxicity - The minimal invasiveness and nonsystemic toxicity	[130]
nanoparticles (NPs) of chitosan	Cu-carboxylate complexes	-	- As a carrier of photothermal agents shows that the possibility of inhibiting tumor recurrence	[131]
polyethylene glycol-polyethyleneimine-chlorin e6 (PEG-PEI-Ce6) nanoparticles	Wnt-1 siRNA	-	- As a carrier to efficiently deliver Wnt-1 small interfering RNA (siRNA) - in combination with Wnt-1 siRNA, PEG-PEI-Ce6 nanoparticle mediated PDT prevented cell growth and caused a remarkable improvement in the rate of cancer cell annihilation	[132]
PEG-PCL-C3-ICG NPs	indocyanine green (ICG)	visible imaging	- exerted as a novel PPT/PDT agent - superior photothermal conversion stability - decreased cytotoxicity - faster metabolic rate -the capability of PEG-PCL-C3-ICG NPs in causing the simultaneous production of hyperthermia through C3 and creation of reactive oxygen species, as well as a fluorescence-guided effect through ICG for destroying oral squamous cell carcinoma (OSCC) cells	[133]
HPEE–ce6 nanoparticles	photosensitizer chlorin(e6)	confocal laser scanning microscopy (CLSM)	-hyperbranched poly (ether-ester) as a carrier of p photosensitizer chlorine (e6)	[134]
gold ultrasmall nanoparticles	cisplatin	-	-as a carrier of the drug cisplatin -as a photothermal agent -synergistic chemo-photothermal treatment of head and neck squamous cell carcinomas (HNSCCs)	[135]

tumor cells. Phototherapies cause a significantly low rate of side effects while providing a superior selectivity than conventional treatments due to the tumor targeting capacity of suitably designed photosensitizers or photothermal agents, as well as the selective light irradiation of lesion site[101, 102]. As a promising therapeutic approach, PDT proved to be minimally invasive and implicate the combination of two non-toxic components to create a high level of oxidative stress in a biological target, while aiming the goal of treating a varying range of solid tumors and non-malignant diseases . One of these components is a photosensitizer, known as a molecule that converts light energy into chemical

potential, and the other component is the light of a specified wavelength. The adsorbed light by PS leads to the generation of a singlet excited state, which can gradually cross into a very stable energy state known as the excited triplet state through the intersystem crossing[103, 104]. In the following, the excited triplet state of PS can form direct reactions with various molecules in the environment (type I photoreactions) or with molecular oxygens (type II photoreactions). The special stance of Type II photoreactions anticancer PDT is caused by the prevalent behavior of molecular oxygens in tumor locations. The transition of triplet ground state ($3O_2$) towards the singlet excited state in type II photoreactions can be enhanced by the application of PS in the appearance of molecular oxygens ($1O_2$) [103-105]. As a therapeutic method, Hyperthermia implicates the usage of heat to destroy pathogenic cells through an irreversible damaging system, which requires the loosening of cell membranes and denaturing of proteins through a variety of heating sources. Lasers are the key instrument of this technique due to the conversion of laser energy to heat . The amount of generated heat by the direct irradiation of target region with a light source proved to be sufficient. However, there are a number of drawbacks to the usage of Phototherapy that limit its effectiveness in the treatment of cancer. The probability of causing unintended damage to normal tissues as the applied laser travels through all of the tissues in its path has caused some challenges in regards to the direct conversion of light energy to heat energy[17]. Furthermore, the limited medical utility of most PSs, which is due to their hydrophobic nature and poor tissue penetration [106], require the design of ideal photothermal agents with certain features, including biocompatibility, large absorption coefficient, near infrared absorption, and photostability, to perform a selective and efficient photothermal therapy[107]. Nanostructures stand as a suitable candidate for this position due to offering a superior potential for the improvement of therapeutic index[108]. In general, nanotechnology was suggested as an applicable strategy to surpass these obstacles in recent years. The goal of this field in phototherapy is to enhance the water compatibility of hydrophobic drugs / photosensitizers (PS), inhibit drug degradation, provide the prolonged release of drug, extend the rate of drug bioavailability , strengthen tumor selectivity, and facilitate superior penetration depths for treating deep-seated tumors, which would consequently heighten the efficacy of treatment and decrease the inducement of side effects[109-111]. The majority of current Phototherapy nanotechnology investigations are focused on either enhancing the available clinically authorised PS formulations or developing targeted delivery vehicles. However, this technology can also pave the way for improving the solubility of poorly water-soluble drugs, inhibit their degradation, provide a longer shelf life, and extend the drug bioavailability. Furthermore, the other benefits of nanoparticles include multidrug loading capacity that can facilitate combination therapies, as well as the design of NPs with several functionalities such as cancer cell targeting along with providing image contrast[111-113] (Fig. 2).

Some of the most important potential utility of nanotechnology that are suggested in terms of critical anticancer PDT enhancements to achieve an improved efficacy and safety include: the delivery of PS to its action site, improving the pharmacokinetics of PS[114], in vitro and in vivo experimental models (Table 2), and the exertion of numerous types of nanomaterials in association with phototherapy for the treatment of oral cancer with promising results.

CONCLUSIONS

This work presented a summary on the most recent advances of NPs in the field of oral diagnostic and therapeutic applications. Their distinctive physicochemical properties, such as ultrasmall sizes, high reactivity, and tunable functional modification, can facilitate accurate tools for the early diagnostic of oral cancer and extremely effective therapy options. As a result, it is highly expected to see the exertion of nanomedicine in the modern diagnosis and treatment of oral cancer in near future.

ACKNOWLEDGEMENT

The figure was designed on the BioRender website

CONFLICT OF INTEREST

The authors declare no conflicts of interest

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